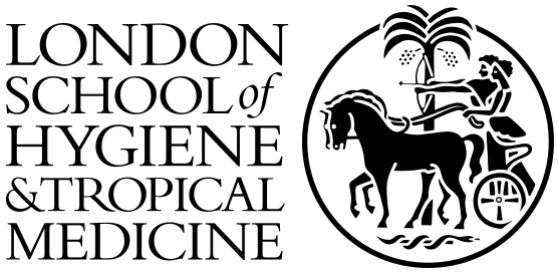



# The safety of influenza vaccination in pregnancy:

# Examining major congenital malformations as potential adverse outcomes using UK electronic health records

**MARIA PEPPA**

Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy of the University of London

March 2020

Department of Infectious Disease Epidemiology

Faculty of Epidemiology and Population Health

London School of Hygiene & Tropical Medicine

Funded by the National Institute for Health Protection Research Unit in Immunisation

## Declaration

I, Maria Peppa, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Maria Peppa (26/03/2020)

## Funding

Maria Peppa was supported by a studentship from the National Institute for Health Research Health Protection Research Unit in Immunisation.

***'Επιστήμη χωριζομένη δικαιοσύνης και της άλλης αρετής, πανουργία ου σοφία φαίνεται'***

– Plato

# Abstract

The aim of this thesis was to examine the safety of maternal influenza vaccination with respect to major congenital malformations in live-born infants. UK electronic health records from the Clinical Practice Research Datalink were used and work was conducted using linked primary care, hospitalisation and mortality data.

The first study systematically reviewed existing methods for identifying congenital malformations in UK electronic health records, and the results of any validation studies. Studies relied on stand-alone primary care or hospitalisation data to identify congenital malformations; none examined linkage between these. Overall, congenital malformations recorded in primary care data had a high positive predictive value (80-100%) but the validity in hospitalisation data was not explored.

Methods from these studies informed the development of a comprehensive algorithm to identify major malformations in live-born infants. Using linked primary care, hospitalisation and mortality data, the second study in this thesis demonstrated that just 20% (95% CI, 19-21) of infants with a major malformation had evidence of their condition in both primary care and hospitalisation data. Almost 65% (95% CI, 64-66) only had evidence in hospitalisation data.

The third study demonstrated that the overall prevalence of major malformations established in primary care data using this algorithm was slightly higher than published estimates from other studies using UK primary care records (Prevalence ratio, 1.2; 95% CI, 1.2-1.3). Comparisons of linked data with population-based registry data demonstrated a four-fold higher prevalence for major malformations overall in the linked electronic health records (Prevalence ratio, 4.3; 95% CI, 4.1-4.5). This was primarily driven by the high prevalence of some of these conditions in hospitalisation data, which could potentially be explained by non-specific codes used to record certain malformations that could have related to either major or minor conditions.

The fourth study examined the association between the trivalent seasonal inactivated influenza vaccine and major malformations. Among 78,150 live-birth pregnancies, 6,872 (8.8%) were vaccinated in the first trimester whilst 46,669 (59.7%) were unvaccinated throughout pregnancy. There was no evidence to suggest an association between first-trimester vaccination and major malformations recorded in first year of infant life in models adjusted for confounding (HR, 1.06; 99% CI, 0.94-1.19; p=0.23). The fifth study, which examined the safety of the monovalent pandemic inactivated influenza vaccine, showed similar results (HR, 1.02; 99% CI, 0.72-1.46; p=0.86). However, although these vaccine safety studies did not find evidence for an association between vaccination and major malformations, terminations due to foetal anomaly were not included. Therefore, the possibility of an increased risk of the specific subtypes of major malformations typically detected during antenatal scans and subsequently terminated could not be discounted.

These results provide additional evidence on the safety of maternal influenza vaccination but highlight the need for further explorations of major malformations among pregnancies that do not result in live-births. The component of this work relating to the methods used to identify major malformations highlights the potential to increase ascertainment through the use of linked data whilst underscoring the need for further studies, particularly in hospitalisation data, to establish the validity of codes used to record these conditions.

## Acknowledgements

First and foremost, I would like to acknowledge those individuals around the world living with congenital malformations. I hope that the methodological aspects of this research can play a small part in improving the visibility of these conditions and contribute to further research.

I am grateful to Prof Sara Thomas, Prof Punam Mangtani, Dr Caroline Minassian and Dr Helen McDonald for their guidance and mentorship over the course of this PhD. I have learnt so much from each of you that I will take forward. I am also grateful for the advice of Dr Jemma Walker, Professor Nick Andrews and Dr Steve Kempley, members of the Electronic Health Records Group at LSHTM and the Health Protection Research Unit in Immunisation at PHE.

I am indebted to my mum and dad, Jane and Dimitris Peppas. Thank you for teaching me that knowledge has value and can never be taken or lost. Above all, thank you for the sacrifices you have made to help me overcome life hurdles in the pursuit of learning. To my little brother, Nick, thank you for always lifting my spirits, especially during the long writing process. Writing would have been very dull without our chat breaks.

I am especially thankful to the Captain Stefanos Foundation for the personal support I have received over many years. Cynne and George, without you I would never have been able to do any of the things I've done over the last decade. Thank you for making it all possible.

I have been lucky to meet and learn from a number of colleagues on their own journeys in office LG21. I am especially grateful to Helena Carreira, Anu Jain and Maud Amon for their friendship and support. Thank you for your humour and encouragement, and for always being there when times were tough. It would not have been as fun without you.

Finally, Tom, there is no concise way to thank you for all the times you have provided support and comfort. This chapter has been particularly difficult for all sorts of reasons and I would not have made it through without you on my team. Thank you for being in the trenches with me, through all of it – and now, forward!

# Contents

## List of Figures

## List of Tables

## List of Abbreviations

| | |
|---|---|
| WHO | World Health Organization |
| SIIV | Seasonal Inactivated Influenza Vaccines |
| PIIV | Pandemic inactivated influenza vaccines |
| CM | Congenital Malformations |
| MCM | Major congenital Malformations |
| RCT | Randomized control trials |
| CI | Confidence Interval |
| BMI | Body-mass Index |
| GP | General practitioner |
| OR | Odds Ratio |
| EUROCAT | European Concerted Action on Congenital Anomalies and Twins programme |
| EMSYCAR | East Midlands and South Yorkshire Congenital Anomaly Register |
| NorCAS | Northern Congenital Abnormality Survey |
| SWCAR | South West Congenital Anomaly Register |
| CAROBB | Congenital Anomaly Register for Oxfordshire, Berkshire & Buckinghamshire |
| WANDA | Wessex Antenatally Detected Anomalies Register |
| WMCAR | West Midlands Congenital Anomaly Register |
| YHCAR | Yorkshire and the Humber Congenital Anomalies Register |
| NHS | National Health Service |
| CPRD | Clinical Practice Research Datalink GOLD |
| THIN | The Health Improvement Network |
| HES | Hospital Episode Statistics |
| ONS | Office for National Statistics |
| QOF | Quality and Outcomes Framework |
| ICD-10 | International Classification of Diseases, 10th Revision |
| OPCS-4 | Classification of Surgical Operations and Procedures, 4th Revision |
| EHR | Electronic health records |
| ACE | Angiotensin-converting-enzyme |
| OXMIS | Oxford Medical Information System |
| PPV | Positive predictive value |
| QUADAS-2 | Quality Assessment of Diagnostic Studies tool |
| PR | Prevalence ratio |
| LSOA | Lower-layer super output areas |
| BPA | British Paediatric Association |
| MBL | Mother-Baby Link |
| IQR | Interquartile range |
| IMD | Index of Multiple Deprivation |
| HR | Hazard Ratio |

# Background Section

This thesis examines the safety of maternal influenza vaccination during pregnancy with respect to major congenital malformations using multiply-linked, routinely-collected UK electronic health records.

The background to this work is described in two chapters:

**Chapter 1** begins with a synopsis of influenza vaccines, their safety during pregnancy, and the research covered by this thesis. **Sections 1.2-1.4** summarize the rationale for maternal influenza vaccination and the determinants of vaccine uptake in pregnant women. **Section 1.5** provides details of maternal influenza vaccination in the UK. **Section 1.6** describes the available evidence on maternal influenza vaccination safety with respect to congenital malformations; **Section 1.7** describes methodological considerations when carrying out safety assessments with congenital malformations as an outcome of interest and **Section 1.8** sets out the research aims and objectives of this PhD.

**Chapter 2** presents a systematic review of the methods used by other researchers to identify and validate congenital malformations in UK electronic health records, and the results of these validation studies. This was used to inform the identification of major congenital malformations in the research described here.

# 1. Background

## 1.1 Synopsis

### 1.1.1 Influenza virus and vaccines

Influenza is a viral respiratory illness whose clinical manifestations range from mild to severe.[1] Although most individuals recover on their own, infection-related complications can result in hospital admission and death. Newborn infants and young children, pregnant women, the elderly and those with underlying health conditions are considered to be the most vulnerable to such complications.[1]

Annual influenza epidemics of varying severity occur as a result of influenza A and B viruses evading immunity in the population through antigenic drift, a process by which minor mutations cause changes in the surface proteins of the virus.[2, 3] In the UK, these epidemics last eight to ten weeks and peak between December and February.[4] Seasonal influenza vaccines can provide protection against influenza and related complications but must be reformulated frequently to mitigate antigenic drift.[5] The World Health Organization (WHO) carries out surveillance of circulating strains and makes annual recommendations on the seed strains to be used in the vaccine.[5]

Seasonal influenza vaccines are commonly: inactivated (i.e. there is no potential for viral replication), non-adjuvanted (i.e. do not contain substances used to enhance the immune response to the vaccine) and either trivalent or quadrivalent (i.e. protecting against two influenza A strains and either one or two influenza B strains).[5] Henceforth, these will be referred to as **seasonal inactivated influenza vaccines (SIIVs)**. Live-attenuated and adjuvanted seasonal influenza vaccines are available but will not be discussed in detail as they are not recommended for use in pregnant women in the UK.

On rare occasions, a novel influenza A virus for which there is very little or no population immunity emerges through antigenic shift, a process by which major mutations result in new

surface proteins on the virus, and causes a pandemic which may result in high levels of mortality and morbidity, including in pregnancy.[2, 6] The most recent pandemic occurred in 2009/10 following the circulation of a new H1N1 subtype of the influenza A virus.[6] In the prior century there were three pandemics: one in 1918/19, one in 1957/58 and one in 1968/69.[2, 6]

Pandemic influenza vaccines can only be manufactured once the novel virus has been isolated and characterized. In the UK, two pandemic influenza vaccines were available in 2009/10: Pandemrix and Celvapan. Both were inactivated and monovalent, but only Pandemrix contained an adjuvant.[7] Henceforth, these two vaccines will be referred to as **pandemic inactivated influenza vaccines (PIIVs)**.

### 1.1.2 Use and safety of influenza vaccines in pregnant women

In 2005, the WHO recommended maternal seasonal influenza vaccination in any trimester to protect both women and, through passive immunity, newborn infants.[8] Despite this, vaccination policies between countries were largely inconsistent prior to the 2009/10 pandemic. For example, the USA recommended vaccination for all pregnant women in any trimester whilst the UK restricted recommendations to pregnant women with underlying conditions and Germany made no recommendations at all.[9, 10] Although the UK and other countries began to expand recommendations to include all pregnant women in any trimester after the pandemic, some continued to restrict vaccination to the 2nd and 3rd trimesters or to pregnant women with underlying conditions.[11-14]

Many factors have been shown to influence the uptake of influenza vaccine by pregnant women but one of the most consistently reported factors is concern for the foetus.[15-17] A large number of post-licensure observational studies have demonstrated good safety profiles for SIIVs and PIIVs with respect to adverse pregnancy outcomes such as preterm delivery, low birth weight, small size for gestational age and foetal death.[18-24]

A number of observational studies have also been carried out to examine the safety of SIIVs and PIIVs with respect to congenital malformations (CMs). Whilst these have not raised

concerns, at the time of this work there were calls for further evidence to address the limitations of existing studies, particularly for SIIVs.[20, 23] Limitations included low numbers of pregnant women vaccinated in the first trimester (the critical period for organogenesis), short infant follow-up resulting in the under-ascertainment of CMs, inadequate adjustment for confounders and a need to assess safety in a setting other than the US where most studies were conducted.[20, 23]

### 1.1.3 Research presented in this thesis

The aim of this PhD was to address some of the limitations in the available literature by using UK electronic health records to assess the safety of SIIVs and PIIVs received during pregnancy with respect to major congenital malformations (MCMs). The objectives to achieve this were:

1. To systematically review the methods used by other researchers to identify and validate congenital malformations in UK electronic health records and the results of any such validations (**Chapter 2**).

2. To use the findings from the systematic review to inform the development of a detailed and comprehensive algorithm to identify MCMs in live-born infants using linked primary care records, hospital admissions and mortality data (**Chapter 5**).

3. To establish the value of these different data sources in identifying infants with MCMs, and their agreement (**Chapter 7**).

4. To compare the rates of MCMs in stand-alone and linked data with rates from the available literature and national surveillance data (**Chapter 7**).

5. To examine the association between maternal vaccination with SIIVs and MCMs in live-born infants, stratified by trimester of vaccination (**Chapter 8**).

6. To examine the association between maternal vaccination with PIIVs and MCMs in live-born infants, stratified by trimester of vaccination (**Chapter 9**).

## 1.2 Risks associated with influenza infection in pregnancy and early infancy

### 1.2.1 Risks pertaining to pregnant women

The increased risk of mortality among pregnant women during influenza pandemics has been well-documented. During the 1918/19 pandemic, for example, the case fatality rate for influenza-related pneumonia in the USA was 50% in pregnant women compared to 33% in the general population.[25, 26] The risk of mortality and of adverse pregnancy outcomes such as premature deliveries increased with gestational age and were highest in the third trimester.[26] A systematic review of observational studies during the recent 2009/10 pandemic noted an increased risk of hospitalisation (n=3 studies), intensive care admission (n=7 studies) and mortality (n=8 studies) in pregnant women compared to non-pregnant women.[27] However, for intensive care admission and mortality, risks varied considerably between individual studies and, in some, evidence was weak or absent.[28-36] The review also noted that evidence was limited due to low numbers of women, infrequent laboratory confirmation of infection and a tendency to group pregnant and post-partum women together.[27]

Seasonal influenza epidemics do not generate the levels of morbidity and mortality seen in pandemics but can still be serious for pregnant women. Influenza-related hospitalisation rates during seasonal epidemics have been shown to be higher among pregnant women compared to those in the post-partum period or those not pregnant, with rates increasing with gestational age.[37, 38] Pregnant women are also thought to be at increased risk of mortality during severe seasonal epidemics.[37] A report on maternal mortality in the UK between 2009-2012 (which included the 2009/10 pandemic and subsequent seasonal epidemics) noted that influenza accounted for 1 in 11 maternal deaths and stressed the importance of vaccination in this population.[39]

### 1.2.2 Risks pertaining to the foetus

Evidence regarding adverse foetal outcomes following maternal influenza infection is inconsistent, with high-quality evidence generally limited to the 2009/10 pandemic.[40, 41]

In a systematic review of 16 observational studies examining preterm birth following maternal infection, just four demonstrated an increased risk (two examining seasonal influenza and two examining pandemic influenza).The remaining studies showed no evidence for an association in either direction.[40] However, of these four studies, only the two examining pandemic influenza were assessed as "good quality". The methodological quality across most of the 16 studies was judged to be "very low".[40]

The same review also examined the risk of foetal death following maternal infection. Out of nine such studies, four demonstrated an increased risk (two examining seasonal influenza and two examining pandemic influenza).[40] The review authors stressed that conclusions regarding foetal death were difficult to draw due to low numbers of outcome events and variable foetal death definitions.[40]

### 1.2.3 Risks pertaining to newborn infants

Although evidence on adverse foetal outcomes is limited, influenza has been shown to pose considerable morbidity burden to infants under six months of age who are not eligible for vaccination.[42-44] Infants under six months old experience 104 excess hospitalisations for cardiorespiratory disease per 10,000 infants during an influenza season (95% CI, 89-119), compared to hospitalisations during the rest of the year.[42] This is more than double the excess number of hospitalisations in any other age group.[42]

## 1.3 Effectiveness of maternal influenza vaccination

### 1.3.1 Influenza vaccine effectiveness in pregnant women

Although pregnant women are usually excluded from clinical trials, evidence from randomized control trials (RCTs) in low- and middle-income countries suggests that SIIV reduces laboratory-confirmed influenza illness in pregnant women (**Table 1.1**). In Mali and South Africa, SIIV was shown to have an efficacy of 70% (95% CI, 42-86) and 50% (95% CI, 15-71), respectively.[45, 46] In Nepal, however, there was no evidence to suggest protective efficacy from the vaccine (31%;

95% CI, -10-56).[47] An RCT in Bangladesh did not examine laboratory-confirmed influenza illness as an outcome but demonstrated a 36% reduction in maternal respiratory illness with fever (95% CI, 4-57).[48]

Evidence from observational studies conducted in high-income countries was often of low quality; studies were frequently underpowered or did not confirm influenza infection using laboratory techniques.[49-52] Among those that examined laboratory-confirmed influenza illness or hospitalisation as the outcome, vaccine effectiveness ranged from 31-70% (**Table 1.1**).[45, 46, 53-58] Based on evidence from RCTs and observational studies, it appears influenza vaccination is moderately effective at protecting against influenza in pregnant women and is not dissimilar to the effectiveness seen in adults aged 18-65 years.[59]

### 1.3.2 Influenza vaccine effectiveness in newborn infants

RCTs in Mali, South Africa, Nepal and Bangladesh all concluded that SIIV receipt during the 2nd or 3rd trimester was associated with a reduction in laboratory-confirmed influenza illness in newborn infants (**Table 1.2**).[45, 46, 48, 56] The efficacy did, however, vary between countries. It was lowest in Mali (33%; 95% CI, 4-54) and Nepal (30%; 95% CI, 5-48), but higher in South Africa (49%; 95% CI, 12-70) and Bangladesh (63%; 95% CI, 5-85).[45, 46, 48, 56]

Observational studies from high-income countries were limited for the same reasons as described in the previous section. Among those examining laboratory-confirmed influenza illness or hospitalisation as the outcome, vaccine effectiveness ranged from 30% to 92% (**Table 1.2**).[54, 60-64] Based on evidence from RCTs and observational studies, influenza vaccination during pregnancy appears to provide moderate to good protection against influenza in the first few months of the infant's life.

**Table 1.1 - Effectiveness of maternal influenza vaccination against maternal laboratory-confirmed influenza illness or hospitalisation.**

| Author | Period | Vaccine | Study Design | Country | Total number of pregnant women (no. vaccinated) | Trimester vaccinated | Outcome | Vaccine efficacy or effectiveness (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Tapia[46] | 2011-2014 | SIIV | RCT | Mali | 4,193 (2,108) | 3rd | LCI-illness | 70 (42-86) |
| Madhi[45] | 2011-2012 | SIIV | RCT | South Africa | 2,116 (1,062) | 2nd, 3rd | LCI-illness | 50 (15-71) |
| Steinhoff[56] | 2011-2013 | SIIV | RCT | Nepal | 3,693 (1,847) | 2nd, 3rd | LCI-illness | 31 (-10-56) |
| Mølgaard-Nielsen[54] | 2010-2017 | SIIV | Test-negative | Denmark | 626 (50) | Any | LCI-illness | 64 (29-82) |
| Thompson[57] | 2010-2016 | SIIV | Test-negative | Canada, Israel, Australia, USA | 1,030 (169) | Any | LCI-hospitalisations | 40 (12-59) |
| Thompson[58] | 2010-2012 | SIIV | Case-control | USA | 292 (154) | Any | LCI-illness | 44 (5-67) |
| Haberg[53] | 2009-2010 | PIIV | Retrospective cohort | Norway | 113,331 (59,266) | Any | LCI-illness or clinical diagnosis | 70 (66-75) |
| Richards[55] | 2009-2010 | PIIV | Retrospective cohort | USA | 3,367 (1,165) | 3rd | LCI-illness or clinical diagnosis | 61 (16-83) |

RCT, Randomized control trial; LCI, lab-confirmed influenza; CI, confidence interval; SIIV, seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine.

**Table 1.2 - Effectiveness of maternal influenza vaccination against laboratory-confirmed influenza illness or hospitalisation in newborn infants.**

| Author | Period | Vaccine | Study Design | Country | Total number of live-born infants (no. of maternal vaccinations) | Trimester vaccinated | Outcome | Vaccine efficacy or effectiveness (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Tapia[46] | 2011-2013 | SIIV | RCT | Mali | 4,105 (2,064) | 3rd | LCI-illness | 33 (4-54) |
| Madhi[45] | 2011-2012 | SIIV | RCT | South Africa | 2,049 (1,026) | 2nd, 3rd | LCI-illness | 49 (12-70) |
| Steinhoff[56] | 2011-2013 | SIIV | RCT | Nepal | 3,520 (1,757) | 2nd, 3rd | LCI-illness | 30 (5-48) |
| Zaman[48] | 2004-2005 | SIIV | RCT | Bangladesh | 316 (159) | 3rd | LCI-illness | 63 (5-85) |
| Mølgaard-Nielsen[54] | 2010-2017 | SIIV | Test-negative | Denmark | 920 (75) | Any | LCI- illness | 57 (25-75) |
| Dabrera[63] | 2013-2014 | SIIV | Case-only | UK | 37 (5) | Any | LCI-illness | 71 (24-89) |
| | 2013-2014 | SIIV | Case-only | UK | 32 (5) | Any | LCI-hospitalisations | 64 (6-86) |
| Shakib[64] | 2005-2014 | SIIV/PIIV | Retrospective cohort | USA | 658 (20) | Any | LCI-illness | 67 (48-79) |
| | 2005-2014 | SIIV/PIIV | Retrospective cohort | USA | 151 (3) | Any | LCI-hospitalisations | 83 (45-95) |
| Benowitz[60] | 2000-2009 | SIIV | Case-control | USA | 247 (33) | 2nd, 3rd | LCI-hospitalisations | 92 (62-98) |
| Eick[61] | 2002-2005 | SIIV | Prospective cohort | USA | 1,160 (573) | 2nd, 3rd | LCI-illness | 41 (7-63) |
| Poehling[62] | 2002-2009 | SIIV | Case-control | USA | 1,510 (294) | Any | LCI-hospitalisations | 45 (5-68) |
| Walker[65] | 2013-2014 | SIIV | Case-only | UK | 37 (7) | 2nd, 3rd | LCI-hospitalisations | 66 (18-84) |
| | 2014-2015 | SIIV | Case-only | UK | 81 (19) | 2nd, 3rd | LCI-hospitalisations | 50 (11-72) |

RCT, Randomized control trial; LCI, lab-confirmed influenza; CI, confidence interval; SIIV, seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine.

## 1.4 Maternal determinants of influenza vaccine uptake during pregnancy

Understanding vaccine confidence and barriers to vaccination is a complex task and a field in its own right. A detailed review of the maternal determinants of influenza vaccination will not be attempted here. Instead, a comprehensive overview of the salient points will be given.

Studies have converged upon three key factors related to vaccine confidence among pregnant women. The first appears to be a lack of knowledge about the effectiveness of the vaccine and the protection it provides against serious disease.[17, 66-68] The second, and perhaps most frequently reported factor, is a widespread concern about safety of influenza vaccine for the foetus.[16, 17, 66-69] In the UK, an online survey of pregnant women and mothers found that 95% of women cited the safety of their child as their primary concern when considering vaccination in pregnancy.[15] A lack of recommendation of the vaccine by health-care workers is the third key factor.[17, 66-68] Pregnant women have been shown to be more likely to accept vaccination if it is recommended by a health-care worker such as a midwife.[17, 66-68] Evidence has, however, emerged to suggest that a large proportion of health-care workers in the UK do not feel confident providing advice about vaccination in pregnancy and are concerned about a perceived lack of safety studies in pregnant women.[16, 67] Providing further good evidence of vaccine safety is therefore key in addressing the concerns of pregnant women, increasing confidence among health-care workers, and ultimately in sustaining and increasing vaccination uptake.

In addition to the above, a number of sociodemographic maternal factors are thought to be associated with vaccine uptake. Young pregnant women have consistently been shown to be less likely to receive the vaccine than older women.[17, 66, 67] A number of studies have also shown lower vaccine uptake among ethnic minorities.[17, 67, 68] Reasons for this are inadequately described in the literature and whilst it is possible that variation in knowledge of benefits, social norms and cultural beliefs may play a role, it is also well-recognized that there are barriers in access to health services for these groups.[70] Distal factors such as greater socio-

economic deprivation, measured by numerous indicators including education level, employment, income and insurance, have also been associated with low vaccine uptake.[17, 67] More proximal reproductive factors have not been widely explored although there is evidence to suggest that primiparous women are more likely to be vaccinated than multiparous women.[17]

Health status and lifestyle factors have been infrequently examined but there is evidence to suggest that some may be associated with vaccine uptake. Pregnant women without underlying health conditions are, unsurprisingly, less likely to receive the vaccine.[17, 67] Whilst the evidence on alcohol consumption doesn't point to a clear relationship with vaccination, there is evidence that pregnant smokers are less likely to be vaccinated.[17, 66, 67] In the UK, obesity was recently classified as a clinical risk group for which vaccination was recommended, suggesting that uptake among pregnant women in this group is likely to rise.[5] Evidence on the association between body-mass index (BMI) at the start of pregnancy and vaccine uptake is limited, although in the general population there is evidence that low BMI is associated with lower uptake of the vaccine.[66] It is possible that such a relationship persists in pregnancy.

## 1.5. Maternal influenza vaccination in the UK

### 1.5.1 Influenza vaccination policy for pregnant women in the UK

Prior to the 2009/10 pandemic, pregnant women in the UK were offered SIIV in any trimester if they were part of a clinical risk group (**Figure 1.1**).[13] This included those vulnerable to influenza-related complications due to chronic respiratory, heart, renal, liver or neurological diseases, diabetes or immunosuppression.

During the 2009/10 pandemic, SIIV continued to be offered only to those pregnant women in clinical risk groups at any time in their pregnancy. Conversely, PIIV was offered to all pregnant women in any trimester, regardless of clinical risk group status, once it became available on October 21, 2009 (**Figure 1.1**).[12]

Guidelines for the subsequent 2010/11 influenza season recommended that pregnant women in any trimester should be offered SIIV regardless of clinical risk group - unless they had already received PIIV (**Figure 1.1**).[13] During this season, PIIV was also available for use in case of a depletion of SIIV stocks. From 2011/12 onwards, SIIV has continued to be offered to pregnant women in any trimester regardless of clinical risk group status (**Figure 1.1**).[4, 13]

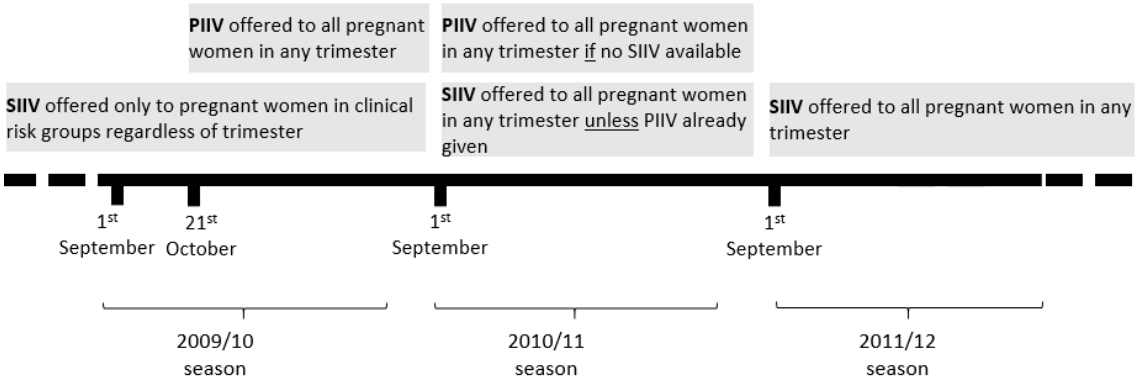



**Figure 1.1 - Availability of seasonal and pandemic influenza vaccines for pregnant women in the UK**

Currently, the UK maternal influenza vaccination programme is delivered primarily through general practice although vaccinations can be given in pharmacies and a small number of antenatal care services have introduced vaccinations by midwives in recent years.[4, 71, 72] It is, however, a contractual requirement for general practitioners (GPs) to document vaccinations occurring outside of the practice.[73]

### 1.5.2 Influenza vaccines recommended for pregnant women in the UK

**Seasonal influenza vaccines**

In the UK, SIIVs are available as early as September and vaccination can continue into March.[73] Until recently, all SIIVs in the UK were trivalent, inactivated and un-adjuvanted. In 2013/14, a quadrivalent SIIV became available (**Table 1.3**).[74]

Live-attenuated and adjuvanted seasonal influenza vaccines have also been introduced over the course of the last decade (**Table 1.3**). In 2012, live-attenuated vaccines were

recommended only for those aged two to less than 17 years and a phased rollout was initiated the following year.[74] Whilst the ages of cohorts eligible to receive live-attenuated vaccines differ between the devolved administrations, the latest cohort to be eligible in England during the 2019/20 influenza season was children aged two to 10 years. Therefore, during the period that the work in this thesis was conducted, no pregnant individual would have received the live-attenuated vaccine. Adjuvanted vaccines are only recommended for elderly populations and were also unavailable during the time the work described in this thesis was conducted (**Table 1.3**). SIIVs that could have been received by pregnant women during the time this work was carried out are shown in **Table 1.4**.

**Table 1.3 - Seasonal influenza vaccines recently introduced in the UK.**

| Influenza vaccine Type | Season introduced | Recommended/Target Population |
|---|---|---|
| Live-attenuated trivalent vaccine[a] | 2012/13 | Phased rollout among children aged 2-17 years with no contraindications[b] |
| Egg-based quadrivalent inactivated vaccine[a] | 2013/14 | At risk[c] adults aged 18-64 years **including pregnant women**<br>At risk[c] children aged 6 months – 2 years<br>Children aged 2-17 years unable to receive the live vaccine |
| Live-attenuated quadrivalent vaccine[a] | 2014/15 | Phased rollout among children aged 2-17 years with no contraindications[b] |
| Adjuvanted trivalent inactivated vaccine | 2018/19 | Adults aged ≥65 years |
| Cell-based quadrivalent inactivated vaccine[a] | 2019/20 | At risk[c] adults aged 18-64 years **including pregnant women**<br>Adults aged ≥65 years |

[a]Do not contain an adjuvant, [b]E.g. immunodeficiency, [c]Those with conditions for which there is an increased risk of morbidity and mortality associated with influenza infection.

**Pandemic influenza vaccines**

The influenza strain responsible for the 2009/10 pandemic was not included in SIIVs prepared for the 2009/10 influenza season and was manufactured at a later date. PIIVs were available in the UK from October 21, 2009.[12] In the UK there were two PIIVs, Pandemrix and Celvapan, of which just Pandemrix was adjuvanted (**Table 1.4**).[7] Due to the absence of an adjuvant, two doses of Celvapan were required three weeks apart to provide a sufficient immune response. Pandemrix was the recommended vaccine for pregnant women as a single dose conferred protection. Though both of these PIIVs could be used, the overwhelming majority of individuals vaccinated received Pandemrix.[75]

**Table 1.4– Seasonal and pandemic influenza vaccines available for use in pregnant women between 2009 and 2016.**

| Product Name (Supplier) | Vaccine Type | Formulation | Influenza season in which the specified vaccine was available | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 2009/10 | 2010/11 | 2011/12 | 2012/13 | 2013/14 | 2014/15 | 2015/16 |
| Agrippal (Novartis/MASTA) | Trivalent SIIV | Surface antigen | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Begrivac (Novartis) | Trivalent SIIV | Split virion | ✓ | ✓ | | | | | |
| CSL inactivated influenza vaccine (Pfizer/Wyeth) | Trivalent SIIV | Split virion | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Enzira (Pfizer/MASTA/Wyeth) | Trivalent SIIV | Split virion | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Fluarix (GlaxoSmithKline/MASTA) | Trivalent SIIV | Split virion | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Fluarix Tetra (GlaxoSmithKline) | Quadrivalent SIIV | Split virion | | | | | ✓ | ✓ | ✓ |
| Fluvirin (Novartis) | Trivalent SIIV | Surface antigen | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| Inactivated influenza vaccine BP (Sanofi Pasteur MSD/MASTA) | Trivalent SIIV | Split virion | | | | ✓ | ✓ | ✓ | ✓ |
| Imuvac (Abbott/MASTA) | Trivalent SIIV | Surface antigen | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Inflexal (Crucell/Janssen-Cilag) | Trivalent SIIV | Surface antigen | | | | ✓ | ✓ | | |
| Influvac (Abbott) | Trivalent SIIV | Surface antigen | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Intanza (Sanofi Pasteur MSD) | Trivalent SIIV | Split virion | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Optaflu (Novartis) | Trivalent SIIV | Surface antigen | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| Preflucel (Baxter) | Trivalent SIIV | Split virion | | | ✓ | | | | |
| Viroflu (Sanofi Pasteur MSD/Crucell/Janssen-Cilag) | Trivalent SIIV | Surface antigen | ✓ | | ✓ | ✓ | ✓ | | |
| Pandemrix (GlaxoSmithKline) | Monovalent PIIV | Split virion, adjuvanted | ✓ | ✓ | | | | | |
| Celvapan (Baxter) | Monovalent PIIV | Whole virion | ✓ | ✓ | | | | | |

Abbreviations: SIIV, Seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine.

### 1.5.3 Uptake of the influenza vaccine by pregnant women in the UK

GPs submit data on influenza vaccine uptake among target groups at their practice to the Department of Health '*ImmForm*' website. Public Health England subsequently publish aggregated data for the UK and the devolved administrations. Based on these data, influenza vaccine uptake among pregnant women in the UK is thought to have increased since its introduction, with an uptake of 52% for the 2018/19 influenza season compared to 40% in 2011/12 (**Figure 1.2**).[76, 77]

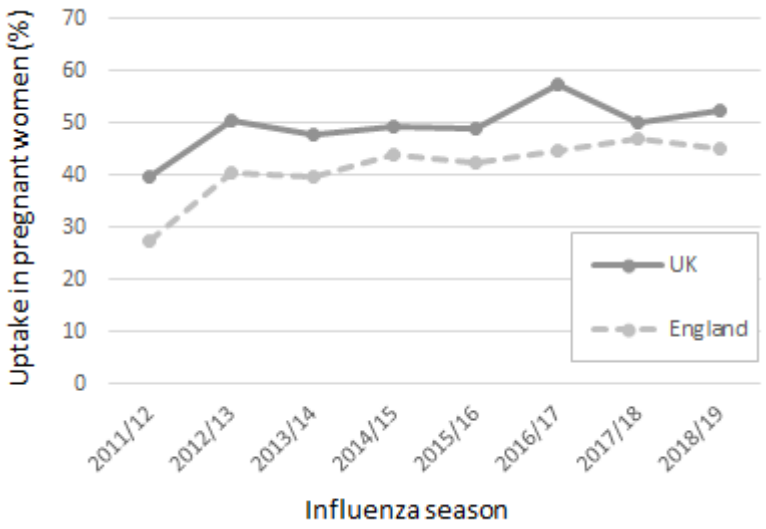



**Figure 1.2 - Influenza vaccine uptake in the UK and England among pregnant women, by season. Data are based on Public Health England national surveillance through the '*ImmForm*' system.[76,77]**

Although this is similar to or higher than the uptake seen in other countries, it is below a 75% coverage target aimed at by the WHO.[78] There is also considerable variation in uptake by region. In 2018/19, for example, uptake at the level of clinical commissioning groups ranged from 29% in Enfield to 69% in Stockport.[77] These uptake rates should, however, be interpreted with caution as identifying pregnant women and non-pregnant women accurately over the course of each influenza season is challenging and may introduce uncertainty in the denominators.[4, 72]

## 1.6 Maternal influenza vaccination safety and major congenital malformations

### 1.6.1 The aetiology and importance of congenital malformations

Congenital malformations are defined as structural or functional defects that arise *in utero* and are present at birth.[79] Globally, they are estimated to affect 2-6% of viable pregnancies and are a leading cause of infant mortality and morbidity.[80-83] In the UK and other high-income countries, congenital malformations are responsible for up to 25% of neonatal deaths and those who survive are likely to have disabilities resulting in considerable health and social care needs over their lifespan.[83, 84] This is particularly true of those with major congenital malformations (MCMs) which represent severe conditions and are, therefore, of particular public health importance.[85] Conversely, minor malformations are those not associated with serious medical needs or functional impairment of individuals and have limited cosmetic importance.[86]

The causes of congenital malformations can be divided into those that occur prior to conception and those that occur after (**Figure 1.3**).[81] Pre-conception causes of congenital malformations include genetic abnormalities such as single gene defects and chromosomal aberrations that may be inherited or may occur spontaneously without any prior family history.[81] After conception, congenital malformations are thought to arise chiefly through *in utero* exposure to mechanical forces, vascular disruptions or teratogens which disturb the normal development of the foetus. Teratogenic agents include maternal infections that can be transmitted across the placenta to infect the foetus (e.g. rubella), certain drugs or chemicals (e.g. thalidomide) and radiation (e.g. x-rays). A third of congenital malformations are known to be multifactorial, occurring as a result of an interaction between genetic abnormalities that have occurred before conception and environmental exposures.[81] Despite the large amount of research carried out to determine the above, up to half of congenital malformation cases have no known aetiology.[81]

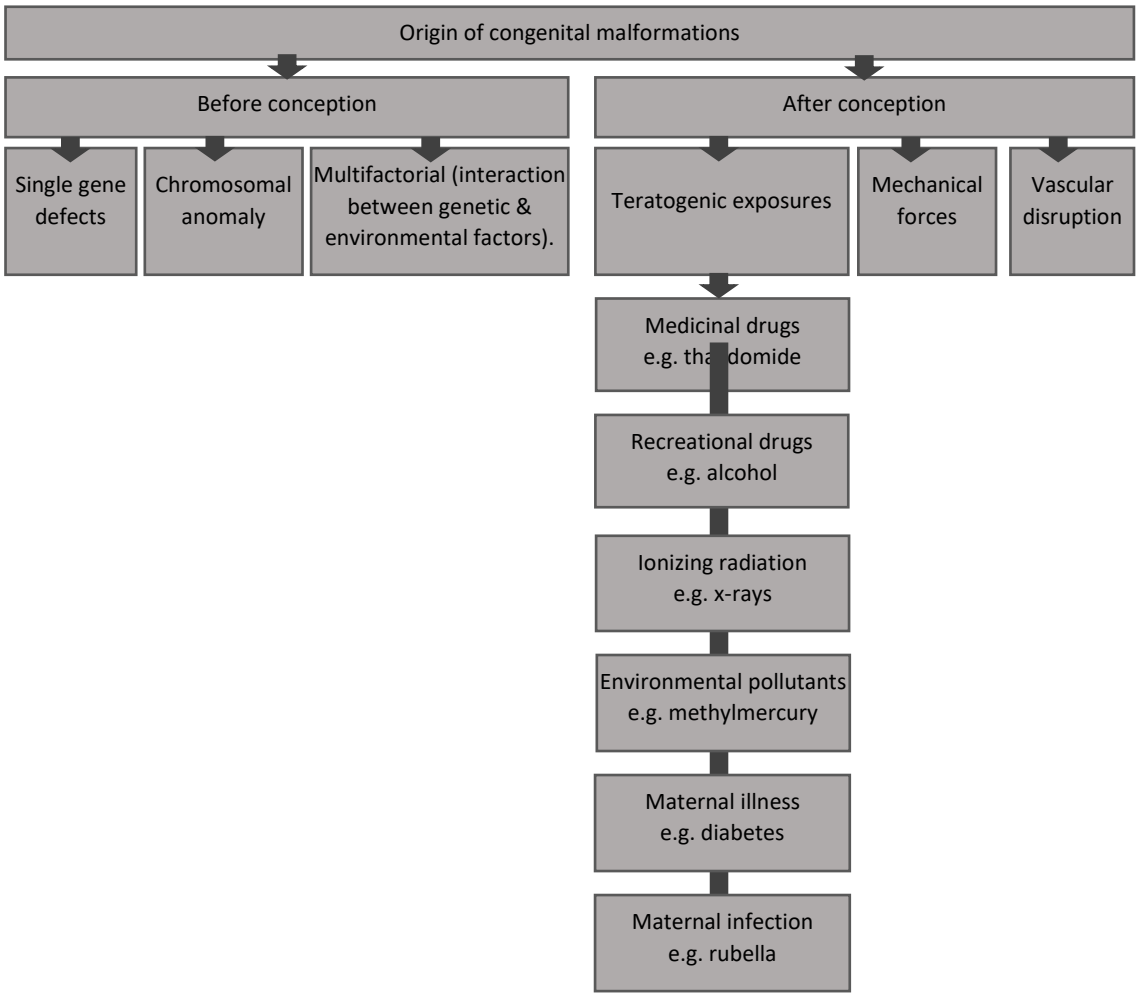



**Figure 1.3 - Aetiology of congenital malformations.**
Based on the 'Global Report on Birth Defects' by Christianson *et al.*[81]

Congenital malformations received global attention in the 1960s following the thalidomide disaster.[87] Thalidomide was widely prescribed to pregnant women as an anti-emetic for morning sickness but was eventually found to be a teratogen responsible for congenital malformations in 10,000 live-born infants worldwide.[87] This disaster resulted in changes to legislation around drug regulation as well as an understanding of the need for post-marketing drug surveillance.[88] The latter is of particular importance for pregnant women who are often not included in RCTs carried out as part of the drug licensing process. As vaccination during pregnancy has been increasingly recommended to prevent illness in pregnant women and/or their infants, congenital malformations have become an important outcome of interest in post-marketing vaccine safety studies. This is particularly the case for first-trimester vaccination as this is when most organogenesis occurs.

The theoretical mechanisms by which vaccines could cause congenital malformations depend on the formulation of the vaccine.[89] Live-attenuated vaccines are often contraindicated in pregnancy due to the theoretical risk of the virus infecting the foetus after crossing the placenta.[89] This is not a concern for inactivated vaccines but other mechanisms may still pose a risk. Ingredients added to the vaccine such as adjuvants (especially those that are novel and for which safety data is lacking), preservatives, emulsifiers, stabilisers or those that are part of the manufacturing process could theoretically act as teratogens.[89] The available evidence on the safety of maternal influenza vaccination with respect to congenital malformations is described below.

### 1.6.2 Current safety evidence for maternal influenza vaccination and congenital malformations

The majority of evidence on maternal influenza vaccination safety has been obtained from observational studies. Whilst the RCTs described in **Section 1.3** did not produce any safety signals of concern, they were not powered to detect rare outcomes. Since 2015, five systematic reviews have examined evidence on the safety of maternal influenza vaccination with respect to congenital malformations from available observational studies and all have concluded that there is no evidence for an association.[20-24] **Table 1.5** summarizes all 20 observational studies included across the five systematic reviews.

Before the work conducted in this thesis began, the largest available systematic review was by Polyzos *et al.* and included 15 studies with more than 36,000 vaccinated pregnant women in total (>4,700 vaccinated in the first trimester).[23] Only two of these studies assessed SIIV, the remaining studies focused on PIIV. Authors pooled effect estimates from all 15 studies and found no evidence of an association between maternal influenza vaccination and congenital malformations (Odds Ratio (OR), 0.96; 95% CI, 0.86-1.07). Similar results were found when restricting to the eight studies that examined first-trimester vaccination (OR, 1.03; 95% CI, 0.91-1.18) and the seven of these which assessed MCMs (OR, 0.98; 95% CI, 0.83-1.16).[23] A sub-

analysis of adjuvanted and unadjuvanted inactivated vaccines also showed no evidence for an association. A systematic review by McMillan *et al.* covered a subset of the studies examined by Polyzos *et al*. and demonstrated similar results.[20, 23]

**Limitations of the available safety evidence for major congenital malformations:**

Despite finding no evidence for an increased risk, these two systematic reviews that included a total of 15 studies highlighted the limitations of existing research. These included:

1. A focus on PIIV, with limited evidence on SIIVs. Of the 15 primary studies, just two examined SIIVs alone[50, 90] and one examined PIIV alongside SIIV.[91]

2. A limited number of studies examining vaccination in the first trimester despite this being the critical period for organogenesis. Of the 15 primary studies, seven examined first-trimester vaccination and MCMs[90-96] and only one of these examined SIIV alone.[90]

3. Small sample sizes in the context of the rarity of congenital malformations, especially in the studies examining vaccination in the first trimester. The single study examining SIIV in the first trimester had fewer than 500 vaccinated pregnant women.[90] Only one study examining the safety of PIIV in the first trimester included more than 1,000 pregnant women.[94]

4. Limited infant follow-up, precluding the identification of diagnoses made later in childhood. Follow-up time among the 15 studies was generally short; just one study examining PIIV identified congenital malformations up until the first birthday.[96] The majority identified congenital malformations at the time of delivery or shortly after.

5. Inadequate adjustment for confounders in several studies, particularly among those that focused on first-trimester vaccination. Among the 15 studies, seven did not adjust for any factors.[90, 91, 93, 97-100]

6. Inconsistent definitions of congenital malformations and inconsistent handling of hereditary disorders across studies. Furthermore, studies often did not examine malformation subgroups and tended to focus on malformations as aggregate outcomes.[20] Associations of vaccination with specific types of malformations were therefore less likely to be detected and the totality of evidence for any particular malformation subgroup was limited.

After the work described in this thesis began, a further five primary studies were published.[101-105] Two examined PIIV, with one including over 14,000 first-trimester vaccinated pregnancies and following infants up for a year.[102, 105] Neither of these found evidence of an association with aggregate congenital malformations although one study did find evidence to suggest an association with oral cleft when comparing vaccination in the first eight weeks of pregnancy with vaccination after eight weeks (OR, 1.6; 95% CI, 1.01-2.65; p value not reported).[105] However, as the lower confidence interval is close to the null, these results should be interpreted with caution.

The other three studies examined the safety of SIIV receipt, including in the first trimester.[101, 103, 104] None of these studies found evidence of an association with congenital malformations. One of these studies, conducted by Kharbanda *et al.*, is the largest safety study examining SIIV received in the first trimester to date.[103] Using the Vaccine Safety Datalink, which collects vaccination data from several different sites in the US and links these to other healthcare data (e.g. inpatient, outpatient and emergency admissions to hospital), almost 53,000 infants whose mothers received SIIV in the first trimester were followed-up for a year and compared to those unexposed in the first trimester and those unexposed throughout pregnancy. The adjusted prevalence ratio for MCMs was the same in both analyses (1.02; 95% CI, 0.94-1.10).[103] MCM subgroups were also examined but none of these showed an association with vaccination.

In the time since the work for this thesis began, three further systematic reviews were published in addition to the five primary studies described above.[21, 22, 24] The largest of these included 19 of the 20 known observational studies (**Table 1.5**), including the five most recently published primary studies. There was no evidence to suggest an association between maternal influenza vaccination during pregnancy and congenital malformations, even after adjusting for the gestational age at vaccination.[24] Results from the other two most recent systematic reviews were consistent with this.[21, 22, 24]

Although results from studies so far are reassuring, further investigations in different settings can increase confidence in the available evidence. Whilst the recent study by Kharbanda *et al.* assessed the safety of first-trimester SIIV in a large study population and ascertained MCMs in the first year of life, the study relied on the Vaccine Safety Datalink which requires participants to be insured. The health-seeking behaviour of participants may therefore differ from the general population.[106] Indeed, vaccine coverage rates among participants have been shown to be higher than the national average for some vaccines.[106] If those included in the Vaccine Safety Datalink are more likely to be vaccinated than those not included, and if they also differ in their underlying risk factors for MCMs, this may mean that results are not generalizable to those outside of the Vaccine Safety Datalink. This can be addressed by confirming evidence of safety in different settings and with different methods.

No large safety studies of maternal influenza vaccination and MCMs have been carried out in the UK and all studies of SIIV have been carried out in North America. The generalizability of results to the UK could be affected by differences in healthcare systems (universal coverage vs insurance-based care), vaccine confidence, antenatal screening for congenital malformations and terminations, as well as possible differences in the available influenza vaccines for pregnant women. Assessing safety in the UK provides an opportunity to address some of the limitations in the available literature whilst also establishing whether results can be replicated elsewhere.

**Table 1.5 - Available safety evidence on maternal seasonal or pandemic influenza vaccination and congenital malformations.**

| Author | Study Period | Country | Study Design | Total no. of vaccinated pregnancies (No. vaccinated in 1st trimester) | Follow-up from delivery | Outcome Examined | | | | | Calculated measures of effect for 1st trimester vaccination? | Were any associations with vaccination detected? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Any CM | Any MCM | MCM subgroups | Limb defects | Heart defects | | |
| **SIIV** | | | | | | | | | | | | |
| Munoz[50] | 1998-2003 | US | Cohort (R) | 252 (0) | Around delivery [a] | ✓ | | | | | | No |
| Sheffield[90] | 2003-2008 | US | Cohort (R) | 10,225 (439) | Around delivery [a] | | ✓ | | | | ✓ | No |
| Chambers[101] | 2010-2014 | US, Canada | Cohort (P) | 1,263 (457) | 1 year | | ✓ | | | | ✓ | No |
| Kharbanda[103] | 2004-2013 | US | Cohort (R) | 52,856 (52,856) | 1 year | | ✓ | ✓ | ✓ | ✓ | ✓ | No |
| Louik[104] | 2011-2014 | US | Case-control | 711 (711) | 6 months | | ✓ | ✓ | | ✓ | ✓ | No |
| **PIIV** | | | | | | | | | | | | |
| Trotta[107] | 2009-2010 | Italy | Cohort (R) | 6,246 (0) | Around delivery [a] | | ✓ | ✓ | ✓ | ✓ | | No |
| Rubinstein[100] | 2010-2011 | Argentina | Cross-section | 7,293 (2,874) | 1 week | ✓ | | | | | | No |
| Launay[98] | 2009-2010 | France | Cohort (P) | 320 (0) | Around delivery | ✓[b] | | | | | | No |
| Lin[108] | 2009-2010 | Taiwan | Cohort (R) | 198 (10) | 8 weeks | ✓[b] | | | | | | No |
| Fabiani[102] | 2009-2010 | Italy | Cohort (R) | 2,003 (0) | Delivery; 6 months | ✓ | ✓ | ✓ | ✓ | ✓ | | No |
| Cleary[93] | 2008-2010 | Ireland | Cohort (R) | 2,996 (246) | Around delivery [a] | ✓ | | | | | ✓ | No |
| Kallen[94] | 2009-2010 | Sweden | Cohort (R) | 18,612 (3,197) | Unclear | ✓ | ✓ | ✓ | | ✓ | ✓ | No |
| Heikkinen[109] | 2009-2010 | Netherlands, Italy, Argentina | Cohort (P) | 2,295 (92) | 3 months | | ✓ | | | | | No |
| Pasternak[96] | 2009-2010 | Denmark | Cohort (R) | 6,989 (345) | 1 year | | ✓ | | | | ✓ | No |
| Oppermann[95] | 2009-2010 | Germany | Cohort (P) | 323 (55) | 8 weeks | ✓ | ✓ | | | | ✓ | No |
| Mackenzie[99] | 2009-2010 | UK | Cohort (P) | 97 (10) | Delivery | ✓ | | | | | | No |
| Ludvigsson[105] | 2009-2011 | Sweden | Cohort (R) | 40,983 (14,385) | 1 year | ✓[c] | | ✓ | ✓ | ✓ | ✓ | Yes[d] |
| Deinard[e,97] | 1976-1977 | US | Cohort (P) | 189 (NS) | 8 weeks | ✓ | | | | | - | No |
| PIIV or SIIV | | | | | | | | | | | | |
| Chambers[f,92] | 2009-2012 | US, Canada | Cohort (P) | 841 (328) | Around delivery [a] | | ✓ | | | | ✓ | No |
| Louik[91] | 2009-2011 | US | Case-control | 1,524 (NS) | Unclear | | ✓ | ✓ | | | ✓ | Yes[g] |

[a]Follow-up not specified but conditions identified around time of birth; [b]CMs not specified but no exclusions mentioned; [c]Excluded hip dislocation, undescended testes, ear malformations, tongue tie, neoplastic naevus, pyloric stenosis, patent ductus arteriosus; [d]$OR_{adj}$ for oral cleft following maternal vaccination in the first 8 weeks versus vaccination after 8 weeks: 1.6 (95% CI, 1.0–2.7); [e]Restricted access to full-text; [f]Adjusted for SIIV exposure; [g]$OR_{adj}$ for specified eye malformations following 1st trimester vaccination: 8.7 (95% CI 1.1-68.5). Abbreviations: CM, congenital malformation; MCM, major congenital malformation; NS, not specified; CI, confidence interval; SIIV, seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine; $OR_{adj,}$ Adjusted odds ratio; R, retrospective; P, prospective.

## 1.7 Methodological considerations for safety studies examining major congenital malformations

### 1.7.1 Available UK data sources

In the UK, the following data sources have been used to carry out post-licensure safety assessments of medications used in pregnancy with CMs as the outcome of interest:

1. Pregnancy exposure registries.
2. Population-based surveillance registries.
3. Electronic health records.

**Pregnancy exposure registries**

Pregnancy exposure registries enrol pregnant volunteers into prospective cohort studies to examine the association between drugs or vaccines given in pregnancy and adverse foetal outcomes such as MCMs.[110] Some may examine a broad range of medications, as is the case with the UK Teratology Information Service.[111] Others, such as the UK Epilepsy & Pregnancy Register, may enrol only those on specific treatments.[112, 113] Typically, information about the drug or vaccine used is collected as well as basic clinical, obstetric and demographic data. Outcomes are usually ascertained by standardized questionnaires sent to GPs shortly after the estimated delivery date.[114]

Pregnancy exposure registries are particularly limited in their scope due to their reliance on the voluntary enrolment of women. Due to low levels of enrolment, these registries are typically only able to detect major teratogenicity. Furthermore, voluntary enrolment can introduce concerns around selection bias and generalizability. Vaccine safety studies using such registries could be vulnerable to these concerns if those choosing to receive the vaccine were more likely to enrol and have lower or higher risk of the outcome. Finally, such registries typically identify outcomes around the time of delivery and collect minimal information on potential confounders.

**Population-based surveillance registries**

Population-based surveillance registries aim to identify individuals with particular conditions, such as MCMs, within a defined population. By collecting additional data on medications received during pregnancy, post-licensure safety assessments can be conducted.[115] At the time of this work, there were seven regional registries in England collecting data on MCMs among live-births, stillbirths, spontaneous abortions and pregnancy terminations due to foetal anomaly (**Table 1.6**).[116,117] These were the:

- East Midlands and South Yorkshire Congenital Anomaly Register (EMSYCAR),
- Northern Congenital Abnormality Survey (NorCAS),
- South West Congenital Anomaly Register (SWCAR),
- Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB),
- Wessex Antenatally Detected Anomalies Register (WANDA),
- West Midlands Congenital Anomaly Register (WMCAR), and the
- Yorkshire and the Humber Congenital Anomalies Register (YHCAR).

Registries employ both active and passive ascertainment procedures to identify MCMs.[118] They receive notifications of congenital malformations from multiple sources, some of which include: maternity units, neonatal units, child health systems, paediatricians, cardiologists, midwives, ultrasonographers, geneticists and surgeons.[119] Over the years, registries have developed close working relationships with local health services: setting up regular multi-disciplinary meetings to link hospitals with other services (e.g. cytogenetics services) and performing cross-validations of cases using available data sources.[120-122] Registries that have established close links with regional cytogenetics centres and tertiary care centres (e.g. cardiology units) also receive case lists from these routinely.[117, 120, 121] Increasingly, registries are also receiving electronic data on congenital malformations from NHS Trusts – with over 500 NHS providers sharing data with registries as of 2015.[123] Population-based registries are not limited by issues around voluntary enrolment and are generally better-placed for post-

marketing safety assessments than pregnancy exposure registries. However, the availability of resources can impact the potential for active case finding and long-term follow-up, with some registries under-ascertaining conditions in the postnatal period despite high levels of ascertainment in the antenatal period.[120, 121, 124]

Several registries contribute data to the 'European Concerted Action on Congenital Anomalies and Twins' programme (EUROCAT) which is a consortium of population-based registries covering over 30% of the European birth population that has been used for the post-marketing surveillance of medications in pregnancy.[86] Data submitted to EUROCAT by registries are standardized; registries must follow EUROCAT guidelines to code MCMs and must also collect and submit additional data on the infant (e.g. birth weight, sex), obstetric characteristics (e.g. gestational length, type of outcome) and maternal characteristics (e.g. maternal age). Registries can opt to collect data on drug exposures during pregnancy, maternal illness before and during pregnancy, family medical history and sociodemographic information on an ongoing basis. However, as resources for this are often limited, these data may instead be collected in an ad-hoc way for specific studies.

On 1st April 2015, these regional registries were incorporated into the new National Congenital Anomaly and Rare Disease Registration Service, overseen by Public Health England.[116] As part of this change, a single data management system was established and paper notifications were ceased in favour of electronic notifications.[123] Until recently, no registries covered the highly populated areas of London and South East England, nor the East of England or North West regions. Three new reporting regions have been created for these and the first national coverage data are expected.

In addition to the above UK registries, there are also malformation-specific population-based registries. An example of such a registry is the Cleft Registry and Audit Network, which receives information on children born with a cleft lip and/or cleft palate from 15 hospitals across England, Wales and Northern Ireland.[125]

**Table 1.6 – Characteristics of English congenital malformation registries.**

| Name of Registry | EUROCAT member? | Year Established | Geographic coverage | Annual births | Upper age limit for diagnoses | Source of denominator data since 2005 | Are any exposure data recorded? |
|---|---|---|---|---|---|---|---|
| East Midlands & South Yorkshire Congenital Anomaly Register (EMSYCAR) | Yes | 1997 | South Yorkshire, Derbyshire, Nottinghamshire, Lincolnshire, Leicestershire, Rutland and Northamptonshire | 74,000 | None | ONS | Type of data collected not specified[a] |
| Northern Congenital Anomaly Survey (NorCAS) | Yes | 1985 | North East England, North Cumbria, Northumberland, Newcastle upon Tyne, North Tyneside, Gateshead, South Tyneside, County Durham, Darlington and Tees | 33,000 | 12 years | ONS | Maternal diabetes, maternal medications, maternal smoking, major maternal medical problems, maternal weight and height[a] |
| South West Congenital Anomaly Register (SWCAR) | Yes | 2002 | South West Strategic Health Authority | 60,000 | 18 years | ONS | Maternal age, maternal medications, maternal smoking, maternal deprivation status |
| Congenital Anomaly Register for Oxfordshire, Berkshire and Buckinghamshire (CAROBB)[b] | Yes | 1991 | Local authority regions for Oxfordshire, Berkshire and Buckinghamshire | 31,000 | 1 year | ONS | Maternal chronic illness, details of assisted conception, invasive tests in pregnancy and maternal alcohol abuse[a] |
| Wessex Antenatally Detected Anomalies Register (WANDA)[c] | Yes | 1994 | Old 'Wessex' region, Jersey and Guernsey | 31,000 | None[d] | Hospital labour wards | Maternal chronic illness, details of assisted conception, invasive tests in pregnancy and maternal alcohol abuse[a] |
| West Midlands Congenital Anomaly Register (WMCAR) | No | 1995 | West Midlands Strategic Health Authority | 72,500 | 2 years | ONS | Maternal age and ethnicity |
| Yorkshire and the Humber Congenital Anomalies Register (YHCAR) | No | 2011 | No available information | 45,000 | No available information | No available information | No available information |

[a]Recorded if available; [b]Also known as the Thames Valley Register; [c]Merged with SWCAR in 2015; [d]Despite no upper age limit, data are considered unreliable after the neonatal period.

**Electronic health records**

In the UK, healthcare is provided by the National Health Service (NHS) and is free at the point of delivery.[126] The first point of contact with the health service for most individuals in the UK is the general practice, with almost 99% of the population registered with one.[126] General practitioners provide patients with primary care services but also act as the gatekeeper for access to further services. Therefore, a patient's general practice record will contain details of any consultations with practice staff as well as information on referrals and feedback from secondary or tertiary care services.[127] As general practitioners use clinical management software to record consultations, prescriptions and other clinical data, general practice records are digitized and can be used for research purposes.[128]

At the time this work began, three UK-wide electronic primary care databases were available: The Clinical Practice Research Datalink GOLD database (henceforth referred to as 'CPRD'), The Health Improvement Network (THIN) and the Q-Research database (**Table 1.7**). Although none of these databases provide investigators with access to the primary care records of the entire UK population, records are available for a large enough proportion of the population that the examination of rare outcomes such as MCMs is possible.[127] Primary care data can also be linked to other data including hospital admissions from the Hospital Episode Statistics database (HES) and Office for National Statistics (ONS) mortality data, thus providing a rich source of information on patients. This potential was further improved following the introduction of the Quality and Outcomes Framework (QOF) in 2004 which financially incentivized the recording of a number of diagnoses and other key variables in primary care.[126]

Based on the above, UK electronic primary care data have considerable potential for use in pharmaco-epidemiological research and are increasingly used in post-licensure studies examining the association between drug or vaccine exposures during pregnancy and congenital malformations.

**Table 1.7 – Examples of electronic primary care databases available in the UK**

| Database | Established | No. active[a] patients in data | No. general practices contributing[b] | Data collection | Information collected |
|---|---|---|---|---|---|
| Clinical Practice Research Datalink GOLD | 1987 | 4.4 million | 685 | During or after an appointment at a contributing general practice using **Vision** software. | Demographics, Diagnoses, Prescriptions, Referrals, Test results. |
| The Health Improvement Network | 2002[c] | 3.7 million | 587 | During or after an appointment at a contributing general practice using **Vision** software. | Demographics, Diagnoses, Prescriptions, Referrals, Test results. |
| Q-research | 2003[c] | 5.1 million | 950 | During or after an appointment at a contributing general practice using **EMIS** software. | Demographics, Diagnoses, Prescriptions, Referrals, Test results. |
| Clinical Practice Research Datalink Aurum[d] | 2017[c] | 7 million | 738 | During or after an appointment at a contributing general practice using **EMIS** software. | Demographics, Diagnoses, Prescriptions, Referrals, Test results. |

[a]Active patients are those alive and registered at a practice. [b]Some practices contribute to multiple databases. [c]For some practices, data may be available prior to the year the database was established. [d]Aurum became available after the work described in this thesis started.

### 1.7.2 Potential maternal risk factors for congenital malformations

In order to identify potential confounders for vaccine safety analyses, it is helpful to consider risk factors for MCMs that may also be associated with vaccine uptake. Extensive research has been carried out to elucidate risk factors for MCMs but the relationship is not always consistent between studies, regions and among major malformation subgroups. Below, potential risk factors for MCMs that were later considered to be potential confounders are described.

#### Age

The association between advanced maternal age and malformations resulting from chromosomal anomalies is well-established. However, the relationship between maternal age and non-chromosomal MCMs is less clear.[129-131] A number of studies have suggested an increased risk of MCMs in young mothers (<20 years), particularly for gastroschisis and anencephaly.[130, 132-134] Others have suggested an association between advanced maternal age

(≥35 years) and MCMs such as congenital heart defects, though this too has been inconsistent.[129, 133, 135-138]

A study using data from population-based MCM registries across 15 European countries found that the relationship between maternal age and non-chromosomal MCMs varied by country.[130] This suggested that maternal age itself may not be a risk factor, but rather that age is associated with other demographic, social or behavioural risk factors that differ across countries.[130]

**Ethnicity**

Ethnicity may be associated with MCMs as a result of varying socioeconomic, cultural or genetic factors. In a cohort study from Bradford in the UK, infants born to Pakistani mothers were shown to be at greater risk of having an MCM compared to infants of white British mothers or other ethnicities.[139] Education was found to have a protective effect but adjustment for deprivation did not make a difference. The latter findings contradicted those from another UK study that demonstrated an increased risk of congenital heart defects in Asian and Black infants and an increased likelihood of these populations living in more deprived areas than white infants.[140] Consanguinity was reported to account for a third of MCMs in infants of Pakistani ethnicity in the cohort study in Bradford.[139] However, this was inconsistent with other studies that have assigned consanguinity a much smaller role in the development of MCMs. A meta-analysis of 17 studies across six countries estimated that the excess risk of MCMs attributable to consanguinity was just 3%.[141] The Bradford study did not explore other factors that are likely to contribute to the increased risk seen in this population, such as language barriers and inequalities in access to healthcare. Conflicting results in the literature highlight the difficulty in teasing apart the relationship between ethnicity and MCMs and the potential usefulness of ethnicity as a proxy for other risk factors that may be hard to define.

**Socioeconomic status**

Socioeconomic status is thought to be associated with adverse infant outcomes and, although not extensively reported in the literature, is likely to be associated with MCMs.[142, 143] A study using data from four UK population-based registries for MCMs demonstrated increased risk with increasing deprivation as measured by the Carstairs deprivation index.[144] An increased risk was also seen for heart and digestive malformation subgroups but not for others. Studies in the US which have used parental education, occupation, income and insurance status to define socioeconomic status have also found associations with MCMs although not always for the same subgroups.[145, 146] A meta-analysis of 33 observational studies in the USA, Europe, Asia and Africa found an increased incidence of congenital heart defects among the most socioeconomically deprived groups, regardless of whether this was measured by education, income or occupation.[147] However, only the association with income persisted when meta-analyses were restricted to studies in North America and none of the associations persisted when meta-analyses were restricted to studies in Europe.

**Geographic region**

The prevalence of MCMs has been shown to differ by geographic region when comparing data from population-based registries in different parts of the UK as well as when comparing hospital catchment areas.[148, 149] These differences have been shown to persist after adjusting for factors such as maternal age and deprivation.[149] Ascertainment bias caused by differences in diagnostic expertise, availability of relevant specialist units for diagnosis, recording practices, prenatal screening or uptake of termination could explain regional variation. It has been suggested that studies examining MCMs should adjust for region to account for differential case ascertainment.

**Alcohol consumption**

Exposure to alcohol in pregnancy, especially if excessive, can result in foetal alcohol spectrum disorders which can affect organogenesis and impair physical and mental development.[81]

Outside of this, the association between alcohol consumption and MCMs is unclear. A meta-analysis of seven observational studies suggested that prenatal binge-drinking was associated with congenital heart defects.[150] Whilst most studies have not shown an association between low to moderate alcohol consumption and MCMs overall, others have suggested an increased risk for particular conditions such as neural tube defects and specified congenital heart defects.[150-152] Available evidence has generally been limited by methodological weaknesses including recall bias, inconsistent definitions of congenital malformations and lack of adjustment for confounders.

**Smoking**

Smoking during pregnancy is known to be associated with adverse pregnancy outcomes, likely as a result of vascular disruption. Most studies have not found evidence of an association between smoking during pregnancy and congenital malformations overall; a meta-analysis of 38 studies that included almost 70,000 cases of malformations did not detect an association and these results were further supported by a more recent population-based study in Denmark that included more than 800,000 live-born singletons.[153, 154]

However, both the systematic review and Danish study showed associations between smoking and particular malformation subgroups. Whilst there was some variation between studies in the subgroups associated with smoking, both studies observed an increased risk of congenital heart defects, orofacial and gastrointestinal malformations. Although it was not possible to control for alcohol use in the Danish study, the authors were able to show a dose-response relationship between the daily number of cigarettes smoked and the risk of malformation subgroups, strengthening the evidence for an association.[154] In the systematic review, associations with malformation subgroups persisted after restricting to studies that identified smoking status prospectively and those that adjusted for potential confounders.[153]

**Infections**

Some maternal infections can cross the placenta and act as teratogens, affecting the development of the foetus. These are known as congenital infections and are thought to account for up to 3% of all congenital malformations.[155] They include: rubella, toxoplasmosis, syphilis, HIV, varicella-zoster, herpes simplex virus, parvovirus, and cytomegalovirus.[155]

For others infections, such as influenza, the association with congenital malformations is uncertain. A systematic review which included a meta-analysis of 22 observational studies suggested an association between maternal influenza-like illness (with or without serological confirmation) in the first trimester and the risk of particular malformation subgroups including neural tube defects and congenital heart defects.[156] Results were consistent with evidence from another systematic review that suggested an association between hyperthermia and neural tube defects.[157] However, the authors cautioned that many primary studies did not adjust for confounding and that the risk of ascertainment bias or publication bias could not be discounted. Furthermore, it was not clear what role medication taken for influenza infection could have played.

**Chronic illness**

There is strong evidence that some chronic maternal illnesses are associated with congenital malformations. Pre-gestational diabetes and associated hyperglycaemia are well-established risk factors for congenital malformations and have been shown to increase the risk of congenital heart defects and neural tube defects.[158, 159] Other conditions, such as epilepsy, have been found to increase the risk of MCMs primarily as a result of the medications used for treatment.[160]

Relationships between other chronic illnesses, the drugs used to treat them and congenital malformations are less well-understood but are important to consider. For instance there is a suggestion that asthma, a common condition that is likely to affect a substantial proportion of pregnant women, may be a risk factor for congenital malformations.[161] A meta-analysis of 14

cohort studies found evidence of an association between asthma and congenital malformations, which persisted after restricting to those studies that adjusted for confounders, as well as evidence of an association with orofacial malformations. Overall, the evidence from the systematic review did not suggest a large role for asthma medications in this association.

Chronic pre-gestational hypertension is becoming increasingly common in pregnant women and is frequently treated with angiotensin-converting-enzyme (ACE) inhibitors which have been associated with the development of MCMs.[162-164] Recently, two large cohort studies from the US have suggested that the underlying hypertension may have a role in this association. The first cohort study demonstrated an increased risk of congenital heart defects among pregnancies exposed to ACE inhibitors compared to those without hypertension or any hypertensive treatment.[165] The increased risk among those using ACE inhibitors disappeared when compared to those with hypertension but no treatment.[165] In the second study, normotensive individuals were compared to treated and untreated individuals with chronic hypertension; the risk of heart defects was similarly increased in both the treated and untreated groups.[166]

**Obesity**

Nutritional deficiency during pregnancy has long been recognized as a determinant of MCMs, with folate deficiency in particular being associated with neural tube defects. More recently, evidence has started to emerge that BMI at the start of pregnancy may also be associated with MCMs. Potential mechanisms for this include reduced folate levels, underlying hyperglycaemia or reduced sensitivity of ultrasound scanning. A meta-analysis of 18 studies found that obesity was associated with an increased risk of neural tube defects, congenital heart defects, limb reduction defects, and orofacial defects.[167] A recent Swedish cohort study using registry data on over 1 million singleton live-births supported these findings and showed an increasing risk of congenital heart defects, nervous system and limb malformations with increasing BMI.[168]

Results from both the meta-analysis and Swedish study were robust to the exclusion of women with gestational diabetes which is known to be associated with MCMs and increased BMI.

Whilst most studies have focused on maternal obesity, some studies have also shown maternal underweight to be associated with an increased risk of congenital malformations. A study using registry data from the UK found that obesity was associated with congenital malformations as previously suggested, but that maternal underweight was also a risk factor for some malformations including atrial septal defects.[169] Two additional studies have supported the latter.[170, 171]

**Parity**

Some studies have suggested an association between increasing parity and MCMs. A meta-analysis of 14 observational studies found evidence to suggest an increased risk of congenital heart disease with increasing maternal parity, independently of maternal age, and demonstrated a dose-response relationship.[172] Mechanisms suggested to explain this include a greater risk of nutrient depletion among non-nulliparous women, the exposure of the developing foetus to viruses carried by other children in the household, changes in the uterine environment and increased maternal stress with increasing parity.[172]

Conversely, others have demonstrated a relationship in the opposite direction. A study using a UK population-based surveillance registry demonstrated a lower prevalence of MCMs in second pregnancies compared to first pregnancies.[173] This supported results from a multi-site case-control study of almost 18,000 cases that found certain MCMs such as hydrocephaly and limb reduction defects to be more likely to occur among nulliparous women compared to primiparous women.[174] A history of MCMs in pregnancy may affect family planning decisions which may explain these findings.

## 1.8 Thesis rationale, aims and objectives

### 1.8.1 Rationale

Although several studies have examined the safety of influenza vaccination in pregnancy with respect to MCMs, there have been calls for additional work to assess the safety of SIIV given during the first trimester. To date, only one large cohort study has examined MCMs following first-trimester vaccination with SIIV and this was conducted in the US between 2004 and 2013 within a population selected on the basis of health insurance. The safety of PIIV has been examined more frequently, including when given in the first trimester. However, no such study has been carried out using UK data. In addition to limited power, available safety evidence has been further limited by inconsistent definitions for MCMs, inadequate adjustment for potential confounders and short-term infant follow-up. Most studies examined outcomes around the time of delivery only, and although some studies attempted to ascertain outcomes in the first year of life, none extended this to capture those diagnosed later in childhood.

Whilst registries have been important in monitoring the safety of newly-authorized medications, population-based electronic health records are increasingly being used for this purpose. These data cover large populations and are collected routinely, allowing for the examination of rare outcomes and reducing the potential for under-ascertainment and selection bias. Ascertainment can be further maximized by linkage of primary care records to hospital admissions and mortality data and long-term follow-up. Finally, because data collection occurs routinely, electronic health records have the potential to provide information on risk factors for MCMs that can then be adjusted for in analyses.

The overarching aim of this work was to use UK electronic health records to assess the safety of maternal influenza vaccination with respect to MCMs which are of particular public health importance. Although both PIIV and SIIV were examined, the emphasis was on first-trimester receipt of SIIV. As part of addressing this aim, the work carried out here included a considerable methodological component that may serve to inform future safety studies. This

work offered the opportunity to: explore the way MCMs have been identified in other studies, develop methods to define MCMs using electronic health records, and assess the value of linked data and long-term follow-up in the ascertainment of these conditions. This work also provided the opportunity to capitalize on a newly-developed Pregnancy Register (which identifies pregnancy episodes in electronic health records and enables the identification of individual trimesters) and explore its use in safety studies.

### 1.8.2 Aims and Objectives

The principal aim of this research was to evaluate the safety of SIIV and PIIV administration during pregnancy and stratified by trimester with respect to MCMs. The objectives to achieve this were:

**Objective 1.** To systematically review the literature on the methods used to identify and validate congenital malformations in UK electronic health records and the results from any validation studies.

**Objective 2.** To develop a comprehensive algorithm to identify MCMs recorded in linked Clinical Practice Research Datalink primary care records, hospital admission data from Hospital Episode Statistics and Office for National Statistics mortality data.

**Objective 3.** To establish the value of each of the above data sources in identifying infants with MCMs and the agreement between them.

**Objective 4.** To compare the prevalence of MCMs in stand-alone and linked data sources with published prevalence estimates from other electronic health record databases and with national surveillance data from EUROCAT registries.

**Objective 5.** To use linked data to examine the association between maternal vaccination with SIIVs and MCMs in live-born singletons, stratified by trimester.

**Objective 6.** To use linked data to examine the association between maternal vaccination with PIIVs and MCMs in live-born singletons, stratified by trimester.

**Table 1.8 - Thesis Objectives**

| Objective | Study Design | Population | Exposure | Outcomes | Effect measures | Relevant chapter |
|---|---|---|---|---|---|---|
| 1. Systematically review the methods used to identify CMs in UK electronic health records and results from any related validation studies | Systematic review and meta-analysis | Individuals of any age with any type of CM identified in primary or secondary care data in the UK | - | 1. Methods used to develop code lists<br>2. Results of validation studies<br>3. Results of CM prevalence rate comparisons with external data sources | Positive predictive values; Prevalence ratios | 2 |
| 2. Develop an algorithm to identify MCMs recorded in CPRD, HES and ONS mortality data. | Methodological | - | - | 1. Develop Read code lists to identify MCMs recorded in CPRD<br>2. Develop ICD-10 code lists to identify diagnoses and causes of death recorded in HES and ONS mortality data, respectively.<br>3. Develop OPCS-4 code lists to identify procedures for the treatment of MCMs recorded in HES. | - | 5 |
| 3. Assess the value of stand-alone CPRD, HES and ONS and linked data in identifying individuals with MCMs. | Cohort | Live-born singletons | - | 1. Comparison of prevalence rates between stand-alone CPRD, HES and linked data.<br>2. Comparison of proportion of infants with MCM recordings in single and multiple data sources. | Prevalence ratios | 7 |
| 4. Compare rates of MCMs in stand-alone and linked CPRD, HES and ONS mortality data with rates from THIN and UK EUROCAT data. | Cohort | Live-born singletons | - | 1. Comparison of MCM prevalence rates in the first year of life with THIN data.<br>2. Comparison of MCM prevalence rates in the first year of life with UK EUROCAT data. | Prevalence ratios | 7 |
| 5. Examine the association between maternal vaccination with SIIV and MCMs. | Cohort | Live-born singletons delivered during a period when all pregnant women were eligible for seasonal influenza vaccination and had an opportunity of at least one week to be vaccinated. | SIIV received in pregnancy, stratified by trimester | **Primary**:<br>1. Any MCM recorded in the first year of life<br>**Secondary**:<br>1. Any MCM recorded between delivery and the end of the study period<br>2. Any major congenital heart defect recorded between delivery and the end of the study period<br>3. Any major limb defect recorded between delivery and the end of the study period | Odds ratios; Hazard ratios | 8 |
| 6. Examine the association between maternal vaccination with PIIV and MCMs | Cohort | Live-born singletons delivered during a period when all pregnant women were eligible for pandemic influenza vaccination and had an opportunity of at least one week to be vaccinated. | PIIV received in pregnancy, stratified by trimester | **Primary**:<br>Any MCM recorded in the first year of life<br>**Secondary:**<br>Any MCM recorded between delivery and the end of the study period | Odds ratios; Hazard ratios | 9 |

Abbreviations: CM, Congenital malformation; MCM, Major congenital malformation; THIN, The Health Improvement Network; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics; SIIV, Seasonal inactivated influenza vaccine; PIIV, pandemic inactivated influenza vaccine; ICD-10, International Classification of Diseases (10$^{th}$ Revision); OPCS-4, Classification of Surgical Operations and Procedures (4$^{th}$ Revision).

# 2. The identification and validity of congenital malformation diagnoses in UK electronic health records: A systematic review

## 2.1 Introduction

This chapter presents a systematic review of the methods used by other researchers to identify and validate congenital malformations in UK electronic health records (**Objective 1**). Results from any validation studies are also presented. Results from the systematic review informed the development of a comprehensive algorithm to identify MCMs in linked primary care, hospital admission and mortality data (**Objective 2; Chapter 5**). This chapter is presented in the form of a research paper prepared for submission.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

## SECTION A – Student Details

| | | | |
|---|---|---|---|
| **Student ID Number** | 1300677 | **Title** | Miss |
| **First Name(s)** | Maria | | |
| **Surname/Family Name** | Peppa | | |
| **Thesis Title** | The safety of influenza vaccination in pregnancy: Examining major congenital malformations as potential adverse outcomes using UK electronic health records | | |
| **Primary Supervisor** | Professor Punam Mangtani | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

## SECTION B – Paper already published

| | | | |
|---|---|---|---|
| Where was the work published? | | | |
| When was the work published? | | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | | | |
| Have you retained the copyright for the work?* | Choose an item. | Was the work subject to academic peer review? | Choose an item. |

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

## SECTION C – Prepared for publication, but not yet published

| | |
|---|---|
| Where is the work intended to be published? | Pharmacoepidemiology & Drug Safety |
| Please list the paper's authors in the intended authorship order: | Maria Peppa, Punam Mangtani, Caroline Minassian, Sara L Thomas |

| | |
|---|---|
| Stage of publication | **Not yet submitted** |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | The scope of the systematic review was decided by P Mangtani, S Thomas and myself. I developed the search strategy (including the search terms) and the eligibility criteria used following detailed discussions with P Mangtani and S Thomas. I screened abstracts and full-text publications and a random sample of abstracts were also screened by P Mangtani and S Thomas to check consistency. With the exception of quality assessments, which were carried out jointly with S Thomas to ensure agreement and consistency, I conducted all analyses. I drafted the initial manuscript and revised it based on comments by co-authors. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | Maria Peppa |
| **Date** | 19.03.2020 |

| | |
|---|---|
| **Supervisor Signature** | Punam Mangtani |
| **Date** | 20.03.2020 |

## 2.2 Paper 1: The identification and validity of congenital malformation diagnoses in UK electronic health records: A systematic review.

**Authors:** Maria Peppa*[a], Punam Mangtani[a], Caroline Minassian[a], Sara L Thomas[a].

[a]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom

*Corresponding author

## Abstract

**Purpose**

To describe the methods used to identify and validate congenital malformations recorded in UK electronic health records, and the results of any such validation studies.

**Methods**

Medline and Embase were searched for publications that involved the identification of congenital malformations in UK electronic health records using diagnostic codes between 1987 and 2019. Retrieved publications, reviews and bibliographies of UK electronic health record databases were searched to identify additional studies. The methods and code lists used to identify congenital malformations were examined, as well as the methods and results of any validation studies.

**Results**

We identified 54 eligible studies; 36 used primary care records to identify congenital malformations and 18 used secondary care data alone or in combination with birth and/or death records. Studies using primary care data were frequently found to use Read codes outside of the 'P' chapter dedicated to congenital malformation diagnoses. Conversely, studies using secondary care data relied on the 'Q' chapter for congenital malformations in ICD-10. Eight studies attempted to validate congenital malformations identified in primary care data, with most using GP questionnaires or a mixture of further information from primary care. Congenital malformations overall, major malformations and heart defects had a high positive predictive value (80-100%) whilst this was lower for neural tube defects (71%) and developmental dysplasia of the hip (56%). Although the positive predictive value was high for most conditions, the validity of the reference standard used was often uncertain.

**Conclusions**

Studies using primary care data to identify congenital malformations provide limited details about the identification methods used, whilst studies using secondary care data have not attempted to validate diagnostic codes. Studies using primary care data frequently use non-'P'

chapter codes which can increase the ascertainment of congenital malformations in these data. However, the validity of these codes has not been explored. Further assessments of validity in both data sources and of further malformation subgroups should be considered.

## Introduction

Post-licensure safety studies of drugs and vaccines given in pregnancy increasingly rely on the use of large databases of anonymised, routinely-collected electronic health records (EHR).[175, 176] UK EHR used for safety research include primary care databases, such as the Clinical Practice Research Datalink (CPRD), which contain information recorded in general practice for a representative sample of the population.[126] Secondary care databases, such as the Hospital Episode Statistics Admitted Patient Care (HES-APC) database, capture information on all patients admitted to NHS hospitals in England and are also available for research.[177] Data from primary and secondary care databases, as well as data from other sources such as death certificates, can be provided to researchers pre-linked, thus maximizing the ascertainment of important but rare safety outcomes.[126, 177]

Congenital malformations are important outcomes in post-licensure safety studies of drugs or vaccines given in pregnancy. The methods developed for their identification in EHR are therefore of particular interest. In primary care, clinical data including diagnoses and procedures are currently coded using the hierarchical Read coding system (some databases previously used Oxford Medical Information System (OXMIS) codes).[126] Secondary care databases include diagnoses and procedures coded using the 10th Revision of the International Classification of Diseases (ICD-10) and the 4th Revision of the Classification of Interventions and Procedures (OPCS-4), respectively.[177] Underlying and contributing causes of death on death certificates are also coded using ICD-10.[178]

Chapters 'P' in Read and 'Q' in ICD-10 are dedicated to congenital malformation codes. However, clinical coders in primary and secondary care may choose to code a congenital malformation with a code from outside these chapters. For example, an individual with a congenital pulmonary valve malformation could have their condition recorded using the code for '*pulmonary valve anomalies*' from the Read 'P' chapter on congenital malformations or the

code for '*pulmonary valve disorders*' from the 'G' chapter on circulatory system diseases (which may not be congenital in origin).

Researchers who want to identify individuals with a specific congenital malformation in EHR data have to develop a list of relevant diagnostic and procedural codes ('code lists') that can then be used to search patient records.[179] To aid code list development, researchers may refer to published guidelines which define the codes for particular conditions or provide an idea of relevant key terms which can be used to identify equivalent codes. For example, the European Network of Population-based Registries for Congenital Malformations (EUROCAT) publishes the guidelines used by individual registries to code and classify congenital malformations using modified ICD-10 codes.[86] Such guidelines are not used by clinical coders in primary and secondary care to encode congenital malformations. Researchers therefore need to consider that a wider range of codes may be used in routine clinical practice.

When developing code lists, the inclusion of broad-ranging codes from outside the dedicated chapters enables more complete capture of congenital malformations in EHR but also increases the risk of including some conditions that are not congenital in nature. The wide array of congenital malformations and the lack of a standardized algorithm for their identification complicate their ascertainment and may result in a variety of approaches, affecting replicability across studies and the validity of the findings. Previous reviews have highlighted that the validity of diagnostic codes in UK EHR is good in general.[180, 181] However, to date, no study has systematically assessed the validity of code lists developed and used to identify congenital malformations in these data.

This systematic review aimed to inform future safety studies by describing the methods used to identify individuals with congenital malformations from UK electronic health records and by summarizing the results of any associated validations.

## Methods

We carried out a systematic review of studies that involved the identification of congenital malformations in UK EHR. The systematic review was registered with PROSPERO (registration number: CRD42017037168).

**Eligibility criteria**

Studies were included if they involved the use of diagnostic codes to identify congenital malformations in UK EHR and were published after 1987 (the year the first database, CPRD, was established).[126] As the main objective of this study was to review the methods used to identify congenital malformations from large electronic datasets, case series and case reports were excluded but all other study designs were permitted. We excluded studies if the population examined was sourced from a tertiary care setting or a specialist registry as we considered that the differences in case mix and coding practices in these settings would seriously limit the generalizability of results. Studies restricted to congenital malformations with known causes that are frequently excluded from safety studies (for example, chromosomal abnormalities and single gene defects) were not included. Conference abstracts were also excluded as they did not contain sufficient methodological detail to meet the objectives of this review.

Validations of diagnostic codes for congenital malformations, reported within the EHR studies identified as eligible, were included if they used any of the following methods: manual review of the entire patient record (including anonymised free-text when available), additional information from GPs (e.g. via questionnaires or provision of hospital letters or death certificate data), comparison with records in an external database, or comparison of prevalence with that derived from external population-based data (providing this was a study objective and not simply referred to in the discussion section to provide context to the study results). Validation studies also needed to report ≥1 validity measurement (sensitivity,

specificity, positive predictive value or negative predictive value), or provide data that allowed their calculation.

**Search strategy and study selection**

The search for this review was a component of a wider search strategy for studies examining congenital malformations or pervasive developmental disorders using UK or US health data. Medline and Embase were searched up to 20 September 2019 for English-language publications using keywords and subject headings for 'congenital malformations' and 'electronic health records' (**Appendix 1**). This was supplemented with a manual search of the bibliographies of three of the main UK primary care EHR databases (CPRD, The Health Improvement Network (THIN) and Q-Research) and the Boston Collaborative Drug Surveillance Programme.[182-185] Reference lists of relevant reviews and eligible studies were subsequently hand-searched for further studies.

The titles and abstracts of studies identified in the search were screened by one author (MP) to determine those eligible for full-text review. A sample of abstracts was also screened by ST and PM to establish consistency, with any differences resolved through discussion.

**Data extraction**

Details of the methods used to identify congenital malformations were extracted using a standardized form. The key data extracted from each study included: the congenital malformations identified and any exclusions or subsequent classification into subgroups, the use of any externally-developed guidelines to inform case definitions, details of the identification process (including whether code lists for malformations were developed and the methods used to develop them, whether a computerized search using pre-prepared code lists was conducted versus a manual review of infant records to identify possible malformations) and any published code lists or algorithms. Code lists that were not included in published papers but were publicly available elsewhere (e.g. in a report or thesis) were identified or were requested from authors.

When studies examined the diagnostic validity of recorded congenital malformations, the following data were also extracted: the main conditions validated, the methods used (e.g. the information used to validate diagnoses, the proportion of identified diagnoses that authors chose to validate and the rationale for their selection, the response rate for any information requests authors made and the reasons for non-responses, and the reported results. When validation comprised prevalence comparisons with external data sources, we extracted information about the external data-source, the period of comparison and any results.

**Quality assessment**

A modified version of the Quality Assessment of Diagnostic Studies tool (QUADAS-2) was used to assess the quality of studies performing validations.[186] Six areas from the tool considered to be applicable to EHR were adapted for use, relating to: enrolment of patients, patient exclusions, blinding to the reference standard results, the validity of the reference standard, consistent use of the reference standard, and inclusion of patients in the analysis (see **Supplementary Table 1**).

**Data synthesis and analysis**

Studies were stratified according to whether congenital malformations were identified in primary or secondary care. The methods used to identify individuals with congenital malformations and the methods and results of any validation studies, were summarized for each group and by type of congenital malformation when possible. When validation studies presented a validation measure without 95% confidence intervals (CIs), these were calculated using the Wilson method. As only a very small number of studies performed validations, with a diversity of methods after stratifying by malformation subtype, summary estimates of validation measures were not attempted. Between-study heterogeneity in validity estimates within strata was investigated using $\chi 2$ tests.

## Results

We retrieved 54 eligible studies that identified congenital malformations from UK EHR (**Figure 1**). Individuals with congenital malformations were identified from primary care data in 36 studies, most of which aimed to assess drug safety during pregnancy.[187-222] More than half of these 36 studies used stand-alone CPRD (n=21) and major malformations were the most frequently identified condition (n=19). Only one study used primary care records linked to HES. This study identified congenital malformations in CPRD and subsequently validated identified diagnoses using HES data.[222]

The remaining 18 studies used secondary care data to identify individuals with congenital malformations and typically aimed to assess health service delivery, surgical outcomes and disease trends.[223-240] Almost all these studies used HES (n=16) and the most commonly identified congenital malformations were heart and orofacial defects (n=4). Eight of the secondary care studies also used linked (n=6)[223-227, 237] or unlinked (n=1)[228] death certificate data or linked birth data (n=2).[237, 238]

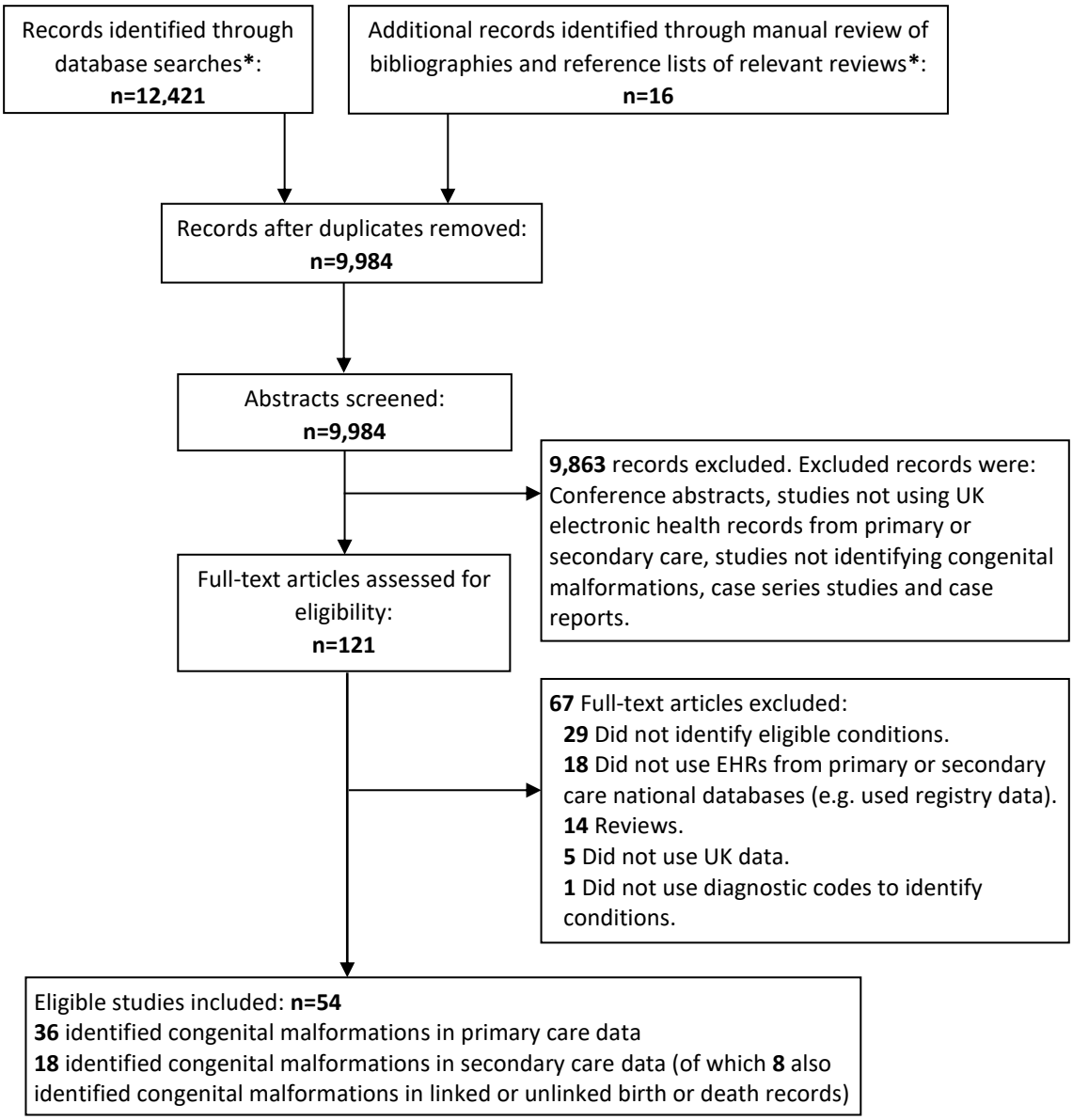



**Figure 1 - Identification of eligible studies.** *This was part of a larger search strategy that included studies identifying pervasive developmental disorders and studies using electronic health records in the US, neither of which were considered here.

## Defining and identifying congenital malformations in primary care data

The 36 studies using primary care data often relied on published guidelines to develop case definitions for the congenital malformations of interest, especially when identifying a wide array of conditions that required the exclusion of minor diagnoses or further classification of diagnoses into malformation subgroups (**Table 1**). Of the 22 studies that identified 'any' or 'major' malformations, 91% (n=20) referred to guidelines, the majority using EUROCAT (n=16).[187, 189-202, 206] Four studies indicated that they sought clinical input alongside the guidelines to define and further classify conditions of interest (**Table 1**).[189-191, 218]

Once defined, the methods used to identify the congenital malformations of interest within the data were rarely detailed in publications. Just three studies specified the use of a computerized search.[203-205] Feedback from authors clarified that a manual review of the data was conducted in another three studies[189, 192, 207] of which two did not refer to pre-prepared code lists of malformations when reviewing recorded events in their study populations.[189, 192]

The majority of the other 34 studies were known to use code lists because they were publicly available (n=11)[195-202, 206, 219, 222] or could be obtained from authors (n=12)[193, 194, 203-205, 207, 208, 210, 213, 218, 220, 221] and another three were thought likely to have used them based on our communication with authors and the nature of the studies (**Table 2**).[209, 215, 216] The use of a code list was therefore uncertain for the remaining 8 studies.[187, 188, 190, 191, 211, 212, 214, 217]

A small number of studies examined additional data for evidence of congenital malformations. Three studies described manually reviewing anonymised free-text in maternal records to identify evidence of congenital malformations among pregnancies that did not result in a live-born infant (e.g. terminations, stillbirths, miscarriages) (**Table 1**).[188, 192, 193] Another two requested and reviewed complete paper records (n=2) and anonymised free-text (n=1) to inform the classification of identified congenital malformations as major or minor.[190, 191]

Methods used to develop code lists were described briefly in 17 studies (**Table 1**). In almost all studies, code list development relied on relating relevant ICD codes to equivalent Read/OXMIS codes (n=16) (**Table 1**).[193-205, 207, 208, 218] Few studies described how this mapping was achieved

(n=3)[193, 194, 218] but two approaches were identified. In the first approach, search terms were created using ICD code descriptions and applied to Read/OXMIS dictionaries to identify relevant codes (and potentially closely related codes in the Read/OXMIS hierarchy).[193, 194] Alternatively, potential Read/OXMIS codes of interest were identified by examining all codes in the patient's records and those thought to correspond to relevant ICD codes were included.[218] Reference ICD codes were often determined using published guidelines (n=14), with EUROCAT guidelines again being the most frequently referred to (n=11) (**Table 1**).[193-206, 218]

We examined the codes used to identify congenital malformations in the 24 studies known or thought likely to have used Read code lists (two of the studies known to use code lists only used OXMIS codes and were not explored).[193-206, 209, 210, 213, 215, 216, 218-222] For 16 of these, the level of detail was sub-optimal and only broad code lists were available which included some codes that were not part of the final congenital malformation case definition but were not marked as such (**Table 2**).[193-206, 210, 218] Another 3 only provided the subset of codes identified in the study population rather than all possible malformation codes.[209, 215, 216] Specific detailed code lists were available for just 5 studies (**Table 2**).[213, 219-222]

All 24 studies considered 'P' chapter Read codes when identifying congenital malformations. However, most studies also considered codes from other chapters, although this was rarely described in the published methods. The most frequently considered codes from other chapters were those related to procedures (n=20) (e.g. '*repair of cleft lip operations*') and diagnostic codes (n=19) (e.g. '*mitral stenosis*' from the 'G' chapter on diseases of the circulatory system) (**Table 2**). Studies also frequently considered codes indicating that an individual had a history of a congenital malformation (n=14) (e.g. '*personal history of congenital malformations*') and administrative codes relating to transfers of care, monitoring or counselling of individuals with malformations (n=12) (e.g. '*transfer of care from paediatric congenital heart services*'). Codes relating to testing or screening for malformations (e.g. '*screening for congenital eye anomaly*') or observations of conditions made on examination (e.g. *'observed on examination – pigeon chest*') were least frequent (n=2).

**Table 1 - Studies identifying congenital malformations using primary care data.**

| Author | Study Aim | Data Source | Identification Period[a] | Population | Methods used to identify evidence of malformations | Classifications used for malformations and exclusions | Guidelines used to define, classify or exclude malformations | Code list development described? |
|---|---|---|---|---|---|---|---|---|
| **Any congenital malformation** | | | | | | | | |
| Cea-Soriano 2018[187] | Assess the safety of non-insulin antidiabetic drugs in pregnancy | THIN | 1995-2013 | Live-born infants | **Read codes** were identified in infant records anytime in the identification period. Maternal records were also searched for codes during pregnancy (methods not described). | **Classified** into subgroups. **Excluded** minor and genetic conditions and birth marks in safety assessments. | EUROCAT | No |
| Baril 2015[188] | Assess the safety of the human papillomavirus vaccine in pregnancy | CPRD | 2008-2011 | Live-born infants<br>Terminations<br>Miscarriages<br>Stillbirths | **Medcodes**[b] were identified in infant clinical or referral files in the first 12 weeks of life and entity types were examined.<br>**Free-text** in the maternal record was examined for other pregnancy outcomes. | **Classified** as major or minor. | Metropolitan Atlanta Congenital Defects Program Report | No |
| Ruigomez 1999[189] | Assess the safety of antacids in pregnancy | CPRD | 1991-1997 | Live-born infants<br>Terminations<br>Stillbirths | **Manual review** of infant records in the first year of life by two physicians. Maternal records were also thought to be examined (methods not described). | **Classified** as major or minor and into subgroups. **Excluded** genetic conditions. | EUROCAT, with physician input[c] | N/A (Authors communicated that no code list was developed) |
| **Major congenital malformations** | | | | | | | | |
| Petersen 2017[190] | Assess anticonvulsant safety in pregnancy. | THIN | 1995-2014 | Live-born infants | **Read codes from the 'P Chapter'** were identified in infant records. | **Excluded** minor conditions. | EUROCAT, with GP input. | Only identified 'P' codes, unclear if code list used. |
| Petersen 2016[191] | Assess the safety of antipsychotics in pregnancy. | CPRD & THIN | 1995-2012 | Live-born singletons | **Read codes from the 'P Chapter'** were identified in infant records during the first year of life. Codes were also identified from maternal records during pregnancy. | **Excluded** minor conditions and Down syndrome. | EUROCAT, with GP input[d] | Only identified 'P' codes in the infant records, unclear if code list used. |
| Charlton 2015[192] | Assess the safety of inhaled corticosteroids in pregnancy. | CPRD | 2000-2010 | Live-born singletons<br>Terminations<br>Stillbirths | **Manual review** of clinical, referral and test files of infants during the identification period to identify Read codes. **Free-text** in the maternal record that was associated with other pregnancy outcomes was searched for evidence. | **Classified** into subgroups. **Excluded** minor conditions & syndrome-related defects in infants with syndromes. | EUROCAT. | N/A (Authors communicated that no code list was developed) |
| Charlton 2011[193] | Assess the safety of anticonvulsants in pregnancy. | CPRD | 1990-2006 | Live-born infants<br>Terminations<br>Stillbirths<br>Neonatal deaths | **Read and OXMIS** codes were identified in clinical, referral and test files of infants during the identification period. **Free-text** in the maternal record was searched. It was examined from 2 months before until 4 months after a termination or 6 months after a stillbirth or neonatal death. | **Classified** into subgroups. **Excluded** minor conditions, genetic conditions & those not plausibly drug-induced. | EUROCAT. | Created search terms using ICD-9 codes 740-759. Read codes containing the terms were identified |
| Charlton 2010[194] | Assess the identification of major malformations in CPRD | CPRD | 1990-2006 | Live-born infants | **Read and OXMIS** codes were identified in clinical, referral and test files of infants during the identification period. | **Classified** into subgroups. **Excluded** minor conditions. | EUROCAT. | Created search terms using ICD-9 codes 740-759. Read codes containing the terms were identified |

| Author | Study Aim | Data Source | Identification Period[a] | Population | Methods used to identify evidence of malformations | Classifications used for malformations and exclusions | Guidelines used to define, classify or exclude malformations | Code list development described? |
|---|---|---|---|---|---|---|---|---|
| Dhalwani 2015[195] | Assess nicotine replacement therapy in pregnancy. | THIN | 2001-2012 | Live-born infants | **Read codes** were identified in the medical file of infants during the identification period. | **Classified** into subgroups. **Excluded** minor defects and those due to known teratogens | EUROCAT. | Relevant ICD-10 codes were used to identify equivalent Read codes. |
| Ban, 2014a[196] 2014b[197] 2014c[198] 2015a[199] 2015b[200] | Assess the risks in pregnancy of: 1) depression & therapy 2) inflammatory bowel disease & therapy 3) anxiolytics/hypnotics 4) anti-epileptics & 5) coeliac disease | THIN | 1990-2009 1990-2010 1990-2010 1990-2013 1990-2013 | Live-born singletons | **Read codes** were identified from infant records during the identification period. | **Classified** into subgroups. **Excluded** minor and genetic conditions and those due to known teratogens. | EUROCAT. | Relevant ICD-10 codes were used to identify equivalent Read codes. |
| Sokal 2013[201] 2014[202] | Compare prevalence of MCMs in THIN with: 1) EUROCAT, 2) other population-based data. | THIN | 1990-2010 | Live-born singletons | **Read codes** were identified in infant records during the identification period. | **Classified** into subgroups. **Excluded** minor conditions. | EUROCAT. | Relevant ICD-10 codes were used to identify equivalent Read codes. |
| Vasilakis-Scaramozza 2013a[203] 2013b[204] 2013c[205] | Assess the risk of: 1) asthma treatment, 2) depression, & 3) hypertension in pregnancy. | CPRD | 1991-2002 | Live-born singletons Terminations Stillbirths | **Read codes** were identified in infant records during the identification period. **Cause of death** for stillbirths and terminations was checked for evidence.[e] | **Classified** into subgroups. **Excluded** minor and genetic conditions and those associated with prematurity among preterm births. | Centers for Disease Control & Prevention guidelines. | ICD-9 codes 740-7599 were used to identify equivalent Read codes. |
| Tata 2008[206] | Assess asthma and treatment in pregnancy. | THIN | 1988-2004 | Live-born infants | **Read codes** were identified in infant records during the identification period. | **Classified** into subgroups. **Excluded** minor conditions. | EUROCAT. | No |
| Jick 1999[207] | Assess the safety of antifungals in pregnancy | CPRD | Not specified | Live-born infants | **Manual review** of infant records for evidence at birth. If a malformation was suspected, relevant paper records were requested from the GP for further information. | **Classified** into subgroups. | Defined as those needing surgery or treatment. | ICD-8 codes 7400-7590 were used to identify equivalent OXMIS codes[f] |

| Author | Study Aim | Data Source | Identification Period[a] | Population | Methods used to identify evidence of malformations | Classifications used for malformations and exclusions | Guidelines used to define, classify or exclude malformations | Code list development described? |
|---|---|---|---|---|---|---|---|---|
| Jick 1997[208] | Assess the safety of anticonvulsants in pregnancy. | CPRD | 1988-1993 | Live-born infants | **OXMIS codes** were identified in infant records around the time of birth. | **Excluded** minor conditions, hypospadias, hernias, & those that could not be drug-induced. | N/S | ICD-8 codes 7400-7590 were used to identify equivalent OXMIS codes |
| **Neural Tube Defects** | | | | | | | | |
| Devine 2008[209] | Examine the validity of neural tube defects recorded in CPRD. | CPRD | 1987-2004 | Live-born infants<br>Terminations<br>Stillbirths<br>Miscarriages | **Read and OXMIS codes** for anencephaly, encephalocele, spina bifida & meningocele were identified in infant records in the 1st year of life. The 1st code was included. Codes on January 1st were excluded unless within 30 days of birth.<br>**Read and OXMIS codes** within 210 days of a pregnancy record were identified in maternal data. The 1st code was included. Codes were excluded if: within 60 days of the 1st code, if on January 1st and not within 30 days of a pregnancy record, or, if within 180 days of a code in the infant. | **Classified** anencephaly, cephaloceles, meningoceles and spina bifida separately for some analyses. | N/S | No |
| Tata 2005[210] | Assess the risks of celiac disease in pregnancy. | CPRD | 1987-2002 | Live-born infants | **Read codes** for meningocele, meningomyelocele, spina bifida and hydrocephalus were identified in infant records during the identification period. | None described | N/S | No |
| Lawrenson 2001[211] | Estimate prevalence and incidence of renal failure and replacement therapy in those with neural tube defects. | CPRD | Prior to 1997 | Patients aged 10-69 | **Diagnostic codes** for neural tube defects were identified in the identification period (methods were not described further). | None described | N/S | No |
| Lawrenson 2000[212] | Estimate mortality and prevalence rates of neural tube defects. | CPRD | Prior to 1997 | Patients aged 10-69 | **Diagnostic codes** for meningocele, meningomyelocele, spina bifida and hydrocephalus were identified in the identification period (methods were not described further). | None described | N/S | No |

| Author | Study Aim | Data Source | Identification Period[a] | Population | Methods used to identify evidence of malformations | Classifications used for malformations and exclusions | Guidelines used to define, classify or exclude malformations | Code list development described? |
|---|---|---|---|---|---|---|---|---|
| **Orofacial defects** | | | | | | | | |
| Chi 2011[213] | Assess the safety of topical corticosteroids in pregnancy. | CPRD | 2000-2006 | Live-born singletons | **Read and OXMIS codes** were identified in clinical files of infants. | **Classified** by cleft type. **Excluded** syndromic cleft. | N/S | No |
| **Heart defects** | | | | | | | | |
| Petersen 2016[214] | Assess antidepressant safety in pregnancy. | THIN | 1990-2011 | Live-born singletons | **Read codes** were identified from infant records during the first five years of life. | **Excluded** Down syndrome. | N/S | No |
| Margulis 2013[215] Hammad 2013[216] | Assess the safety of anti-depressants in pregnancy; Validate specific heart defects. | CPRD | 1996-2010 | Live-born singletons | **Read codes** indicating a heart defect or related procedure were identified from infant records in the first year and first six years of life. | **Classified** by heart defect. **Excluded** genetic conditions and sequences.[g] | Published development-based classification system.[241] | No |
| Billett 2008[217] | Estimate the prevalence of comorbidities, health service use & recording of clinical indicators in those with heart defects. | Q Research | N/S-2005 | All patients | **Read codes** indicating a heart defect or related procedure were identified during the identification period. | **Classified** by complexity. **Excluded** cardiomyopathies, isolated arrhythmias, isolated dextrocardia, bicuspid aortic valve, mitral valve prolapse, cardiac tumours, Marfan's syndrome | Modified version of a published classification system based on anatomical hierarchy.[242] | No |
| Wurst 2007a[218] | Compare the prevalence of heart defects between CPRD, NCAS and EUROCAT. | CPRD | 2001-2003 | Live-born infants | **Read and OXMIS** codes were identified in the infant's first year and first six years of life. | **Classified** by heart defect. **Excluded** minor conditions and vascular defects. | EUROCAT & National Congenital Anomaly System guidelines, with input from a paediatric cardiologist. | Identified potential Read/OXMIS codes and then selected those equivalent to ICD-9 codes 7450-59, 7460-69, 7470-74. |
| Wurst 2007b[219] | Examine the validity of specific heart defects recorded in CPRD. | CPRD | 1992-2005 | Live-born infants | **Read and OXMIS codes** for diagnoses and procedures were identified from infant records during the identification period. | **Classified** by heart defect. **Excluded** codes synonymous to the conditions of interest but which did not contain the specified terms. | N/S | Identified only those codes that included the terms: 'ventricular septal defect', 'tetralogy of Fallot', 'coarctation of the aorta', 'COA', 'VSD', or 'TOF' |

| Author | Study Aim | Data Source | Identification Period[a] | Population | Methods used to identify evidence of malformations | Classifications used for malformations and exclusions | Guidelines used to define, classify or exclude malformations | Code list development described? |
|---|---|---|---|---|---|---|---|---|
| **Gastroschisis** | | | | | | | | |
| Bannister 2018[220] | Assess the incidence of infections in children with gastroschisis | THIN | 1990-2013 | Live-born infants | **Read codes** were identified from infant records during the first five years of life. | **Excluded** other major malformations. | EUROCAT | No |
| **Genitourinary tract or inguinal region malformations and developmental hip dysplasia** | | | | | | | | |
| Perry 2012[221] | Assess the presence of malformations in those with Perthes disease. | CPRD | 1990-2008 | All patients in the study | **Read codes** were identified from records anytime in the identification period. | **Classified** into subgroups for analyses. | N/S | No |
| **Developmental hip dysplasia** | | | | | | | | |
| Broadhurst 2019[222] | Estimate incidence of developmental hip dysplasia | Linked CPRD & HES | 1990-2016 | All patients aged 1-8 years | **Read codes** were identified from records anytime in the identification period and the first code was considered the first diagnostic evidence. | **Excluded** those with neuromuscular conditions, syndromes or traumatic hip dislocation that could result in developmental hip dysplasia. | N/S | No |

[a]The period in which congenital malformations were identified was not always explicitly defined by authors and did not always correspond to the study period. When possible, it was estimated from available information; [b]CPRD medcodes, corresponding to Read codes; [c]If the classification of identified conditions was uncertain, complete paper records were reviewed for further information; [d]If the classification of identified conditions was uncertain, free-text from THIN or complete paper records from CPRD were reviewed for further information; [e]This appeared to involve examination of maternal records but methods were not described further; [f]The authors communicated that they conducted a manual review but also provided information for a code list; [g]These are groups of related malformations typically occurring as a result of an MCM disrupting the development of surrounding tissues.
Abbreviations: MCM, Major congenital malformation; CPRD, Clinical Practice Research Datalink (formerly the General Practice Research Database); THIN, The Health Improvement Network; OXMIS, Oxford Medical Information System; ICD, International Classification of Diseases; GP, General Practitioner; N/A, Not applicable; N/S, Not specified.

**Table 2 - Read and Oxford Medical Information System (OXMIS) codes used to identify congenital malformations in primary care data.**

| Study | Used a code list? | Level of detail in code list published or provided upon request | Source of code list *or* reason list not available | Codes included? | Types of Read and/or OXMIS codes included in code lists to identify malformations | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Diagnosis | Diagnosis from 'P' chapter in Read | Diagnosis from other Read chapters | Procedure | Testing/ Screening | History[a] | Observation[b] | Administrative[c] |
| Any malformations | | | | | | | | | | | | |
| Cea-Soriano, 2018[187] | N/S | None | No response to request for further information | Read[d] | ✓ | N/S | N/S | N/S | N/S | N/S | N/S | N/S |
| Baril, 2015[188] | N/S | None | No response to request for further information | N/S | N/S | N/S | N/S | N/S | N/S | N/S | N/S | N/S |
| Ruigomez, 1999[189] | No | None | No code list used | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Major malformations | | | | | | | | | | | | |
| Petersen, 2016<br>Petersen, 2017 | N/S | Subset (most common codes identified in the study population) | No response to request for further information | Read | ✓ | ✓ | No | No | No | No | No | No |
| Charlton, 2015[192] | No | None | No code list used | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Charlton, 2010[194]<br>Charlton, 2011[193] | Yes | Broad | Author | Read & OXMIS | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Tata, 2008[206]<br>Sokal, 2013[201]<br>Sokal, 2014[202]<br>Ban, 2014a-c[196-198]<br>Ban 2015a-b[199, 200]<br>Dhalwani, 2015[195] | Yes | Broad | Published[e] | Read | ✓ | ✓ | ✓ | ✓ | No | ✓ | No | ✓ |
| Vasilakis-Scaramozza, 2013a-c[203-205] | Yes | Broad | Author | Read | ✓ | ✓ | ✓ | No | No | No | No | No |
| Jick, 1999[207]<br>Jick, 1997[208] | Yes | Broad[f] | Author | OXMIS | ✓ | No | No | N/S | N/S | N/S | N/S | N/S |
| Neural Tube Defects | | | | | | | | | | | | |
| Devine, 2008[209] | Likely | Subset (only codes in the study population that were validated) | Published | Read & OXMIS | ✓ | ✓ | ✓[g] | ✓ | N/S | N/S | N/S | N/S |
| Tata, 2005[210] | Yes | Broad | Author | Read & OXMIS | ✓ | ✓ | ✓ | ✓ | N/S | N/S | No | ✓ |
| Lawrenson, 2000[212]<br>Lawrenson, 2001[211] | N/S | None | No access to study material | N/S | ✓ | N/S | N/S | N/S | N/S | N/S | N/S | N/S |

| Study | Used a code list? | Level of detail in code list published or provided upon request | Source of code list *or* reason list not available | Codes included? | Types of Read and/or OXMIS codes included in code lists to identify malformations | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Diagnosis | Diagnosis from 'P' chapter in Read | Diagnosis from other Read chapters | Procedure | Testing/ Screening | History[a] | Observation[b] | Administrative[c] |
| Orofacial malformations | | | | | | | | | | | | |
| Chi, 2011[213] | Yes | Specific | Author | Read & OXMIS | ✓ | ✓ | No | ✓ | No | ✓ | No | No |
| Heart Defects | | | | | | | | | | | | |
| Petersen, 2014[214] | N/S | Subset (most common codes identified in the study population)[h] | No response to request for further information | Read | ✓ | ✓ | N/S | N/S | N/S | N/S | N/S | N/S |
| Margulis, 2013[215] Hammad, 2013[216] | Likely | Subset (only codes in the study population that were validated) | Published | Read | ✓ | ✓ | N/S | ✓[d] | N/S | N/S | N/S | N/S |
| Billet, 2008[217] | N/S | None | No access to study material | Read | ✓[d] | N/S | N/S | ✓[d] | N/S | N/S | N/S | N/S |
| Wurst, 2007a[218] | Yes | Broad | Author | Read & OXMIS | ✓ | ✓ | ✓ | No | No | No | No | No |
| Wurst, 2007b[219] | Yes | Specific | Published | Read & OXMIS | ✓ | ✓ | No | ✓ | No | No | No | No |
| Gastroschisis | | | | | | | | | | | | |
| Bannister, 2018[220] | Yes | Specific | Author | Read | ✓ | ✓ | No | ✓ | No | No | No | No |
| Genitourinary tract or inguinal region malformations and developmental hip dysplasia | | | | | | | | | | | | |
| Perry, 2012[221] | Yes | Specific | Author | Read | ✓ | ✓ | ✓ | ✓ | No | ✓ | No | No |
| Developmental hip dysplasia | | | | | | | | | | | | |
| Broadhurst, 2019[222] | Yes | Specific | Published | Read | ✓ | ✓ | ✓ | ✓ | No | ✓ | ✓[i] | ✓[i] |

Studies using the same code list were grouped. [a]Codes for history of congenital malformations ('*history of cleft palate*'); [b]Codes for congenital malformations observed during examination ('*observed on examination – pigeon chest*'); [c]Codes for monitoring, counselling or transfers of care related to congenital malformations (*'transfer of care from paediatric congenital heart service'*); [d]Described in methods; [e]Published as part of a thesis; [f]Author noted a manual review was likely used in one study; [g]Codes for suspected foetal malformations; [h]Published Read terms only; [i]Codes used as supportive evidence of condition. Abbreviations: N/A, Not applicable; N/S, Not specified.

### Defining and identifying congenital malformations in secondary care data

All 18 studies using secondary care data and/or birth and death certificate data used code lists to search the data (**Table 3**). Studies did not specify whether computerized or manual searches were used. However, the ICD-10 code lists used to identify conditions were publicly available for all studies (**Table 3**). All ICD-10 codes were from the 'Q' chapter for congenital malformations. Half of the studies also used OPCS-4 codes, often because procedures were relevant to the study question.

Details of the methods used to develop ICD-10 code lists were publicly available for six studies. These studies examined chronic or life-limiting conditions, of which congenital malformations were a subset.[223, 224, 237-240] The methods described were therefore not specific to congenital malformations although two studies did use EUROCAT guidelines to define and identify them.[223, 224] Only two studies stratified congenital malformations by their severity or complexity.[224, 225] This stratification was based on previously published guidelines, with one study providing the code list for severe conditions.[224] Of the four studies examining orofacial clefts, three stratified clefts by type and described the codes used.[229-231]

**Table 3 - Studies identifying congenital malformations using secondary care data.**

| Author | Congenital malformations identified | Study Aim | Data-source | Identification Period | Study population | Algorithm to identify congenital malformations of interest | Algorithm to identify subgroups, excluded conditions or those used in sensitivity analyses |
|---|---|---|---|---|---|---|---|
| Zylbersztejn, 2019[223] | Chronic congenital malformations | Compare preventable deaths in Sweden and England and assessed the contribution of risk factors. | (UK) HES admissions linked to death certificates | 2003-2013 | Singleton live-births delivered between 2003-2012 | Presence of one of the codes below in hospital admission records from the 31st day of life until the second birthday or on the death certificate as any cause of death until the fifth birthday. | Malformation subgroups not explored. |
| Zylbersztejn, 2018[224] | | Assess the reasons for higher infant mortality in England compared to Sweden | | | | Presence of one of the codes below in the birth admission record, hospital admission records until the second birthday or on the death certificate as any cause of death up until the fifth birthday.<br><br>Codes[a]: Q00-07, Q104, Q107, Q11-12, Q130-134, Q138-139, Q14-16, Q188; Q20-26; Q30-34; Q35-37; Q380, Q383-384, Q386-388, Q39, Q402-403, Q408-409, Q41-42, Q431, Q433-437, Q439, Q44-45; Q500, Q51, Q520-522, Q524, Q540-543, Q548-550, Q555, Q56; Q601-602, Q604-606, Q61, Q620-626, Q628, Q630-632, Q638-639, Q64; Q650-652, Q658-659, Q675, Q682, Q71-74, Q750-751, Q753-759, Q761-764, Q77-78, Q790, Q792-796, Q798; Q820-824, Q829, Q85, Q860-862, Q868, Q878, Q891-893, Q897-899; Q90-93, Q952-953, Q97, Q99 | Sensitivity analysis of severe malformations as defined by the codes below.<br><br>Codes[b]: Q00-07; Q20, Q212-214, Q218-219, Q22-24, Q251-259, Q26, Q282-283, Q289; Q30-34; Q390-394, Q41-45; Q60-64; Q722, Q750, Q752, Q759-762, Q764-767, Q77, Q780-784, Q788-795, Q799; Q81, Q871, Q873-874, Q877-879; Q909, Q913-914, Q917, Q928, Q93, Q950, Q969, Q97-98, Q992, Q998-999 |
| Dimopoulos, 2019[225] | Heart defects | Assess transplant survival rates and the capacity for such procedures. | HES admissions linked to death certificates | 1997-2015 | All | Presence of any 'Q2xx.x' code with a further procedure code indicating a heart or heart-lung transplant (OPCS-4 codes K01-02). | Stratified heart defects by complexity, using guidelines from 32nd Bethesda conference |
| Kempny, 2017[226] | Heart defects | Examine surgical volume and mortality in patients. | HES admissions linked to death certificates | 1997-2015 | All | Presence of any 'Q2x.x' code and evidence of a cardiac surgery (except heart or heart-lung transplants). | Excluded CABG and mitral valve surgery in sensitivity analyses |
| Singhal, 2014[227] | Heart defects; Spina Bifida | Assess the relationship between self-harm/suicide and chronic illnesses. | HES admissions linked to death certificates | 1999-2011 | All | Presence of any Q20-24 code (heart defects) or a Q05 code (spina bifida). | - |
| Billett, 2007[228] | Heart defects | Explore trends in admissions, procedures and patient mortality. | HES admissions, Death certificates (unlinked) from England and Wales | 1995-2004<br>1994-2003 | All | Any Q20-28 code in the primary diagnosis field.<br>Any ICD-9 code for 745-747 for underlying cause of death until 2001 and any ICD-10 Q20-28 code thereafter. | - |

| Author | Congenital malformations identified | Study Aim | Data-source | Identification Period | Study population | Algorithm to identify congenital malformations of interest | Algorithm to identify subgroups, excluded conditions or those used in sensitivity analyses |
|---|---|---|---|---|---|---|---|
| Fitzsimons, 2017[229] | Orofacial clefts | Examine grommet insertion practices in cleft patients. | HES admissions | 1997-2011 | Live-births from 1997 to 2005 | Presence of any diagnostic Q35, Q36, or Q37 code as well as a procedure code for primary cleft repair (OPCS-4 codes F031 or F291). | Clefts were grouped by type using repair codes (F03, F29, F30, F32) and the available diagnosis code. |
| Fitzsimons, 2014[230] | | Examine hospital admissions for dental treatment in cleft. | | 1997-2011 | Live-births from 1997 to 2003 | | Clefts were grouped by type using repair codes (F03, F29, F30, F32) and the available diagnosis code. |
| Fitzsimons, 2013[231] | | Explore hospital admissions and length of stay for cleft patients. | | 1997-2011 | Live-births from 1997 to 2008 | | Clefts were grouped by type using repair codes (F03, F29, F32) and the available diagnosis code. |
| Fitzsimons, 2012[232] | | Assess changes in cleft patient care following service changes. | | 1997-2009 | Live-births from 1997 to 2008 | | Clefts were not grouped by type.<br><br>All 4 studies identified those with additional malformations for separate analyses or exclusion using any of the following codes in any field: D821; Q00-07; Q16; Q18; Q20-28; Q380; Q75; Q86-87; Q90-93; Q95-99 |
| Broadhurst, 2019[222] | Developmental hip dysplasia | Estimate incidence of developmental hip dysplasia | Identified cases in CPRD and then used linked HES admissions data for validation | 1990-2016 | All patients aged 1-8 years | Linked HES admissions data in the 2 years either side of the initial diagnosis in CPRD were searched for supportive evidence in the following order (strongest to weakest evidence):<br>A) A specific diagnosis based on the presence of a Q650-656 code or evidence of a specific procedure (OPCS-4 codes X221-225, X228-229).<br>B) The presence of a related diagnostic code: M244 or R294.<br>C) Evidence of a hospital admission within 6 months.<br>If none of the above were found, CPRD was searched for supportive evidence (≥3 orthopaedic hospital attendances, ≥2 diagnostic codes or related codes such as those for a clicking hip) in the 2 years after the initial diagnosis. | Diagnoses excluded:<br>G80, G800-804, G808-809, Q743, Q796, Q90, Q900-902, Q909, Q980-985, Q824, Q718, Q728, Q999, Q916, G711, G819, Q929, Q824, Q931, Q773<br>Procedures excluded:<br>W651-655, W658-659, W661-664, W668-669, W671-679 |

| Author | Congenital malformations identified | Study Aim | Data-source | Identification Period | Study population | Algorithm to identify congenital malformations of interest | Algorithm to identify subgroups, excluded conditions or those used in sensitivity analyses |
|---|---|---|---|---|---|---|---|
| McAllister, 2018[233] | Developmental hip dysplasia | Assess the risk of surgery for this condition following an intervention. | Scottish Morbidity Record | 1997-2014 | Live-births from 1997-2013 | Presence of any Q650-659 code with a further procedure code (OPCS-4 codes T202, T205, W134, W144, W164, W169, W281, X221–229, W65-66). | - |
| Dharmasena, 2017[234] | Anophthalmia; Microphthalmia; Malformations of orbit; Agenesis of lacrimal apparatus | Estimate hospital admission trends and incidence of eye malformations. | HES admissions | 1999-2011<br><br>1990-1998 | All <1 years old | Presence of any of the following codes in the birth record or subsequent hospital admission record: Q110-Q111 (anophthalmia), Q112 (microphthalmia), Q107 (congenital malformations of orbit), Q104 (agenesis of lacrimal apparatus).<br><br>The ICD-9 code 7431 for microphthalmia was used in further analyses that examined years prior to 1995. | - |
| Lansdale, 2017[235] | Pyloric stenosis | Examine surgical outcomes for infantile hypertrophic pyloric stenosis. | HES admissions & Patient Episode Data for Wales | 2002-2011 | All | Presence of a procedure code for pyloric stenosis (OPCS-4 code G401) that occurred between the 1st day of life and the 1st birthday, as well as a Q400 diagnostic code. | - |
| Wilkinson, 2017[236] | Hypospadias | Estimate the frequency of re-operations and complications following repair of hypospadias. | HES admissions | 1999-2009 | Boys <16 years old | Presence of a procedure code for primary repair of hypospadias (OPCS-4 code M731), with or without a diagnostic Q54 code. Post-surgery admissions for were identified from Q540-543 or Q548-549 codes or codes relating to surgical complications or revisions. | Excluded those with disorders of sexual differentiation recorded with the following codes: Q560-564; Q640-641; E250, E258-259, E345 |

| Author | Congenital malformations identified | Study Aim | Data-source | Identification Period | Study population | Algorithm to identify congenital malformations of interest | Algorithm to identify subgroups, excluded conditions or those used in sensitivity analyses |
|---|---|---|---|---|---|---|---|
| Jarvis and Fraser, 2018[237] | Life-limiting or life-threatening malformations[c] | Compare the identification of these conditions in inpatient data and death records. | HES admissions linked to death certificates & Scottish Birth, Morbidity and Death Records. | 2001-2015<br><br>2003-2014 | Patients aged 0-25 years with a death record | Searched English and Scottish hospital admission data and Scottish birth records for the codes below, except for Q445 and Q748. Death records were searched for codes among the underlying causes of death. If this was not related to a life-limiting condition, then contributing causes of death were checked. | - |
| Jarvis, 2017[238] | | Assess clinical stability in those with life-limiting conditions. | Scottish Birth & Morbidity Records | 2003-2014 | Patients aged 0-25 years | Searched Scottish birth records and hospital admissions data for the codes below except for Q445 and Q748. | |
| Fraser, 2014[239] | | Estimate the prevalence of life-limiting conditions. | HES admissions | 2009-2010 | Patients aged 0-40 years | Searched hospital admissions data for the codes below. | |
| Fraser, 2012[240] | | Estimate the prevalence of life-limiting conditions. | HES admissions | 2000-2010 | Patients aged 0-19 years | Codes: Q000, Q01, Q031, Q039-040, Q042-044, Q046, Q049, Q070, Q200, Q203-204, Q206, Q208, Q213, Q218, Q220-221, Q224-226, Q230, Q232, Q234, Q239, Q254, Q256, Q262, Q264, Q268, Q282, Q321, Q336, Q396, Q410, Q419, Q437, Q442, Q445, Q447, Q601, Q606, Q614, Q619, Q642, Q743, Q748, Q750, Q772-774, Q780, Q785, Q792-793, Q804, Q81, Q821, Q824, Q858, Q860, Q870-872, Q878, Q91, Q920-921, Q924, Q927-928, Q932-935, Q938, Q952. | |

[a]Codes were a subset of those developed by Hardelid *et al.* to identify chronic conditions requiring medical follow-up for more than a year in half or more of cases. [b]Codes were a subset of those developed by Feudtner *et al.* to identify conditions likely to last at least a year and involve multiple organ systems or require tertiary care. [c]Codes for malformations were a subset of those used to identify all life-limiting or threatening conditions. Abbreviations: HES, Hospital Episode Statistics; ICD, International Classification of Diseases; OPCS-4, 4th Revision of the Classification of Interventions and Procedures.

**Validation of codes used to record congenital malformations in primary care.**

Eight studies attempted to validate congenital malformations identified in primary care data, all of which restricted to examining the positive predictive value (PPV) of a coded diagnosis (**Table 4**).[187, 192, 194, 208, 209, 216, 219, 222] Most relied exclusively on GP questionnaires (n=4) as the reference standard, or a mixture of further primary care data such as anonymised free-text or complete paper records (n=3). Just one study used linked HES data to validate diagnoses of congenital malformations identified in CPRD.[222]

Overall, the quality of most studies was assessed as good (**Table 5**). However, the validity of the reference standard was uncertain for studies that used GP questionnaires or requested complete paper records as they often did not provide details of the information used to confirm diagnoses (e.g. whether the GP simply looked at the electronic record or whether they referred to a hospital letter to confirm the diagnosis) (**Table 5**) (**Supplementary Table 2**). Authors also differed in the methods used to calculate PPV, with some authors including in the denominator only those individuals for whom requested information was returned and others calculating a more conservative PPV based on the total number of individuals for whom information was requested.

The one study of any congenital malformations (major or minor) reported a high PPV of 81% (95% CI, 78-84) (**Figure 2**).[187] This was also the case for major malformations across the three studies that examined them, with overall PPV estimates ranging from 85-100% and no evidence of between-study heterogeneity (n=3; $\chi^2$ test=2.7 ; p=0.3).[192, 194, 208] However, the study by Charlton *et al.* demonstrated that the PPV varied according to the reference standard used; the PPV for cases validated by reviewing free-text was lower than that seen when complete paper records were used (**Figure 2,** 78% vs 92%, $\chi^2$ test=7.2; p=0.007).[194]

The two studies of heart defects were found to consistently have PPVs ≥90% (with the lowest lower confidence limit being 81%) (**Figure 2**).[216, 219] The validity of neural tube defects was 71%

(95% CI, 63-78) overall.[209] Among the neural tube defects, spina bifida had the lowest PPV (47%; 95% CI, 36-58) whilst encephalocele had the highest (83%; 95% CI, 36-99). Developmental hip dysplasia had the lowest PPV of any condition examined.[222] Only 34% (95% CI, 30-37) of patients with evidence of the condition in CPRD also had specific evidence of a diagnosis or procedure in HES inpatient data in the two years before or after the CPRD diagnosis. The PPV increased to 56% (95% CI, 53-60) when less specific supportive evidence from CPRD or HES was considered (**Figure 2**). The reference standard in this study was, however, considered suboptimal (**Supplementary Table 2**).

Overall, congenital malformation prevalence in stand-alone primary care data was comparable to or higher than the prevalence in national or regional population-based registries (**Supplementary Table 3**). Between 1990 and 2009, the prevalence ratio for major congenital malformations among live-births between THIN and UK EUROCAT data was 1.18 (95% CI, 1.16-1.20).[201] The prevalence of heart defects was higher in THIN than in EUROCAT (PR, 1.31; 95% CI, 1.26-1.35) but similar for nervous system malformations (PR, 1.06; 95% CI, 0.98-1.14). This was consistent with results from studies comparing the prevalence of heart and neural tube defects between CPRD and population-based registries.[209, 218] Primary care data from THIN did appear to under-ascertain urinary, orofacial, digestive and abdominal malformations as well as rare conditions such as Ebstein's anomaly.[201] However, the prevalence of conditions (including those considered rare) increased in both CPRD and THIN with longer follow-up time.[201, 218]

**Table 4 – Summary of studies performing validations of congenital malformation diagnoses identified in primary care data**

| Author | Malformations validated | Study Population | Validation Method | Method summary | No. cases identified for validation | Response rate (Received/ Requested) | Reasons for non-receipt of requested information from GPs | Positive Predictive Value (95% CI) |
|---|---|---|---|---|---|---|---|---|
| **Cea-Soriano, 2018**[187] | **Any** | Live-births | Manual review of free-text and electronic records | **Authors:** Identified supporting evidence from free-text, comments associated with specialist referrals in the year before or after the first diagnosis, tests or procedures, and repeated records of malformations or symptoms. | 788[a] | N/A | N/A | **81% (78-84)** |
| **Charlton, 2015**[192] | **Major** | Live-births<br>Stillbirths<br>Terminations | GP questionnaire; Manual review of free-text and electronic records | **GP confirmed:** Diagnosis.<br>**Authors:** Identified supporting evidence (e.g. surgery codes). | 622[b] | 88%<br>(127/145)[c] | N/S | **86% (83-89)** |
| **Charlton, 2010**[194] | **Major or could potentially be classed as major under certain criteria** | Live-births | Request for and review of complete paper records and free-text | **Authors:** Requested complete paper records for those registered with a practice and free-text if they could not be provided. Diagnoses were confirmed and those with sufficient information to be classified as major or minor were identified. | 188[b] | 78%<br>(96/123)[d] | 15x No response<br>4x Refused participation<br>1x No records available<br>2x Practice left CPRD<br>1x Transferred out<br>2x No parental permission<br>2x No malformation[e] | **Combined: 85% (79-90)**<br>Records only: 92% (84-96)<br>Free-text only: 78% (67-86) |
| **Jick, 1997**[208] | **Major** | Live-births | GP questionnaire | **GP confirmed:** Diagnosis and diagnosis date. | 16[b] | N/S | N/S | **100% (76-100)**[f] |
| **Hammad, 2013**[216] | **Heart** | Live-births | GP questionnaire | **GP confirmed:** Diagnosis and diagnosis date, type of exam used to determine diagnosis, information used to confirm the diagnosis. | 888[a] | 81%<br>(719/888) | N/S | **1996-2010:**[g] **93% (91-95)**<br>**2006-2010: 94% (91-97)** |
| **Wurst, 2007**[219] | **Heart**<br>VSD<br>TOF<br>COA | Live-births | GP questionnaire | **GP confirmed:** Diagnosis and diagnosis date, age at diagnosis, reason diagnosis suspected, type of doctor that made diagnosis, diagnostic tests and results, referrals to cardiology, surgery, other heart defects and VSD type. | 200[b]<br>104 VSD<br>72 TOF<br>24 COA | 94%<br>(187/200) | N/S | **94% (89-96)**<br>95% (88-98)<br>90% (80-96)<br>100% (81-100) |

| Author | Malformations validated | Study Population | Validation Method | Method summary | No. cases identified for validation | Response rate (Received/ Requested) | Reasons for non-receipt of requested information from GPs | Positive Predictive Value (95% CI) |
|---|---|---|---|---|---|---|---|---|
| **Devine, 2008[209]** | **Neural Tube**<br>Anencephaly<br>Encephalocele<br>Meningocele<br>Spina bifida | Live-births<br>Stillbirths<br>Terminations<br>Miscarriages | GP questionnaire | **GP confirmed:** Diagnosis and diagnosis date, the type of exam used to determine the diagnosis and the information used to confirm it. As this study also identified neural tube defects encoded in the maternal record around the time of pregnancy, GPs were asked to confirm if the diagnosis related to a condition in the mother or her offspring for such cases. | 217[b] | 76%<br>(165/217) | 31x No response<br>18x Transferred out<br>3x Data entry errors[h] | **71% (63-78)[g]**<br>81% (68-89)<br>83% (36-99)<br>64% (36-86)<br>47% (36-58) |
| **Broadhurst, 2019[222]** | **Developmental hip dysplasia** | Children with a first diagnosis between 1-8 years | Review of linked HES records and CPRD records | **Authors:** Identified the initial diagnosis in CPRD and searched for supportive evidence in linked HES data in the 2 years either side of this or in CPRD in the 2 years after. Results were stratified by the strength of the supportive evidence (from strongest to weakest):<br>A) Specific diagnostic or procedural code in HES<br>B) Non-specific code in HES (e.g. '*clicking hip*')<br>C) Hospital admission within 6 months<br>D) No related codes in HES but other coded supportive evidence available in CPRD (≥2 diagnostic codes, ≥3 orthopaedic follow-up visits, other supportive evidence such as Read codes for a clicking hip). | 754[a] | N/A | N/A | **Using most specific supportive evidence**<br>34% (30-37)<br>**Using any available supportive evidence**<br>56% (53-60) |

[a]Number of individuals with malformation(s) identified for validation; [b]Number of malformations identified for validation; [c]Did not specify if questionnaires were requested by individual or by malformation; [d]Received records for 96 patients corresponding to 109 malformations; [e]These were included in the PPV calculation as individuals whose record of a major malformation diagnosis was not validated; [f]95% CI calculated on the assumption that 16 questionnaires were sent to GPs and responses received; [g]Calculated additional PPVs, including PPVs for each code (not shown); [h]Did not include these when calculating PPV. Abbreviations: PPV, Positive Predictive Value; CI, Confidence Interval; GP, General Practitioner; VSD, Ventricular Septal Defect; TOF, Tetralogy of Fallot; COA, Coarctation of Aorta; N/A, Not Applicable; N/S, Not specified.

**Table 5 – Summary of quality assessment of validation studies.**

| Criterion | Risk of bias, by study | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Any malformation | Major malformations | Major malformations | Major malformations | Neural tube defects | Heart defects | Heart defects | Developmental Hip Dysplasia |
| | Cea-Soriano 2018[187] | Charlton 2010[194] | Charlton 2015[192] | Jick 1997[208] | Devine 2008[209] | Wurst 2007[219] | Hammad 2013[216] | Broadhurst 2019[222] |
| Was a consecutive or random sample of patients enrolled? | Low | Low | Low | Low | Low | Low | Low | Low |
| Did the study avoid inappropriate exclusions? | Low | Low | Low | Low | Low | Low | Low | Low |
| Were the index test results interpreted without knowledge of the results of the reference standard? | Low | Low | Low | Low | Low | Low | Low | Low |
| Is the reference standard likely to correctly classify the target condition? | Uncertain | Uncertain | Uncertain | Uncertain | Uncertain | Uncertain | Low | High |
| Did all patients receive the same reference standard? | Uncertain | Low | High | Low | Low | Low | Low | Low |
| Were all patients included in the analysis? | Low | Low | Low | Low | Low | Low | Low | Low |

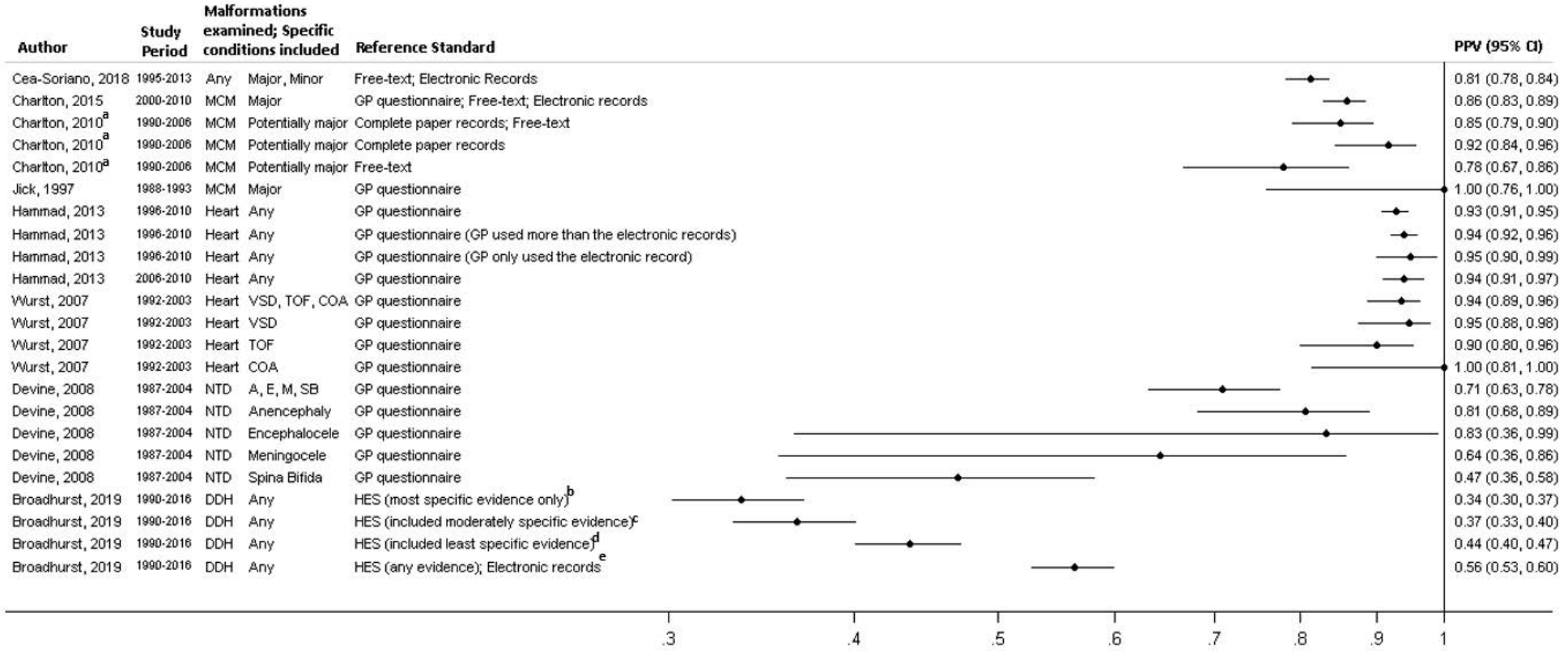



**Figure 2 - Individual-study PPV estimates for congenital malformation diagnoses in primary care data.** [a]Included conditions that could potentially be classified as major under certain criteria; [b]Specific diagnostic or procedural codes in HES; [c]Searched for specific diagnostic/procedural codes or codes that were likely to relate to developmental hip dysplasia (e.g. '*clicking hip*'); [d]Searched for specific or related codes or evidence of a hospital admission within six months of the diagnosis in the primary care record; [e]Searched for any evidence in HES (as defined previously) or supportive evidence anywhere in the electronic primary care record such as multiple records of the diagnosis, regular orthopaedic hospital attendances etc. Abbreviations: PPV, Positive Predictive Value; CI, Confidence Interval; MCM, Major Congenital Malformation, GP, General Practitioner; VSD, Ventricular Septal Defect; TOF, Tetralogy of Fallot; COA, Coarctation of Aorta; NTD, Neural Tube Defects; A, Anencephaly; E, Encephalocele; M, Meningocele; SB, Spina Bifida; DDH, Developmental hip dysplasia, HES, Hospital Episode Statistics

**Validation of codes used to record congenital malformations in secondary care and other UK EHR.**

No formal validation studies of code lists for congenital malformations in secondary care data were identified, although some authors did describe evidence to suggest that the validity of these data were good. Studies identifying orofacial clefts noted that between 2000 and 2009, 85% of almost 9,000 individuals in a UK cleft registry could be linked to HES and that the concordance of diagnoses among linked individuals was >92%.[229-232] A study on developmental hip dysplasia reported 98% concordance between surgical interventions for this condition in Scottish admissions data (identified using ICD-10 and OPCS-4 codes) and a surgical database over the same period.[233]

One study identified children with life-limiting congenital malformations using inpatient HES data or linked Scottish birth and inpatient data.[237] The completeness of recording of life-limiting congenital malformations in linked death certificates (as underlying or contributory causes of death) was examined. Among deceased infants with a life-limiting congenital malformation recorded in inpatient HES (n=6,823) or Scottish data (n=555), 80% and 89% had a concordant or related diagnostic code on their death certificate, respectively.

## Discussion

This systematic review examined 36 studies that identified congenital malformations in UK primary care data and 18 studies that identified these conditions in secondary care data. No primary care study used linked secondary care data to increase identification of congenital malformations. Among the secondary care studies, a few also examined linked death certificate data (typically with death as an outcome of interest) or used birth data as an additional data source.

Primary care studies frequently used published guidelines to develop case definitions for the congenital malformations of interest and to develop Read code lists, with EUROCAT guidelines most commonly used. Although the Read system 'P' chapter is dedicated to congenital malformation diagnoses, studies using primary care data often considered codes from other diagnostic chapters and codes for procedures, medical histories or administrative tasks. The extent to which non-'P' chapter codes were used varied across studies. The inclusion of these additional codes was often only apparent after examining available code lists; typically, researchers did not describe the criteria used to include additional codes, or whether individuals in the study population with such codes were required to fulfil any additional criteria in order to be considered cases. For some studies, there was insufficient detail available to assess the full range of Read codes used.

In contrast, studies using secondary care data all reported the codes used to identify malformations. These studies did not include diagnostic codes outside the 'Q' chapter of ICD-10 that is dedicated to congenital malformations, although half also used OPCS-4 procedure codes. Clinical coders of diagnoses in primary and secondary care records do not follow the coding guidelines used in other contexts for malformations, and so researchers needed to consider what codes might be used. Clinical coders in hospital settings are required to record definitive diagnoses and this coding is central to financial reimbursement for hospital admissions.[177] This may explain why researchers chose to rely on 'Q' chapter codes to define

and capture conditions. However, ICD-10 does not categorize congenital conditions as major or minor and the secondary care studies we identified did not attempt to distinguish between these categories.

Validation studies of recorded congenital malformations were almost entirely limited to primary care data, and only eight primary care studies were identified. The PPV (the sole measure of validity assessed) was high for malformations overall, for major malformations, and for heart defects, ranging from 80-100%.[187, 193, 194, 208, 216, 219] These estimates are in line with findings from a previous systematic review which reported high PPV for 183 different diagnoses in CPRD (median PPV, 89%; range, 24-100%).[180] The PPVs of neural tube defects were slightly lower, at 71% overall, and the PPV for developmental hip dysplasia was markedly lower, at 56%.[209, 222] However, the reference standard for this latter study was a combination of HES hospitalisation data and additional coded CPRD data, which was considered suboptimal. First, cases diagnosed before 1997 (when inpatient HES data were unavailable) and cases treated with non-surgical interventions would not be recorded in HES inpatient data. Second, it was unclear whether the study included children whose first recording of developmental hip dysplasia occurred soon after they registered with the general practice; these could be a historical diagnosis retrospectively recorded in the first few months after registration, and thus unlikely to have further supportive evidence in CPRD.[243] Furthermore, GPs may not consistently encode feedback from secondary care but simply scan in hospital letters, and these are not available to researchers as part of the CPRD electronic data.

No studies examined the validity of congenital malformations recorded in secondary care. The one study that investigated the completeness of life-limiting congenital malformation recordings in death certification data used hospitalisation data as the reference standard, and found 11-20% under-reporting in death certificates.[237] However, as the PPV of congenital malformation diagnoses in hospitalisation data has not yet been established, these results need to be interpreted with caution.

Comparisons of prevalence between primary care data and registry data suggested that the prevalence of congenital malformations overall, and for some anatomical subgroups, were comparable or higher in primary care databases and had the potential to increase with longer follow-up.[201, 209, 218] This may be due in part to some registries ascertaining cases up to a younger age than that examined in primary care records, which can better capture late diagnoses in children.[86, 244] However, the higher prevalence recorded in primary care data may also reflect an imperfect PPV for congenital malformation codes. For example, whilst the use of Read codes from outside the 'P' chapter can increase case ascertainment of malformations, it will decrease the PPV if these codes are also used to record diseases that are non-congenital in nature. The influence of the codes used is also pertinent to studies of secondary care data. A very recent study, published after we completed the search for this review, used three different ICD-10 code lists to identify congenital malformations in UK hospitalisation data.[245] The study showed that the prevalence of malformations markedly depended on the code list applied, ranging from 1.8-4.1% and highlighting the impact that the choice of codes can have on study findings.[245]

**Strengths and Limitations**

To our knowledge, our study is the first to examine systematically the wide array of methods and codes used by researchers to identify individuals with congenital malformations recorded in UK electronic health data, and the results of validation studies of these diagnoses. Our extensive literature search carried out as part of this systematic review, including a comprehensive search strategy and hand-searching of reference lists and bibliographies, is likely to have captured the majority of relevant studies. Our review brings together the ICD-10 code lists used to identify congenital malformations in secondary care data, which were all made publicly available by researchers. This was not always the case for the Read code lists used in primary care studies, but our efforts to contact authors enabled us to obtain additional code lists.

Our findings also have some limitations. First, despite our efforts, it was not possible to obtain detailed Read code lists from all the authors who used primary care data. Available code lists were often broad in nature and included codes that were not part of the final case definition. Therefore, our summary of the codes used to identify congenital malformations in primary care data was incomplete and it was not clear which codes were ultimately used in some studies.

Second, few validation studies have been carried out, with almost all such studies examining the validity of congenital malformations in primary care data and restricted to estimating PPV. Only three different malformation subgroups have been validated in these data, and there were insufficient studies within subgroups to obtain robust summary estimates. Furthermore, the Read code lists used to identify malformations varied across studies; few studies examined the validity of individual Read codes and none compared the validity of Read codes from the 'P' chapter for congenital malformations with codes from other chapters. Furthermore, there was heterogeneity across studies in the reference standard used. We also identified differences in how PPV was calculated for the studies that provided sufficient methodological detail. The authors who included all cases in the denominator, including those for whom the validity of the diagnosis was unclear (for example, due to GP non-response), provided a conservative estimate of PPV. Others restricted the denominator to cases for whom the true diagnosis was ascertained. This adds to the difficulty in comparing results across studies.

In addition, there was a lack of clarity about the robustness of the reference standards used to estimate validity. The underlying assumption in diagnostic validation studies is that the reference standard has perfect sensitivity and specificity for the diagnosis of interest. Our risk of bias assessment for the eight validation studies in primary care data found that the robustness of the reference standard was uncertain in six studies.[187, 192, 194, 208, 209, 219] Most validations relied on GP questionnaires, but studies rarely described the information the GP used to confirm diagnoses. Similarly, for studies that used anonymised free-text (data entered

by the GP alongside electronic coding) or that relied on a manual review of the patient's electronic record, it was not possible to know whether the available information in these data would provide reliable evidence of the presence of a congenital malformation. Our finding that the PPV varied according to the reference standard used, with lower PPV when using free-text compared to when paper records were examined, is consistent with the possibility that electronic free-text less completely captures the evidence for a malformation diagnosis than paper hospital correspondence. This imperfect sensitivity would lead to an underestimation of the PPV. Alternatively, there may be genuine differences in the PPV of the diagnosis among sub-populations assessed using different reference standards. For example, one study requested complete paper records for all cases, and used electronic free-text for the patients for whom records were not provided.[194] Lack of provision could be due to the child de-registering from the practice or dying, or having extensive case notes which take more time for the practice to process. It is feasible that these children could have a higher or lower probability of a genuine congenital malformation compared to children whose paper records were provided.

Use of a different electronic health record dataset as the reference standard may also have imperfect sensitivity. As discussed above, the results from the two studies that used HES hospitalisation data as the reference need to be interpreted with caution, as the sensitivity and PPV of congenital malformation diagnoses in HES are not currently known. Despite an improvement in the accuracy of coding in HES data after the introduction of financial incentives, clinical coders depend on the quality of hospital discharge summaries for accurate coding of diagnoses.[177, 181] Our review highlights the need for validation studies for congenital malformation diagnoses in secondary care data.

It is also important to remember that measures such as PPV are affected by the prevalence of the condition in the population. Some of the studies identified in this review used data that were more than 25 years old. Prevalence of some of the malformations of interest may have

changed over time due, for example, to improved screening methods resulting in increased ascertainment. Thus, the PPV estimates obtained in older studies may be less generalisable to the current data.

Finally, the small number of validation studies identified were insufficient to allow us to assess formally the risk of publication bias in this review. Validations of diagnoses in EHR are often a minor component of the main study. It is possible that validations that resulted in lower PPV estimates were less likely to be included in publications than those that found higher PPV. If this is so, the PPVs reported in this review may be a biased subset of the PPVs that have been carried out.

**Conclusions and recommendations**

This review provides a detailed summary of the range of methods and the code lists used in studies of congenital malformations that use UK EHR. It has highlighted the lack of methodological detail provided in some published studies, and the scarcity of validation studies of malformation diagnoses recorded in these data.

With the 2015 development of reporting guidelines for studies using observational routinely-collected health data, and the opportunity to provide supplementary online material to accompany publications, it is now easier to include a fuller description of study methods and to allow sharing of code lists.[246] Use of linked primary and secondary care datasets in future studies would allow fuller ascertainment of malformations, including those that are diagnosed in later childhood and those that do not need inpatient care. Similarly, the gradual increase in the electronic recording of coded diagnoses in linked UK out-patient hospital data will allow their future use in malformation research studies.

Further validation studies are needed of a range of malformation subgroups, using large representative samples of cases and assessing all measures of validity (PPV, NPV, sensitivity and specificity). In particular, validation studies of diagnoses in hospital data would address

the existing information gap and facilitate interpretation of study findings that use these data. Finally, UK general practices are currently switching from use of Read codes to the SNOMED coding system.[247] Work will therefore be needed to assess the equivalent SNOMED codes to those currently used for congenital malformations, and their validity.

## Acknowledgements

See research paper cover sheet.

## Funding

This research is funded by the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

## References

References are included as part of the main reference list at the end of the thesis.

## Paper 1: Supplementary material

**Supplementary Table 1 – Details of the criteria used to conduct quality assessment.**

| Criterion | Risk of Bias |
|---|---|
| Was a consecutive or random sample of patients enrolled? | **Low risk:** Study attempted to validate all patients or a random/consecutive sample.<br>**High risk:** Study only validated a specific subset of patients.<br>**Uncertain:** Not enough information. |
| Did the study avoid inappropriate exclusions? | **Low risk:** Study only applied exclusion criteria that were related to the study question which were not thought to be associated with validity.<br>**High risk:** Study applied exclusions that could not be justified by the study question and which could be associated with validity.<br>**Uncertain:** Not enough information. |
| Were the index test results interpreted without knowledge of the results of the reference standard? | **Low risk:** The condition was identified in the data before information was received to confirm or refute the diagnosis.<br>**High risk:** The condition was identified in the data after information was received to confirm or refute the diagnosis.<br>**Uncertain:** Not enough information. |
| Is the reference standard likely to correctly classify the target condition? | **Low risk:** Studies that used information from external sources to validate diagnoses (e.g. authors requested the complete paper record which included external information such as hospital letters, or authors requested confirmation of the diagnosis from a GP who relied on an external source of information such as a hospital letter).<br>**High risk:** Use of a reference standard that is unlikely to have high validity for the condition.<br>**Uncertain:** Not enough information (e.g. studies that did not specify what information was examined and how it was used to determine whether the patient did or did not have the condition). |
| Did all patients receive the same reference standard? | **Low risk:** The same type of information was used to validate a diagnosis for all patients (e.g. a GP questionnaire was used for all).<br>**High risk:** Different information was used to validate a diagnosis between patients (e.g. some had their free-text examined whilst others had a questionnaire sent to their GP).<br>**Uncertain:** Not enough information. |
| Were all patients included in the analysis? | **Low risk:** >70% of patients undergoing validation had the information needed to be included in the analysis and were included.<br>**High risk:** ≤70% of patients undergoing validation did not have the information necessary to perform a validation.<br>**Uncertain:** Not enough information. |

**Supplementary Table 2 – Details of the quality assessment carried out.**

| Study | Criterion | Reason for decision | Bias |
|---|---|---|---|
| **Cea-Soriano, 2018[187]** | Was a consecutive or random sample of patients enrolled? | Yes, authors attempted validation for all 788 infants with a recorded congenital malformation. | Low |
| | Did the study avoid inappropriate exclusions? | Exclusions were made to obtain the study population but were not considered inappropriate as they related to the study aim which was to examine the safety of antidiabetic medication in pregnancy. For example, pregnant women were excluded if they were not registered at a practice a year before their pregnancy as information for them would be incomplete. | Low |
| | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes. | Low |
| | Is the reference standard likely to correctly classify the target condition? | The reference standard was supportive evidence from free-text and the full electronic record (e.g. surgical codes, confirmation of diagnoses with imaging, repeated recording of the malformation or associated symptoms). It was unclear what information was in the free-text and whether this could be reliably used to confirm diagnoses. | Uncertain |
| | Did all patients receive the same reference standard? | It was unclear if free-text and electronic records were reviewed for all patients or whether different reference standards were used for different patients. | Uncertain |
| | Were all patients included in the analysis? | Paper records or GP questionnaires were not requested so there was no response rate. The calculated PPV was based on all 788 infants initially identified. | Low |

| Study | Criterion | Reason for decision | Bias |
|---|---|---|---|
| **Devine, 2008**[209] | Was a consecutive or random sample of patients enrolled? | Yes, a validation questionnaire was sent to the GPs of all 217 identified cases. | Low |
| | Did the study avoid inappropriate exclusions? | A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate. For example, authors excluded those with a diagnosis outside the study period and restricted diagnoses to those recorded in childhood (in keeping with the aim of the review which was to identify cases among children for the purpose of conducting safety assessments of drugs given in pregnancy). | Low |
| | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes. | Low |
| | Is the reference standard likely to correctly classify the target condition? | The reference standard was GP questionnaires. Confirmation of diagnoses and information on the evidence reviewed to confirm these was requested. The authors indicated that in 81% of cases, an examination, diagnostic or screening technique was used to confirm or refute diagnoses, but it was not clear what methods were used in remaining cases. | Uncertain |
| | Did all patients receive the same reference standard? | Yes, for all patients for which a response was received, the reference standard was the GP questionnaire. | Low |
| | Were all patients included in the analysis? | The response rate was 76% (165/217). | Low |

| Study | Criterion | Reason for decision | Bias |
|---|---|---|---|
| **Wurst, 2007[219]** | Was a consecutive or random sample of patients enrolled? | Yes, a validation questionnaire was sent to the GPs of all 200 identified cases. | Low |
| | Did the study avoid inappropriate exclusions? | A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate. For example, authors excluded infants born before the study period or those without acceptable clinical or patient details as determined by CPRD. Due to a high number of individuals with ventricular septal defect, authors chose to retain only those patients "who had data entered for staff role of the reporter". The remaining ventricular septal defect cases were randomized and the first 104 selected. It was unclear why the staff role of the reporter was used in this instance. However, because the staff role could include individuals with varying levels of expertise (GPs, nurses, receptions) and because it did not appear staff role was used subsequently to exclude patients, it was decided that this would not bias the sample. | Low |
| | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes. | Low |
| | Is the reference standard likely to correctly classify the target condition? | The reference standard was GP questionnaires. Confirmation and date of diagnosis was requested as well as information on the type of practitioner that made the final diagnosis, the diagnostic tests performed and the findings, whether any referrals or surgeries were performed and whether the patient had any additional defects. It was not clear what information GPs referred to in order to confirm or refute diagnoses (e.g. whether external data such as hospital letters were used), although authors noted that with the exception of the date of diagnosis, only 3% of the data for requested information was missing. | Uncertain |
| | Did all patients receive the same reference standard? | Yes, for all patients for which a response was received, the reference standard was the GP questionnaire. | Low |
| | Were all patients included in the analysis? | The response rate was 94% (187/200). | Low |

| Study | Criterion | Reason for decision | Bias |
|---|---|---|---|
| **Hammad, 2013**[216] | Was a consecutive or random sample of patients enrolled? | Yes, a questionnaire was sent to the GPs of all 888 cases. | Low |
| | Did the study avoid inappropriate exclusions? | A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate. The study identified cases among singletons born in the study period. They excluded those with chromosomal malformations which was in line with their aim to examine the association between selective serotonin reuptake inhibitors and congenital cardiac malformations. | Low |
| | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes. | Low |
| | Is the reference standard likely to correctly classify the target condition? | The reference standard was GP questionnaires. Confirmation and date of diagnosis was requested as well as the exam used to determine the diagnosis and the information used by the GP for confirmation. The authors made a distinction between GPs who only reviewed electronic medical records to confirm/refute diagnoses and those who used additional sources of information (e.g. hospital letters, consultation letters, paper chart). They calculated a PPV for those whose reference standard was based solely on electronic medical records and those based on electronic medical records as well as other information. Results were similar when compared. | Low |
| | Did all patients receive the same reference standard? | Yes, for all patients for which a response was received, the reference standard was the GP questionnaire. | Low |
| | Were all patients included in the analysis? | The response rate was 81% (719/888). | Low |

| Study | Criterion | Reason for decision | Bias |
|---|---|---|---|
| **Charlton, 2010[194]** | Was a consecutive or random sample of patients enrolled? | The authors attempted to validate all cases identified. The full medical records were requested for patients that were registered with a practice at the time of the study. Free-text was requested for all those patients no longer registered with a practice as well as those patients for whom the GP did not respond to the request and those for whom the GP responded but could not provide the information. For 2 individuals, the GP informed the author that neither had a congenital malformation; The full medical record for these individuals was not provided and the free-text not requested. | Low |
| | Did the study avoid inappropriate exclusions? | A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate as they related to the aims of the study, which was to examine the safety of anticonvulsants used in pregnancy. The study population included all babies born to mothers with a diagnosis of epilepsy, seizures or convulsions during the study period. Babies had to be registered and present within a practice 3 months after the end of the pregnancy. Babies that were registered but died earlier than this were included. | Low |
| | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes. | Low |
| | Is the reference standard likely to correctly classify the target condition? | The reference standard was the full medical record for those patients for whom it was available and free-text for the rest. The full medical record was considered to be more reliable than free-text. However, of the 123 patients for whom medical records were requested, >10% (n=19) resulted in no response or refusal to participate. It was considered possible that lack of response or refusal of GPs could be associated with the amount of time needed to send records and could therefore be more likely among unwell patients with large medical files but further information was needed. | Uncertain |
| | Did all patients receive the same reference standard? | The full medical record was received for some patients whilst others received full-text. This was judged to be acceptable as the authors calculated PPVs for each reference standard separately in addition to an overall PPV. | Low |
| | Were all patients included in the analysis? | The response rate for medical records was 78% (96/123). Free-text was received for all individuals it was requested for. | Low |

| Study | Criterion | Reason for decision | Bias |
|---|---|---|---|
| **Charlton, 2015[192]** | Was a consecutive or random sample of patients enrolled? | Yes, the authors attempted to validate all 622 identified malformations. | Low |
| | Did the study avoid inappropriate exclusions? | A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate as they related to the aims of the study which was examine the safety of asthma medication used in pregnancy. The study population included singleton live-births, terminations and stillbirths that belonged to women with an asthma diagnosis during the study period. Syndrome-related major congenital malformations were excluded as they were unlikely to be drug induced. | Low |
| | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes. | Low |
| | Is the reference standard likely to correctly classify the target condition? | The reference standard was GP questionnaires, supportive codes in the electronic record (e.g. codes for related surgeries) and supportive free-text. Further information was unavailable. It was therefore not known what information the GP used to confirm or refute diagnoses, or what information was in the free-text, and overall it was unclear whether these sources of information would be likely to correctly classify the target condition. | Uncertain |
| | Did all patients receive the same reference standard? | No, authors used a mixture of GP questionnaires, free-text and supportive medical codes. However, only an overall PPV was published (not separate PPVs stratified by the reference standard used). | High |
| | Were all patients included in the analysis? | The response rate for questionnaires was 87.6% (127/145) based on personal communication with the author. It was assumed free-text and supporting medical codes were used for remaining cases. | Low |

| Study | Criterion | Reason for decision | Bias |
|---|---|---|---|
| **Jick, 1997[208]** | Was a consecutive or random sample of patients enrolled? | The authors commented that there was complete concordance between GP questionnaires and congenital malformations identified in the study population. The authors did not state how many questionnaires were sent out for the 16 cases identified but it was assumed that this information was requested for all. | Low |
| | Did the study avoid inappropriate exclusions? | A number of exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate as they related to the aims of the study which was examine the safety of anticonvulsants used in pregnancy. Conditions were limited to those that could be drug-induced and identified around the time of birth. | Low |
| | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes. | Low |
| | Is the reference standard likely to correctly classify the target condition? | The reference standard was GP questionnaires. Confirmation and date of diagnosis was requested. It was unclear, however, what information was used to confirm or refute diagnoses. | Uncertain |
| | Did all patients receive the same reference standard? | Yes, all patients received a GP questionnaire. | Low |
| | Were all patients included in the analysis? | The authors commented that there was complete concordance between GP questionnaires and congenital malformations identified in the study population. Based on this, we assumed they received information on all cases. | Low |

| Study | Criterion | Reason for decision | Bias |
|---|---|---|---|
| **Broadhurst 2019[222]** | Was a consecutive or random sample of patients enrolled? | Yes, the authors attempted to validate all 754 patients with a diagnosis of developmental hip dysplasia in CPRD. | Low |
| | Did the study avoid inappropriate exclusions? | Exclusions were applied to obtain the final study population. However, these criteria were not considered inappropriate. For example, patients had to be eligible for linkage to HES as this was the main data source used for validation. Patients were excluded if they had specific neuromuscular diseases or a traumatic hip dislocation as the study question did not include secondary hip dislocations or syndromes. | Low |
| | Were the index test results interpreted without knowledge of the results of the reference standard? | Yes. | Low |
| | Is the reference standard likely to correctly classify the target condition? | The authors developed a validation algorithm that first searched for specific supportive diagnostic or procedural codes in inpatient HES data in the two years before or after the diagnosis in CPRD. If this information was unavailable, the algorithm searched for less specific codes in HES that were considered likely to relate to developmental hip dysplasia (e.g. *'clicking hip'*). If no such evidence was available, evidence of a hospital admission within six months of the CPRD diagnosis was searched for. If no evidence in HES was identified, the authors searched for supportive evidence in CPRD in the following order: 1) ≥3 orthopaedic follow-up hospital attendances, 2) ≥2 diagnostic codes in CPRD, 3) other supportive evidence such as codes for a clicking hip or for splinting of a dislocated hip.<br><br>Inpatient HES and CPRD electronic data were considered sub-optimal reference standards in this study for the following reasons:<br>1) The study included children with a diagnosis of developmental hip dysplasia in CPRD prior to 1997. As HES data are only available from 1997 onwards, diagnoses and procedures recorded during hospital admissions prior to this would not be captured.<br>2) Children not receiving surgical treatment and managed in outpatient hospital departments would not be captured in inpatient HES data.<br>3) GPs may not encode the diagnosis repeatedly or encode all orthopaedic follow-up attendances for children managed in secondary care but may instead simply scan in hospital letters (which are not available to researchers as part of the CPRD electronic data). Supportive evidence would therefore be captured sub-optimally in CPRD.<br>4) It was unclear if the study population included children whose first record of developmental hip dysplasia occurred less than a year after registering with the practice. Such records could be retrospective recordings of an historical diagnosis[243] and the presence of further supportive evidence in CPRD would not be expected. If no surgical treatment was required, supportive evidence in inpatient HES data would also not be expected. | High |
| | Did all patients receive the same reference standard? | No but results were appropriately stratified by reference standard. | Low |
| | Were all patients included in the analysis? | Yes. | Low |

**Supplementary Table 3 - Comparisons of congenital malformations prevalence in electronic health records with prevalence derived from external data sources.**

| Author | Malformations examined | Data sources compared | Comparison measures | Period of Comparison | Prevalence Ratio (95% CI) | Summary |
|---|---|---|---|---|---|---|
| **Sokal, 2014**[202] | Major | THIN vs published literature using data from the North of England Congenital Anomaly Register. | Male: Female prevalence ratios | THIN: 1990-2009<br><br>Register data: 1998-2003 | THIN sex prevalence ratio: 1.26 (1.23-1.30)<br><br>Register sex prevalence ratio: 1.15 (1.11-1.19) | • The overall sex prevalence ratio was slightly higher in THIN compared to published data from the Register, although the latter didn't include chromosomal anomalies, sex-linked urinary malformations and sex-linked genital malformations.<br>• Sex prevalence ratios for system-specific subgroups in THIN were similar to those from the Register except for bladder exstrophy/epispadias for which the ratio was greater in THIN. |
| **Sokal, 2013**[201] | Major | THIN vs EUROCAT | Prevalence per 10,000 live-births | 1990-2009 | 1.18 (1.16-1.20) | • Overall THIN prevalence > EUROCAT.<br>• Prevalence ratios for system-specific subgroups varied, with the following having a lower prevalence in THIN: urinary defects, orofacial clefts, digestive defects, abdominal wall defects, chromosomal and genetic malformations, malformations due to known teratogens and other malformations.<br>• Heart, limb, genital, musculoskeletal and eye malformations had higher prevalence in THIN; Nervous system, respiratory and ear, face and neck malformations had similar prevalence in THIN and EUROCAT.<br>• Prevalence in THIN increased with follow-up time. |
| **Tata, 2008**[206] | Major | THIN vs EUROCAT | Prevalence per 10,000 live-births vs prevalence per 10,000 births[b] | 1988-2004 | N/S | • Overall THIN prevalence similar to EUROCAT prevalence: 289 per 10,000 live-births vs 238 per 10,000 births[b]. |
| **Devine, 2008**[209] | Neural tube | CPRD vs National Congenital Anomaly System | Annual prevalence per 10,000 pregnancies[a]. | 1991-2003 | N/S | • Overall CPRD prevalence > National Congenital Anomaly System: 1.7 - 6.5 per 10,000 pregnancies vs 1 - 2 per 10,000 pregnancies<br>• Prevalence estimates closer after 1997.<br>• Confidence intervals for prevalence in CPRD included estimates from the National Congenital Anomaly System across all years. |
| **Wurst, 2007**[218] | Heart | CPRD vs National Congenital Anomaly System<br><br>CPRD vs EUROCAT | Annual prevalence per 10,000 live-births | 2001<br>2002<br>2003<br><br>2001<br>2002<br>2003 | 2.79 (2.37–3.30)<br>2.78 (2.34–3.31)<br>2.20 (1.83–2.64)<br><br>1.48 (1.21–1.83)<br>1.29 (1.05–1.59)<br>1.42 (1.15–1.77) | • Overall CPRD prevalence > National Congenital Anomaly System.<br>• Overall CPRD prevalence > EUROCAT.<br>• For some specific heart defects, particularly those that were rare, prevalence was lower in CPRD.<br>• Prevalence in CPRD increased with follow-up time. |

[a]Included live-births, stillbirths and terminations; [b]EUROCAT data included live-births, stillbirths, foetal deaths and terminations. Abbreviations: CPRD, Clinical Practice Research Datalink (formerly the General Practice Research Database); THIN, The Health Improvement Network; N/S, Not Specified; CI, Confidence Interval

## 2.3 Summary and conclusions

This chapter described a systematic review of 54 studies that identified congenital malformations in UK electronic health records. Congenital malformations were identified from primary care data in 36 studies and secondary care data (with some also using birth and death records) in 18. No study used linked primary care, secondary care and mortality data to increase the ascertainment of these conditions. Studies using primary care data frequently referred to published guidelines to aid the development of case definitions and code lists, and often used Read codes beyond those in the dedicated 'P' chapter for congenital malformations. Conversely, studies using secondary care data did not rely on published guidelines but did rely on ICD-10 codes in the dedicated 'Q' chapter for congenital malformations. The positive predictive value of congenital malformation diagnoses in primary care data was high for any congenital malformations, major malformations and heart defects (80-100%).[187, 193, 194, 208, 216, 219] No study attempted to validate congenital malformation diagnoses in secondary care data. Further validation studies are needed for additional malformation subgroups and in secondary care data.

# Methods Section

The next four chapters comprise the methods section of this thesis.

**Chapter 3** describes the electronic health records used for this work and includes information about the way the data are collected, their structure and their quality.

**Chapter 4** describes the criteria used to define pregnancies eligible for inclusion in the studies carried out to address **Objectives 3-6**. In addition, the chapter outlines the potential confounding factors for the vaccine safety analyses (**Objectives 5-6**).

**Chapter 5** describes the steps involved in developing a comprehensive algorithm to identify MCMs in multiply-linked data (**Objective 2**). This algorithm was then used to identify MCMs in all the studies that were part of this thesis.

**Chapter 6** describes the methods used to ascertain the vaccination status (including the trimester of vaccination) of pregnant women for the vaccine safety analyses (**Objectives 5-6**).

# 3. Data Sources

Studies were conducted using CPRD GOLD primary care data (referred to as 'CPRD') linked to Hospital Episode Statistics Admitted Patient Care data (referred to as 'HES'), Office for National Statistics (ONS) mortality data and deprivation data. **Section 3.1** describes CPRD data. **Section 3.2** describes the CPRD Mother-Baby Link (MBL) which links maternal and infant records but which does not identify pregnancy episodes. **Section 3.3** describes the CPRD/LSHTM Pregnancy Register (referred to as the 'Pregnancy Register'), which was used to identify pregnancies in this work. HES, ONS mortality and deprivation data are then discussed in **Sections 3.4-3.6**. A summary of the data management involved in this thesis and an overview of the ethical approvals obtained are described in **Sections 3.7-3.8**.

## 3.1 CPRD

The CPRD was established in the UK in 1987, primarily for the purposes of pharmaco-epidemiological research.[126] At the time of this work, CPRD was among the largest collections of anonymised, longitudinal electronic health records from primary care.[126, 248] Consenting general practices across the UK collect data from patients; these data are then de-identified and transmitted to CPRD by the clinical management software system (Vision®) each month.[249] Data are provided for all patients within contributing practices with the exception of those who have opted out.[126]

At the time of this work, CPRD covered approximately 7% of the UK population and patients were thought to be broadly representative in terms of age, sex and ethnicity.[126, 250] The average follow-up time for patients was just over 5 years.[126] Patients may enter and leave contributing practices at any time and so the database itself is considered an open cohort. CPRD data can also be linked to other datasets, a process described below. CPRD data for the studies described here were extracted in September 2017 and included data up until January 2017.

### 3.1.1 Data collection and structure

General practice staff record consultations with patients on practice computers. Once a patient registers at a practice contributing to CPRD, data will be recorded until the practice stops contributing (the last collection date), or the patient dies or leaves the practice (the death or transfer out date).[126] Patient and practice files received by researchers contain pseudo-anonymised identifiers for the patient and practice and include registration, death, transfer out and last collection dates (**Table 3.1**).

Information recorded includes demographic data, diagnoses, symptoms, vaccinations, procedures, diagnostic tests and results, prescriptions, lifestyle/behavioural factors, referrals, and feedback from secondary or tertiary care providers.[126] These data are stored in the clinical, immunisation, therapy, referral and test files, with further clinical details recorded in the 'additional clinical details' file (**Table 3.1**).[126] For each recorded event in these files, an 'event date' is available which refers to the date the event occurred as entered by the GP. An additional date, the 'system date', indicates the date the recording itself was made.

Information across files is recorded in two ways: through coding systems or free-text. Different coding systems are used across different files and for different purposes. Diagnoses and other clinical data are primarily recorded using Version 2.0 Read codes.[126] Entity type codes are used to record structured data (e.g. weight, blood pressure, alcohol use, test results). Immunisation type codes in the immunisation file are used to record vaccine type. Finally, Product codes are used to record prescriptions in the therapy file.[126] The CPRD provides Read and Product code dictionaries which can be used to identify codes relating to clinical data, drugs, or vaccines of interest.[126]

Clinicians can also record patient data using free-text which includes comments made by the GP and communications received about the patient from other care providers.[126] In the past, it was possible to request anonymised free-text data for research but these data are no longer available for routine use.

**Table 3.1 - Overview of the data included in CPRD files.**

| CPRD File | Key information recorded in the file | Types of code that can be used to identify records of interest in the file |
|---|---|---|
| Practice | The practice identifier[a], the practice region (defined according to Strategic Health Authority boundaries for practices in England), the last collection date, the up-to-standard date. | - |
| Staff | The staff member identifier[a], staff member role, staff member gender. | - |
| Patient | The patient identifier[a], year of birth, month of birth (for those aged <16 years), gender, date of death, current registration date, transfer out date. | - |
| Consultation | The patient identifier[a], the staff identifier[a], the type of consultation (e.g. emergency consultation), the consultation identifier (can be used to identify different events recorded in the same consultation), the length of the consultation. | Consultation type codes |
| Clinical | The patient identifier[a], medical history, diagnoses, signs and symptoms, procedures, diagnostic tests and results, lifestyle/behavioural factors (e.g. alcohol use and smoking), demographic factors (e.g. ethnicity), the event date[b]. | Read codes, Entity codes |
| Additional Clinical Details | The patient identifier[a], further specific data relating to a record in the clinical file. | Entity codes |
| Immunisation | The patient identifier[a], type of vaccine, status of vaccination (given, refused or advised), vaccination stage, compound administered, the event date[b]. | Read codes, Immunisation type codes |
| Therapy | The patient identifier[a], the prescribed product, the quantity of the product, the daily dose, the number of days prescribed for, the event date[b]. | British National Formulary codes, Product codes |
| Referral | The patient identifier[a], the requested referral, the referral speciality, the type of referral (e.g. inpatient), the urgency of the referral, the event date[b]. | Read codes |
| Test | The patient identifier[a], the requested test, the result, the normal range of results, the event date[b]. | Read codes, Entity codes |

[a]All identifiers are anonymised; [b]The event date is the date the associated event occurred as recorded by the general practitioner.

### 3.1.2 Data quality and completeness

Although electronic health records have a number of strengths, data are collected for clinical purposes and not research. Data collection and completeness can vary for different variables and may be affected by changes in clinical practice or guidelines over time.

Basic completeness and quality checks are carried out before data are released to researchers by CPRD.[126] An up-to-standard date denotes the time-point after which practice data are considered acceptable for research use.[126, 249] This date is based on the continuity of the recording of clinical and mortality data in the practice. If there are significant gaps in the recording of such data, the up-to-standard date is assigned to the earliest date after this gap. Patients are denoted as being acceptable for research purposes or not based on the continuity of their follow-up, and incomplete or implausible records.[126, 249] For example, patients lacking a recorded birth year or patients aged over 115 years are not deemed 'acceptable' for research purposes and it is advised that such patients are excluded from studies.

In 2004, the Quality and Outcomes Framework (QOF) was introduced which financially incentivized GPs to record a number of key data.[126] These data include chronic diseases such as diabetes and asthma, as well as other data of public health importance such as obesity and smoking status. The completeness of these data in CPRD has improved since the introduction of the QOF.[126] The QOF is reviewed annually and indicators may be added or removed. Patient ethnicity, for example, was added to the QOF in 2006/07 and removed in 2011/12.[251] This change resulted in new patients having their ethnicity recorded in more than 90% of practices and highlights the potential for completeness of data to be affected by changes in the QOF.[251]

The validity of diagnoses recorded in the CPRD have been examined in a number of studies. A systematic review in 2010 examined the validity of 183 unique diagnoses.[180] Across all diseases, a median of 89% of cases were confirmed (with a range of 24-100%).[180] However, the authors of the systematic review noted that the methods used in validation studies were often insufficiently described.[180] For example, few of the validation studies reported the types of

codes used to identify diagnoses so it was not possible to validate specific code lists or algorithms. Furthermore, validation studies generally examined diagnoses among populations that were highly specific (e.g. populations receiving particular treatments) or that had other supportive evidence of the diagnosis in question in their records to begin with.[180] Finally, the authors comment that although the positive predictive value (PPV) of validation studies may be high, this may not be the case for other validity measures such as sensitivity, specificity and negative predictive value.[180] The PPV for congenital malformation diagnoses is high overall and such validation studies are described in **Chapter 2**.[187, 193, 194, 208, 216, 219]

The validity of recorded diagnoses may also be affected by the time at which they are recorded. As described earlier, the 'event date' for a diagnosis (or other clinical event) is entered by the GP. Whilst this date should reflect the date the event occurred, GPs may instead use the date of data entry which can have implications. The incidence of diagnoses may be overestimated, for example, in the first few months after a patient registers with a practice.[243] In such cases, existing conditions may be recorded as new events when the patient registers with a new practice. Alternatively, past or chronic events may only be recorded for the first time some months after a patient registers. For MCMs in the work described here, the above issues were not considered to be a cause for concern because infants were followed-up from delivery in all studies. However, potential confounders relating to the mother could be under-recorded in the first few months after her registration with a practice. In addition, pregnancy data recorded shortly after registration could relate to the woman's obstetric history. Finally, it was important to consider that the 'event date' associated with a congenital malformation or vaccination record might not necessarily be the true date the diagnosis or vaccination occurred.

### 3.1.3 Linkage to other patient data

Patient-level CPRD data can be routinely linked to other datasets (**Figure 3.1**).[126] Linkage can be provided to hospitalisation data, mortality data, deprivation data and disease registries.[126] For linkage to be carried out, practices that contribute data to the CPRD have to consent. Currently, 58% of practices contributing data to the CPRD have consented, all of which are based in England.[126] Patients within consenting practices are eligible for linkage provided they do not opt-out and have the required information for the linkage process. Patient eligibility for linkage is not necessarily the same for all linkages.[252] Despite the above restrictions, patients with linked data have been shown to be broadly representative of those in CPRD[253, 254].

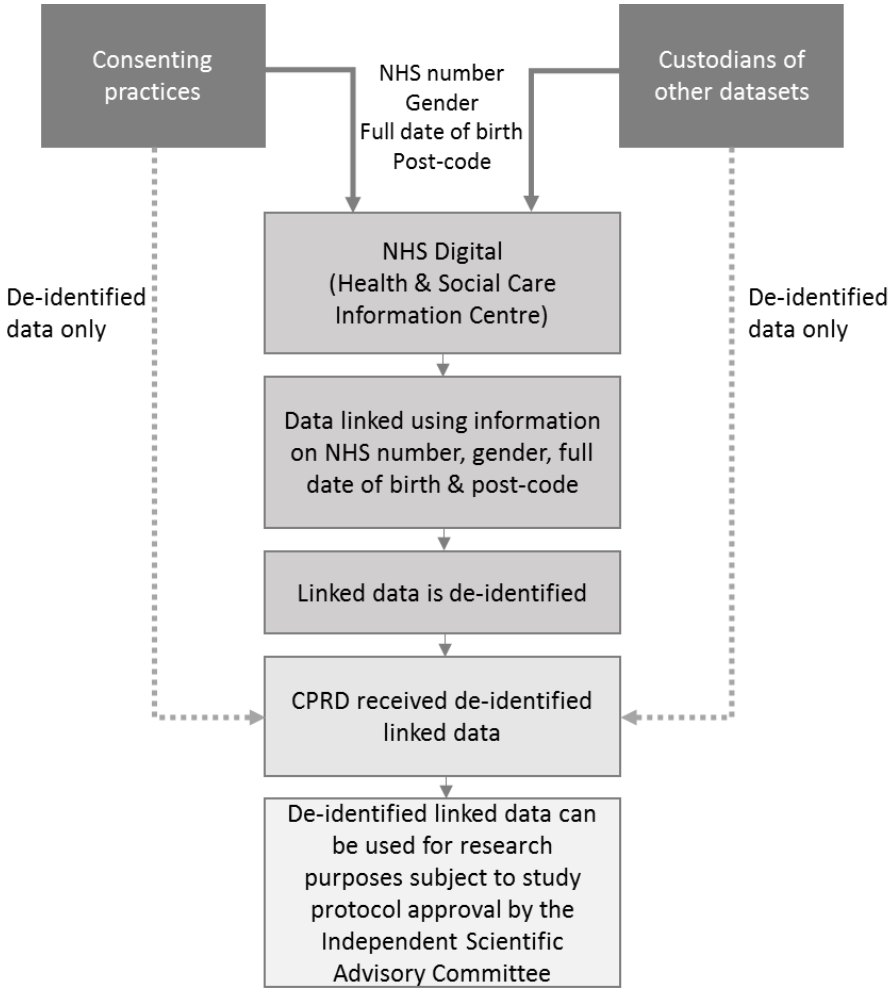



**Figure 3.1 - Linkage of CPRD data to other datasets.** Primary care records are linked to other datasets (e.g. hospital admission data) by NHS digital through the use of the patient NHS number, gender, date of birth and post-code. Following linkage, de-identified data are received by CPRD. Unlinked de-identified data can also be received by CPRD directly from consenting practices or from the custodians of other databases.

Linkage between primary care records and other datasets depends on the matching of patient identifiers (**Figure 3.1**).[252] As CPRD does not receive or hold any patient identifiable data, deterministic linkage is carried out by NHS Digital (also known as the Health and Social Care Information Centre) - a trusted third party and statutory body permitted to receive and oversee such data.[252] Once linkage has been carried out, NHS Digital provides CPRD with de-identified linked data.[252] Linked data requested for the work described here are described in **Sections 3.4-3.6.**

## 3.2 The Mother-Baby link

CPRD provide a Mother-Baby Link (MBL) which contains a list of mothers and their linked live-born infants. The linkage involves the identification of deliveries amongst women aged 12-49 years, the identification of patients born after 1986, and the joining together of the two datasets by practice and family number (a practice-specific number based on residence and used to identify individuals that live in the same household). Links are kept if the delivery date and estimated infant birth date are ≤60 days apart. Because full birth dates are not available in CPRD, the birth date of each potential infant is estimated to be the 15$^{th}$ of the month of birth. If no month of birth is available, the mid-point of the year of birth (June 30$^{th}$) is used. Multiple infants with the same birth date and linked to the same mother are included in the MBL, these are considered to be siblings that were part of the same live-birth delivery.

Some deliveries and infants are excluded from the linkage process. Deliveries are excluded if they were recorded: more than a year before the woman registered at a practice, after they left the practice or after the practice ended data collection for CPRD. Infants are excluded if they were born before 1987, if their registration at a practice occurred before their birth year or if their birth year occurred after the practice ended data collection for CPRD.

## 3.3 The CPRD/LSHTM Pregnancy Register

Whilst the MBL enables linkage of maternal and live-born infant records, it does not enable the identification of complete pregnancy episodes. Pregnancy timings are not recorded systematically in CPRD.[255] A number of algorithms have therefore been developed to identify and characterize pregnancies in CPRD but are limited because they either do not attempt to estimate the start of pregnancy, do not utilize all available pregnancy data to determine timings or do not capture those pregnancies without a recorded outcome.[256-260]

The CPRD/LSHTM Pregnancy Register was developed to systematically identify all pregnancy episodes in CPRD and address the limitations of previous approaches.[255] The initial step in the algorithm was to identify the first and subsequent live-birth or stillbirth delivery records for each woman. Following this, the start of pregnancy was estimated from data in the following order, depending on availability: the projected date for delivery as recorded by the GP, the estimated conception date, the last menstrual period, the gestational age as indicated in antenatal records or the gestational age at delivery.[255] If no such data were available, the pregnancy start was imputed from the delivery record using a fixed duration assigned according to the pregnancy outcome. Antenatal records were then assigned to each delivery. This process was repeated for other pregnancy outcomes (such as early losses) and those pregnancies with no recorded outcome.

The Pregnancy Register identifies all pregnancies occurring since 1987 among women aged 11-49 years in CPRD.[255] Estimates of the pregnancy start date, end date and trimester timings are provided. The start of the first trimester is defined as the date of the last menstrual period and runs through to the end of week 13 of the pregnancy. The second trimester is defined as week 14 through to the end of week 26, whilst the third trimester is defined as week 27 through to the delivery date. The type of information used to estimate the delivery date and pregnancy start date are also provided.

The Pregnancy Register includes information on the pregnancy outcome (**Table 3.2**) and additional information on whether there was any evidence the pregnancy resulted in a pre-term, post-term or multiple delivery. Live-birth pregnancies are linked to single infant identifiers (and, therefore, the infant's records) if linkage is available from the MBL (**Section 3.2**). For multiple pregnancies resulting in more than one live-born infant, additional infants may be identified from the MBL. As the Pregnancy Register also links pregnancy episodes to maternal records, the effect of exposures in the mother during pregnancy can be followed-up in the infant. In some cases, live-births are not linked to infant records. This is discussed further in **Section 4.3.8**.

Internal validation of the Pregnancy Register is ongoing. However, thus far, validation against linked electronic maternity records in hospitalisation data has shown that most pregnancies are well-captured in the Pregnancy Register.[255]

**Table 3.2 – Pregnancy outcomes recorded in the CPRD/LSHTM Pregnancy Register.**

| Pregnancy outcome | Description |
|---|---|
| Live-births with linked infant records | Pregnancies ending in delivery and with a linked infant identified in the Mother-Baby Link (**Section 3.2**). |
| Live-births without linked infant records | Pregnancies ending in delivery and with no linked infant identified in the Mother-Baby link. (reasons for lack of linkage are described in **Section 4.3.8**). |
| Stillbirths | Pregnancies resulting in foetal death after 24 completed weeks of pregnancy. |
| Miscarriages | Pregnancies resulting in foetal death before 24 completed weeks of pregnancy. |
| Terminations/Probable terminations | Pregnancies resulting in or likely to have resulted in a termination based on available evidence in the maternal records. |
| Unspecified losses | Pregnancies resulting in miscarriages or terminations. Evidence in the maternal record was not specific enough to distinguish between the two. |
| Deliveries based on late pregnancy records | Pregnancies for which there were maternal antenatal records indicating an imminent delivery (e.g. '*premature rupture of membranes'*) but for which no delivery record was available. |
| Ectopic pregnancies | Pregnancies in which implantation of the fertilized egg did not occur in the uterus. |
| Molar pregnancies | Pregnancies in which a foetus does not develop. |
| Blighted ovum pregnancies | Pregnancies in which the embryo fails to develop. |
| Outcome unknown pregnancies | Pregnancies for which the outcome was not known (reasons for this are described in Section **4.3.6**). |

## 3.4 HES

The HES database was established in 1989 and contains information on secondary care provided at NHS-funded hospitals in England.[261] Since 1997, it has been possible to link CPRD to HES Admitted Patient Care data for the purposes of research.[262] CPRD records are linked to the full HES record, and so linked data include all past hospital admissions ever recorded for the patient, and any admissions occurring after a patient has transferred out of CPRD.

HES data are updated and published according to the financial year.[177] Studies described in this thesis used the 14th version of HES linked to CPRD which covered the period between 1st April 1997 and 31st March 2016. Only admitted patient care data were requested. Outpatient records were not requested as data completeness is currently poor for diagnoses and procedures.[261]

### 3.4.1 Data collection and structure

In HES data, the period during which a patient is at a particular hospital is known as a 'spell' (**Figure 3.2**).[261] The admission date marks the beginning of the spell whilst the hospital discharge date marks the end. The discharge date can be a result of the patient being discharged from care entirely, or may be due to the death of the patient or their transfer to a different provider (e.g. another hospital) for further care.[261] A spell can be further divided into periods known as 'episodes'. Each time the consultant or clinical team responsible for the patient changes, a new episode is generated (**Figure 3.2**).[261]

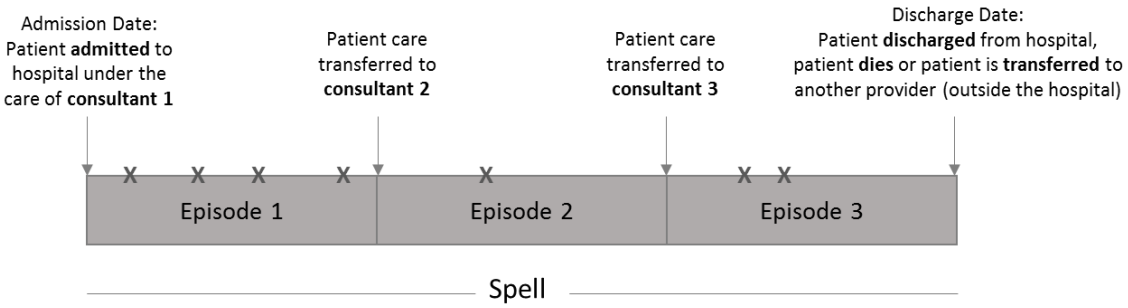



**Figure 3.2 - Spells and episodes of care in HES data.**

Following inpatient stays or day case admissions, diagnoses and procedures from case notes and discharge summaries are encoded by trained clinical coders for hospital reimbursement purposes.[263] Episode data available for researchers hold up to 20 diagnoses, recorded using the 10th version of the International Classification of Diseases (ICD-10), and up to 24 procedures recorded using version 4.6 of the UK Office of Population, Census and Surveys classification (OPCS-4).[261] Specific diagnosis dates are not provided in HES, although dates of procedures are recorded.

A number of data files are available for admitted patient care from HES. For this work, three files were used: the patient file, the file containing all diagnoses by episode and the file containing all procedures by episode (**Table 3.3**). Diagnoses and procedures were extracted from the latter two files, respectively.

**Table 3.3 - Overview of the data included in HES files.**

| HES Admitted Patient Care Files | Information recorded in the file | Types of code that can be used to identify records of interest |
|---|---|---|
| Patient | The patient and practice identifiers[a], ethnicity, an indicator for the quality of the match between HES and CPRD in the linkage process. | - |
| Diagnoses, by episode | The patient identifier[a], the spell number, the episode identifier, dates relating to the start and end of each episode, diagnoses, the order of each diagnosis within an episode (up to 20 can be recorded per episode). | ICD-10 |
| Procedures, by episode | The patient identifier[a], the spell number, the episode identifier, the admission and discharge dates, dates relating to the start and end of each episode, the procedure (up to 24 can be recorded per episode), the order of each procedure within an episode, the date of the procedure. | OPCS-4 |

[a]All identifiers are anonymised

### 3.4.2 Data quality and completeness

HES data were initially established for the purpose of informing decisions around the delivery and management of services.[261] Today, the primary purpose of HES is to provide a structure for reimbursement and this has resulted in an incentive for improved data quality and completeness.[261] Data quality is generally thought to have improved with time; between 2001

and 2011, the accuracy of primary diagnoses is thought to have increased from 74% (IQR, 59-92) to 96% (IQR, 89-96), p=0.02.[261]

## 3.5 ONS Mortality Data

In England and Wales, all deaths and their causes must be registered.[178] For the purposes described in this thesis, linkage to ONS mortality data was requested. The 14th version of ONS mortality data was used, covering the period between the 2nd January 1998 and 17th April 2017. Similarly to linked CPRD and HES data, linked CPRD and ONS data include details of deaths occurring even after a patient has transferred out of the practice and follow-up in CPRD has ended. Linked ONS data will not, however, include details about the deaths of patients that have occurred before registration with a contributing practice.

### 3.5.1 Data collection and structure

After a death has occurred, it is usually certified by the attending doctor through a 'Medical Certificate Of Cause Of Death' which includes the direct and underlying causes of death, and contributory factors.[178] In almost 80% of cases, the causes of death are encoded by specialist software.[178] If the cause of death is unclear, the case is referred to a coroner for further investigation and causes are encoded manually.[178]

Neonatal deaths (i.e. deaths occurring <28 days after delivery) and stillbirths are recorded using a separate certificate in England and Wales.[264] These certificates allow doctors to record conditions in the foetus/infant or mother that contributed to the death as well as other non-clinical factors.[265] As these deaths are recorded differently, they may be more or less likely to record congenital malformations as a cause of death compared to death certificates in later infancy or childhood.

With the exception of cases that are referred to the coroner, it is a legal requirement in England for death certificates to be received by the local death and birth registrar within 5 days of the date of death.[266] Although the timeliness of death registrations has decreased since

2011, 92% of deaths are registered within a month of death.[267] Timeliness of registrations can be affected by the age, circumstances and cause of death. In 2018, for example, 14% of neonatal deaths were certified by a coroner and 7% were subject to a coroner's inquest, compared to 21% and 11% respectively for infant deaths.[265] This reflects the fact that nearly all neonatal deaths occur in hospitals.[265]

Linked ONS mortality data are provided to researchers in a single file. This file contains patient and practice identifiers used in CPRD. It contains the underlying cause of death, coded using ICD-10, as well as the date of death. For each death, up to 15 other causes of non-neonatal death and up to 8 causes of neonatal death are provided.

### 3.5.2 Data quality and completeness

Mortality data in the UK are considered to be of high quality, completeness and coding accuracy.[268] Quality checks are built in at various stages of the data collection process.[178] Registrars, for example, check that the death occurred in the last year and that the death certificate is correctly filled in. They may also cross-check information such as age against birth records. The use of an automated cause coding system ensures the process of determining the underlying cause is standardized across the population.[178] When data are received by ONS, further checks are carried out such as checking that the birth and death dates are consistent with each other.

## 3.6 ONS Deprivation data

For the purpose of the studies described in this thesis, CPRD data were linked to the 2015 ONS Index of Multiple Deprivation (IMD) at the patient and practice levels. The IMD is a measure of relative deprivation between regions in England.[269]

### 3.6.1 Data collection and structure

To calculate IMD, England is first divided into lower-layer super output areas (LSOAs) which have an average of 1,500 residents each. The IMD is then calculated for each of these LSOAs

based on a number of indicators which fall into seven deprivation domains: income, employment, health and disability, education, skills and training, crime, living environment, and housing and services.[269] The LSOAs are then ranked and divided into quintiles, with the first quintile containing the least deprived LSOAs and the last quintile containing the most deprived. Following requests for linkage to deprivation scores, researchers are provided with files that indicate which quintile a patient or practice belongs to based on their post-code. To ensure anonymity, investigators do not have access to the post-codes or IMD scores. In some cases, a patient's post-code cannot be mapped to a LSOA, in which case they will not be assigned to a quintile. In such cases, the quintile of the practice can be used instead.

### 3.6.2 Data quality and completeness

It should be noted that the IMD score is calculated at the level of the LSOA and so may not necessarily correspond to the deprivation status of an individual. Whilst most patients eligible for linkage to ONS deprivation data have post-codes that can be mapped to an LSOA, in some cases this mapping is not possible. This might occur, for example, because the patient has a non-geographic post-code, or a post-code that is not in England. In such cases, the practice post-code can be used.

## 3.7 Data management

The Pregnancy Register was first used to identify eligible pregnancies for the different studies, a process described in **Chapter 4**. To identify MCMs, Read, ICD-10 and OPSC-4 code lists were first developed using EUROCAT guidelines. To identify relevant Read codes, the CPRD Medical Browser was searched by using free-text terms and by searching hierarchically. The ICD-10 and OPCS-4 dictionaries were also searched for relevant codes. Final code lists were agreed with a consultant neonatologist and used to search the records of all eligible infants (**Appendix 2**). MCM evidence was searched for in CPRD (among clinical, referral and test files), HES admissions data (among files for diagnoses and procedures) and ONS mortality data (including all causes of death). The process of identifying MCMs is further described in **Chapter 5**.

Initial Read codes, immunisation type codes and Product codes for influenza vaccination were provided by Sara Thomas (**Appendix 6**). These were used to identify evidence of influenza vaccination in the mother by searching the CPRD clinical, immunisation and therapy files, respectively. In the clinical file, evidence of a vaccine being received, refused or advised was based on the Read code. In the immunisation file, codes were assessed in conjunction with an 'immunisation status' variable to determine whether the vaccine was received, refused or advised. In the therapy file, where records are generated automatically following a prescription, all codes were assumed to relate to the vaccine being received. Further information on determining vaccination status is described in **Chapter 6**.

All data management and analyses were carried out using Stata® version 14.2.

## 3.8 Ethics

The studies in this thesis received ethics approval from the LSHTM ethics committee (reference 13720) and from the Independent Scientific Advisory Committee of the Medicines & Healthcare Products Regulatory Agency (reference 17_040R).

## 3.9 Chapter Summary

This chapter described the data sources used in this thesis. In the following chapters, the criteria used to identify study populations, major congenital malformations and vaccinations are described.

# 4. Identifying eligible pregnancies and defining study populations

## 4.1 Introduction

This chapter describes the inclusion and exclusion criteria for the study populations in **Objectives 3-6**. These objectives are first summarized below.

**Objective 3: To establish the value of stand-alone and linked CPRD, HES and ONS data in identifying infants with MCMs, the unique contribution of each data source and the agreement between them.**

The prevalence of MCMs among live-born infants in the first year of life was compared in stand-alone CPRD, stand-alone HES, linked CPRD and HES (CPRD-HES) and linked CPRD, HES and ONS (CPRD-HES-ONS). The proportion of infants with an MCM that had evidence of their condition in single and multiple data sources was then quantified.

**Objective 4: To compare the prevalence of MCMs in stand-alone and linked CPRD, HES and ONS, using the methods developed for this thesis, with prevalence in external data sources.**

The prevalence of MCMs among live-born infants in the first year of life in stand-alone CPRD data was compared with published prevalence data from 'The Health Improvement Network' (THIN), another UK database of primary care records. Prevalence in stand-alone and linked data was then compared with publicly available prevalence rates from EUROCAT registries.

**Objective 5: Assessing the safety of SIIV with respect to MCMs in live-born infants, by trimester of vaccination.**

The assessment of the safety of SIIV was initially planned to include MCMs identified among live-births, miscarriages, stillbirths and terminations. MCMs would be identified by searching for evidence in maternal records during the antenatal period and, for live-births, by also searching for evidence in the infant's records postnatally. However, an examination of pregnancy losses and terminations suggested that the extent of under-recording of antenatal

diagnoses, their poor validity and the low uptake of vaccination would likely bias the measure of effect (**Section 8.6**). Objectives were revised so that analyses were restricted to live-births and MCMs were identified postnatally from infant records. Live-births without linked infant records were not included as the outcome could not be ascertained (**Section 8.8**).

A historical cohort study was carried out to examine the association between SIIV receipt during pregnancy, by trimester and overall, and MCMs among live-born singletons. The primary analysis examined any MCMs identified in the first year of life using linked CPRD, HES and ONS. Secondary analyses examined any MCMs, major limb defects and major congenital heart defects in early childhood.

**<u>Objective 6:</u> Assessing the safety of PIIV with respect to MCMs in live-born infants, by trimester of vaccination.**

A historical cohort study was used to examine the association between PIIV receipt during pregnancy, by trimester and overall, and any MCMs among live-born singleton infants. Analyses were carried out for MCMs identified in the first year of life in linked CPRD, HES and ONS data. A secondary analysis considered MCMs recorded in early childhood.

The criteria used to define potentially eligible pregnancies were the same for all objectives and are outlined in **Section 4.2**, with **Section 4.3** describing further pregnancy-related exclusion criteria. Pregnancies resulting in miscarriages, stillbirths, terminations and live-births without linked infants were not excluded at this point. **Section 4.4** summarizes the exclusion of pregnancies with evidence of an MCM with a known cause (e.g. a chromosomal abnormality) or evidence of a congenital infection known to increase the risk of MCMs. These exclusions were also applied to all study populations. **Section 4.5** outlines additional, study-specific exclusion criteria for each objective.

The methods used to identify MCMs in the data sources used in this thesis and the methods used to identify the vaccination status of pregnant women are detailed in the next two

chapters of the methods section. Further details on study design, methods and statistical analyses for **Objectives 3-4** are provided in **Chapter 7** whilst details for **Objectives 5-6** are provided in **Chapters 8-9**.

## 4.2 Identifying potentially eligible pregnancies

Pregnancies that were potentially eligible for inclusion in analyses were identified from the Pregnancy Register.

### 4.2.1 Criteria for potentially eligible pregnancies

The estimated delivery date of each pregnancy had to occur between January 1, 2009 and March 31, 2016 (the last date that linked data were available) (**Figure 4.1**). Pregnant women had to conform to CPRD data quality standards; they had to be considered 'acceptable' for research purposes and had to be registered at an up-to-standard practice (**Section 3.1.2**). They were also required to be registered with a practice at least six months before the start of their pregnancy. This criterion was chosen to improve the ascertainment of potential confounders, as information on maternal characteristics, behaviours and medical history could be under-recorded in the immediate period after registration. Pregnant women had to be eligible for linkage to HES to maximize the ascertainment of confounders (such as ethnicity that may be incompletely recorded in CPRD) and MCMs recorded in the antenatal period (**Section 5.6**). For the subset of pregnancies that resulted in a live-birth delivery with a linked infant, the infant also had to conform to CPRD data quality standards (**Figure 4.1**). Live-born infants had to be eligible for linkage to HES and ONS mortality data as MCMs were identified in these data sources as well as in CPRD.

### 4.2.2 Data extraction for potentially eligible pregnancies

CPRD data for potentially eligible mothers and infants were extracted from the January 2017 data build and linked to the 14$^{th}$ version of HES and, for infants, ONS mortality data. Patient level deprivation data were also obtained for those mothers eligible for linkage.

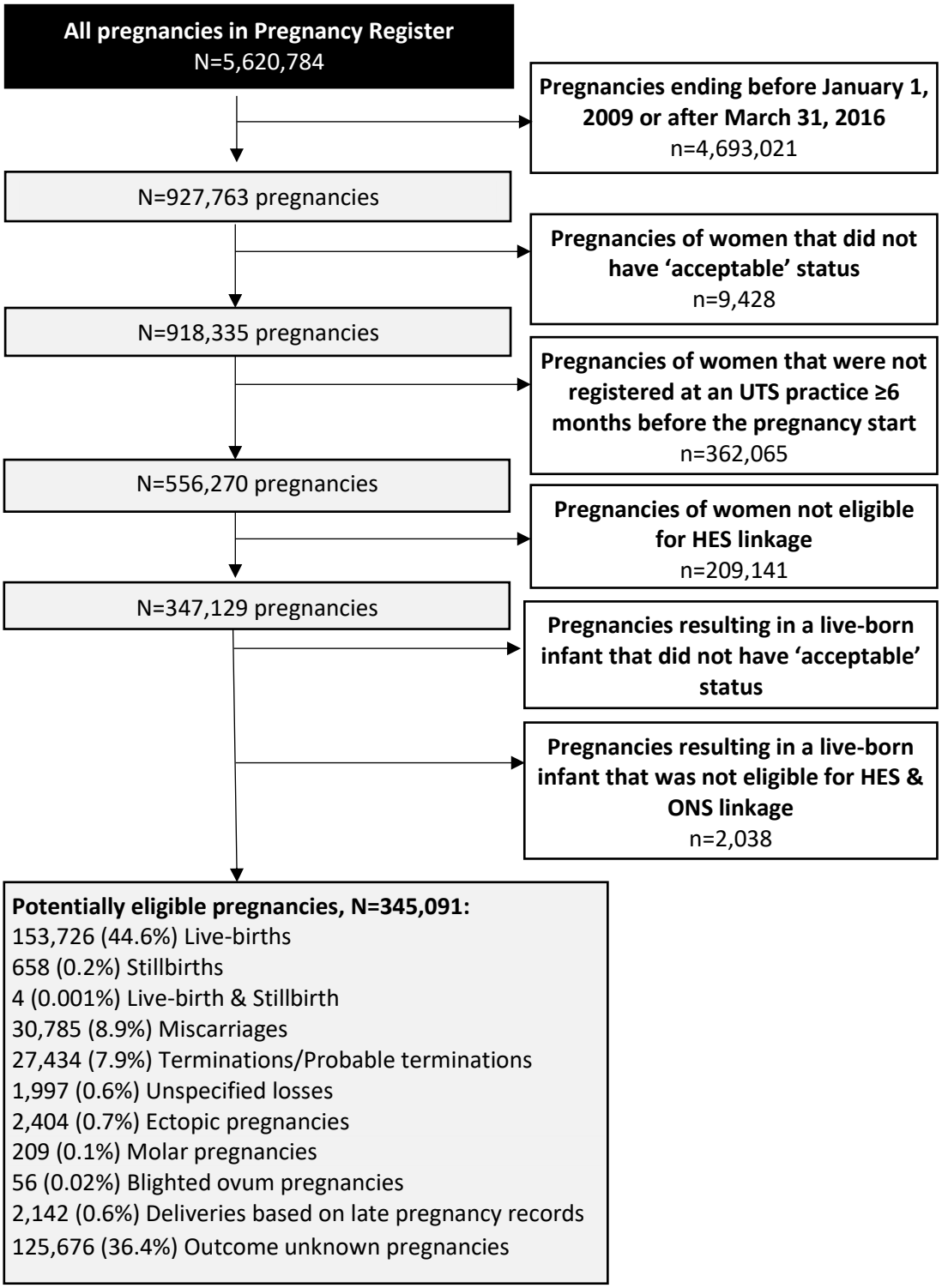



**Figure 4.1 - Identification of potentially eligible pregnancies.** Abbreviations: UTS, up-to-standard date; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data.

## 4.3 Pregnancy-related exclusion criteria

Following the identification of potentially eligible pregnancies, the Pregnancy Register was explored and further pregnancy-related exclusion criteria were applied (**Figure 4.2**).

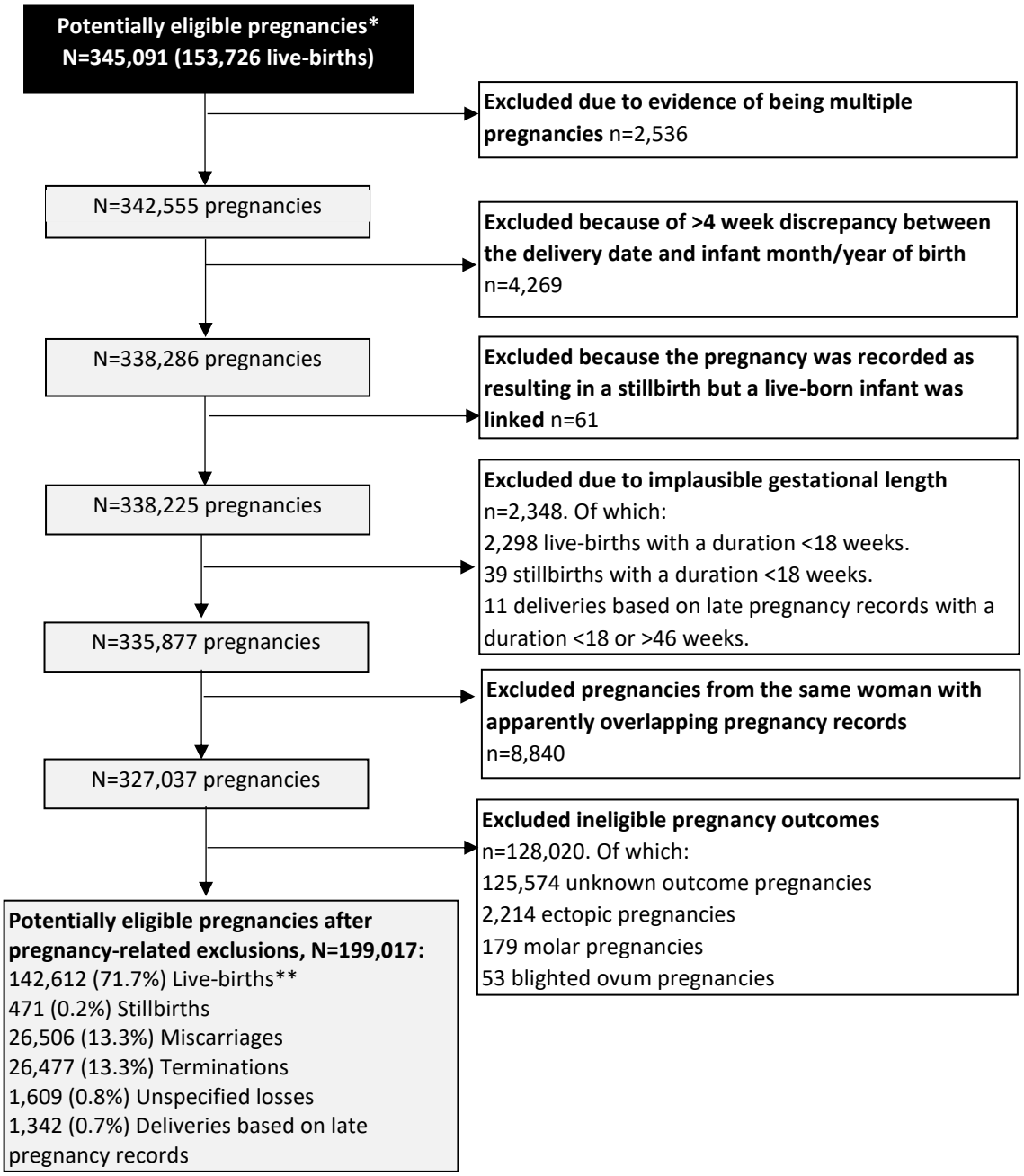



**Figure 4.2 - Potentially eligible pregnancies after the application of pregnancy-related exclusion criteria.** *Pregnancies ended between January 1, 2009 and March 31, 2016 and belonged to women who had 'acceptable' status (as defined by CPRD) and were registered at an up-to-standard practice at least 6 months before the pregnancy start. All women were eligible for HES linkage. Live-born infants also had to have 'acceptable' status and had to be eligible for HES and ONS linkage; **8.5% of live-births were not linked to infant records (n=16,949).

### 4.3.1 Multiple pregnancies

Multiple pregnancies are those with more than one foetus or infant. As described in **Section 3.3**, such pregnancies are included in the Pregnancy Register but are only ever linked to records from a single live-born infant. Analyses were therefore restricted to singleton pregnancies and multiple pregnancies were excluded.

The Pregnancy Register algorithm flags multiple pregnancies based on evidence from antenatal, delivery and infant records. At the time of this study, however, the algorithm did not use evidence from the MBL (which identifies multiple infants with the same month and year of birth born to the same mother, **Section 3.2**) and may have incompletely captured multiple pregnancies.

Relying solely on information in the Pregnancy Register to exclude multiple pregnancies was likely to be inadequate. Therefore, multiple pregnancies were first identified using information in the Pregnancy Register and this was supplemented with evidence from the MBL. In total, 2,536 multiple pregnancies were identified using information in the Pregnancy Register (n=1,460; 57.6%) and MBL (n=1,076; 42.4%), all of which were excluded **(Figure 4.2)**.

### 4.3.2 Live-birth pregnancies with a discrepancy between the delivery date and infant month/year of birth

For some live-birth pregnancies with linked infant records, the estimated delivery date in the Pregnancy Register was found to be earlier than the infant's recorded month/year of birth. Uncertainty about the delivery date could result in the misclassification of overall vaccination status, trimester of vaccination and MCMs (**Figure 4.3**).

There were a number of potential scenarios for such a discrepancy:

1. The infant's month/year of birth was incorrectly recorded as occurring later than it did.
2. The GP recorded information about a historical delivery with a current date during an ongoing pregnancy, but the true delivery occurred later on.

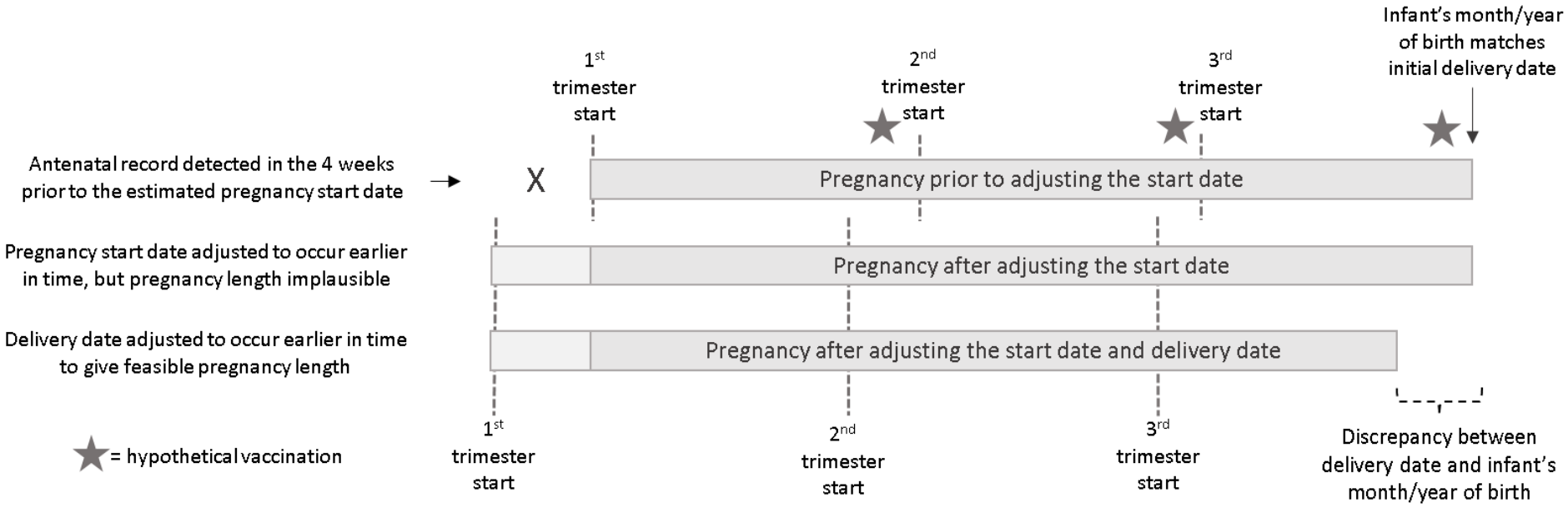



**Figure 4.3 – An example of the potential misclassification of vaccination and MCMs among pregnancies with a delivery date preceding the infant's month of birth.** The Pregnancy Register algorithm adjusts the start of the pregnancy to an earlier point in time if an antenatal record is detected in the 4 weeks prior. The delivery date may also be adjusted to preserve the estimated gestational age. This can result in the delivery date occurring earlier than the infant's month/year of birth. If this adjustment is inaccurate then the pregnancy may be misclassified as unvaccinated if a vaccine was given between the delivery date and the infant's month/year of birth. Furthermore, the trimester of vaccination may be misclassified as occurring later than it truly did. For example, a vaccination that truly occurred in the first trimester could appear to occur in the second trimester. Misclassification of MCMs could also occur; for example, if the delivery date was 8 weeks early, then the end of follow-up would occur 8 weeks before the infant's first birthday and any MCM records in the 8 weeks prior to the first year of life would be missed.

3. An antenatal record was identified by the Pregnancy Register algorithm in the 4 weeks before the start of the pregnancy. As this was unlikely to relate to a woman's previous pregnancy, the estimated pregnancy start date was adjusted by the algorithm to an earlier time-point to incorporate the antenatal record. A similar adjustment was then made to the estimated delivery date to preserve the estimated gestational age of the pregnancy (this example is used in **Figure 4.3**).

It was not possible to know whether the estimated delivery date was reliable among such pregnancies. Those with a discrepancy of >4 weeks between the estimated delivery date and the infant's month/year of birth were therefore excluded from analyses (**Figure 4.2**). As the exact date of birth of the infant is not provided by CPRD in order to preserve anonymity, the mid-point of the infant's month of birth was used to calculate the discrepancy in weeks.

### 4.3.3 Stillbirth pregnancies linked to live-born infant records

A small number of stillbirth pregnancies in the Pregnancy Register were found to be linked to live-born infant records. The Pregnancy Register relies on the MBL for linkage between mothers and infants (**Section 3.2**). As the MBL only links mothers to live-born infants (stillborn infants are never registered at a general practice and so are not included), only live-birth pregnancies in the Pregnancy Register should be linked to an infant. There were 3 potential explanations for these stillbirth pregnancies linked to live-born infant records:

1. It was truly a stillbirth pregnancy incorrectly linked to live-born infant records. Incorrect linkage could occur if the pregnant woman in the Pregnancy Register delivered a stillborn infant around the same time that another woman in the same household delivered a live-born infant. In such a scenario, the MBL could incorrectly link the woman who had a stillbirth pregnancy to the live-born infant.

2. It was actually a live-birth pregnancy, incorrectly recorded as a stillbirth pregnancy. This could occur if a woman with an ongoing pregnancy told her GP about a historical stillbirth pregnancy and the GP recorded this with a current event date. It could then appear that

the woman's current pregnancy resulted in a stillbirth when, in fact, the woman went on to deliver a live-born infant that was correctly linked to her.

3. It was actually a pregnancy resulting in both a live-birth and a stillbirth. This could occur if the pregnant woman delivered both a live-birth and stillbirth, with the latter outcome captured in the Pregnancy Register and the former linked via the MBL.

It was not possible to know whether such pregnancies were truly stillbirths (in which case the linked infant should not be included in analyses examining MCMs among live-born infants), live-births (in which case they should be included in analyses examining MCMs among live-born infants) or multiple pregnancies (in which case they should be excluded from all analyses). All 61 such pregnancies were therefore excluded (**Figure 4.2**).

### 4.3.4 Pregnancies with implausible duration

The length of some pregnancies was implausible in the context of their outcome. In such cases it was likely that the estimated pregnancy start and/or delivery date were inaccurate, which could result in the misclassification of vaccination or MCMs. Exclusion criteria based on pregnancy outcomes and gestational age are described below.

Live-births: A plausible duration was considered to be 22-42 weeks. To ensure consistency with previous decisions, in which up to 4 weeks of imprecision in the estimated delivery date was allowed, live-birth pregnancies were excluded if they had a recorded duration of <18 or >46 weeks in the Pregnancy Register. Of the potentially eligible live-birth pregnancies at this stage, 1.5% (n=2,298) had a duration of <18 weeks and were excluded (**Figure 4.2**). No live-birth pregnancy had a duration of >46 weeks. Just 0.2% (n=378) had a duration of 18-22 weeks and 2.7% (n=4,194) had a duration of 42-46 weeks.

Stillbirths: These were defined as foetal losses occurring after 24 weeks of gestation.[270] The same rules were followed as for live-births. Of the potentially eligible stillbirths, 6.7% (n=39) had a duration of <18 weeks and were excluded (**Figure 4.2**). None of these pregnancies were

>46 weeks long. Stillbirth pregnancies that were 18-22 weeks long (4.7%; n=27) and those with a duration of 42-46 weeks (1.4%, n=8) were retained.

Miscarriages: These were defined as foetal losses occurring before 24 completed weeks of gestation.[271] It was decided that miscarriages with a gestational length of >28 weeks would be excluded but no such pregnancies were identified.

Terminations: In England, these can be conducted at any time in pregnancy but most are carried out before the 24th week.[272] Whilst the distribution of pregnancy duration was examined among terminations, no thresholds were set for exclusion. All pregnancies resulting in termination were <26 weeks long.

### 4.3.5 Overlapping pregnancies

Some pregnancy episodes belonging to the same woman overlap in the Pregnancy Register and are flagged. Pregnancy episodes may overlap because the estimated pregnancy start and/or delivery dates are inaccurate. However, overlap may also occur as a result of GP recording practices. For example, a pregnancy episode resulting in a miscarriage may be found within a live-birth pregnancy episode if the pregnant woman experienced a threatened miscarriage which was recorded by the GP but then resolved, with the woman later delivering a live-born infant.

All overlapping pregnancy episodes were identified. Overlapping pregnancy episodes were excluded with the exception of those that resulted in a live-birth with linked infant records. Because of the presence of linked infant records, it was thought that if such pregnancies overlapped with pregnancies of other outcomes (e.g. miscarriages) then the latter were unlikely to be real pregnancies.

### 4.3.6 Pregnancies with unknown outcomes

The Pregnancy Register algorithm was designed to utilize all the available pregnancy information recorded in the CPRD in order to maximize the ascertainment of pregnancy

episodes.[255] This approach, however, also led to the identification of some pregnancies with an unknown outcome. Such pregnancies could occur if:

1. The woman transferred out of the practice before the pregnancy ended.
2. The woman died before the pregnancy ended.
3. The practice stopped collecting data for CPRD before the pregnancy ended.
4. The woman was not pregnant but the GP recorded historical pregnancy information using a current date.
5. The GP did not record the delivery using Read or entity codes (which were used by the Pregnancy Register algorithm to identify pregnancy-related data) but instead scanned a delivery letter from the hospital or entered information using free-text.
6. The pregnancy was initially reported to the GP but then ended in an unreported miscarriage or termination.

Outcome unknown pregnancies made up 38% of all pregnancies (**Figure 4.2**) and a third of these were found to be a result of truncated follow-up due to reasons 1-3 described above. All outcome unknown pregnancies were excluded from analyses due to the uncertainty in their duration and timing, which could result in the misclassification of vaccination status. Furthermore, ascertaining MCMs among such pregnancies was not possible; none of these pregnancies were linked to infants and an examination of antenatal diagnoses was considered inadequate due to the uncertainty in pregnancy timings.

### 4.3.7 Ectopic, molar and blighted ovum pregnancies

Ectopic, molar and blighted ovum pregnancies are non-viable pregnancies that do not usually extend beyond the first trimester. MCMs are unlikely to be detected antenatally in these pregnancies, or at all for those where the embryo or foetus does not develop. These pregnancies were excluded from analyses.

### 4.3.8 Pregnancy losses, terminations, live-birth deliveries without linked infant records and other pregnancy outcomes

After the above exclusion criteria had been applied, remaining pregnancy outcomes included:

- Miscarriages,
- Stillbirths,
- Unspecified pregnancy losses,
- Deliveries based on late pregnancy records,
- Live-births without linked infant records, and
- Live-births with linked infant records

All outcomes were first explored to assess the potential for bias if they were to be included in vaccine safety analyses (**Section 8.6**). The final study populations for **Objectives 3-6** only included live-birth pregnancies with linked infant records.

Of the 142,612 potentially eligible live-birth pregnancies (**Figure 4.2**), approximately 8.5% (n=16,949) were not linked to infant records and so it would not be possible to search for evidence of MCMs among these postnatally. These pregnancies were excluded from all analyses but were described to demonstrate that their exclusion was unlikely to bias results (**Section 8.8**). There are a number of reasons for incomplete linkage between mothers and infants in the MBL, which would result in the linkage also not being available in the Pregnancy Register (**Table 4.1**). Two reasons for lack of linkage that could be associated with MCMs were:

1. The woman transferring out of the practice to move to another region (either to access specialist care for an infant with an MCM or due to unstable accommodation),

2. The infant having a severe condition resulting in prolonged hospitalisation or death.

Both scenarios would prevent/delay the registration of the infant at the practice and subsequent linkage to the mother. These two scenarios are considered in **Section 8.8.**

**Table 4.1 – Potential reasons for incomplete linkage between mothers and infants in the Mother-Baby Link.**

| No infant to link to | Linkage not attempted | Linkage unsuccessful |
|---|---|---|
| The delivery record was actually a retrospective recording of a past live-birth delivery and so there was no contemporaneous infant to link to. | The infant's year of registration at the practice was recorded as being prior to their birth year and so the infant was excluded from linkage. | The recorded delivery date and estimated date of birth of the infant are more than 60 days apart. |
| The delivery was not a live-birth (the pregnancy outcome is misclassified in the Pregnancy Register) and so there is no infant to link to. | The infant's year of registration at the practice was recorded as being after the last collection year of the practice and so the infant was excluded from linkage. | The delivery matched to more than one infant with different dates of birth. |
| | The mother delivered before 12 years of age and so the delivery was excluded from linkage. | More than one woman matched to the same baby. |
| | The delivery was recorded as occurring more than a year before the current registration date of the mother and so the delivery was excluded from linkage. | |
| | The delivery was recorded as occurring after the last collection date of the practice or the transfer out date of the mother and so the delivery was excluded from linkage. | |
| | The infant was not registered at the mother's practice during the data collection period and so linkage was not possible. | |
| | The mother and infant have a different family number and so linkage was not possible. | |

## 4.4 Congenital malformation exclusion criteria

### 4.4.1 Malformations with known causes

The overarching aim of this work was to assess the safety of influenza vaccination with respect to MCMs. MCMs cover a broad range of conditions, some of which have a known aetiology. These include:

- Chromosomal aberrations (e.g. '*Down syndrome*'),
- Inherited genetic mutations (e.g. '*autosomal recessive polycystic kidney disease*'), and
- Exogenous causes such as exposures to known teratogens (e.g. '*foetal alcohol syndrome*', '*Dysmorphism due to warfarin*').

These MCMs with known aetiology would not plausibly have been caused by maternal vaccination. In addition, including such conditions in analyses could bias the association between vaccination and MCMs. Chromosomal aberrations, single-gene mutations and exposures to exogenous causes may be associated with characteristics that are also associated with vaccine uptake. For example, the risk of having a child with Down syndrome and the likelihood of receiving the influenza vaccine during pregnancy both increase with maternal age.[17, 66] Including these infants, and any of their MCMs, in analyses could bias the association between vaccination and MCMs upwards.

Pregnancies were excluded if an MCM with a known cause was identified in the infant or recorded antenatally in the pregnant woman. The methods used to exclude such conditions are described in **Chapter 5** and the code lists used are described in **Appendix 4.**

In the absence of a diagnosis of an MCM of known cause, it was unclear whether exposure *in utero* to potentially teratogenic drugs or vaccines or hazardous levels of alcohol were responsible for any resulting MCMs. These exposures were therefore considered confounders of the relationship between maternal vaccination and risk of MCMs, and are further outlined in **Section 4.6** and in **Chapter 8**.

### 4.4.2 Congenital infections

Some maternal infections can be transmitted to the foetus *in utero* and cause congenital malformations (**Section 1.7.2**).[273, 274] These are known as congenital infections and include: Syphilis, HIV, varicella zoster virus, parvovirus, rubella, herpes simplex virus, cytomegalovirus and toxoplasmosis.[273, 274] With the exception of syphilis and HIV, infections typically only pose a risk if they are acquired during or around the time of pregnancy.[273, 274] To ensure that MCMs identified in the study population were not caused by congenital infections, pregnancies were excluded from analyses if there was evidence of:

- Varicella, parvovirus, rubella, herpes simplex virus, cytomegalovirus or toxoplasmosis in maternal records during pregnancy, four weeks before or four weeks after (to account for delays in recording infections or imprecision in recorded pregnancy timings, and to identify infections that were likely to be ongoing in the first trimester).
- Syphilis or HIV anytime in the maternal records (to account for the fact that these infections can be acquired years before diagnosis as well as the life-long nature of HIV and the fact that although syphilis can be treated there was no way to know that treatment was completed successfully before conception).
- HIV, syphilis, varicella, parvovirus, rubella, herpes simplex virus, cytomegalovirus or toxoplasmosis anytime in the infant records. Codes had to specify that the infection was congenital in origin to prevent the ascertainment of common infections acquired postnatally (i.e. congenital varicella vs. common childhood varicella).

Read code lists for these congenital infections were used to search infant and maternal clinical, referral and test files in CPRD (**Appendix 5**). Because congenital infections were likely to be ascertained in hospital around the time of delivery, ICD-10 code lists were also used to search for any evidence in HES among infants.

## 4.5 Additional study-specific exclusion criteria

For all studies, eligible pregnancies were first identified as described in **Sections 4.2-4.4**. All other pregnancy outcomes (e.g. miscarriages, stillbirths, terminations, live-births without linked infant records) were excluded at this stage and additional, study-specific exclusion criteria were then applied (**Figure 4.4**).

For **Objective 3**, pregnancies ending after March 31, 2015 (a year before linked data ended) were excluded to allow all infants the potential for a year of follow-up. For **Objective 4**, additional exclusion criteria were applied when carrying out prevalence comparisons with EUROCAT data to increase the comparability of the study populations. Pregnancies ending after December 31, 2013 were excluded, as were pregnancies of women whose practice region did not correspond to a region covered by an English EUROCAT registry.

For **Objectives 5 & 6,** vaccination-specific exclusion criteria were also applied to ensure that all pregnancies had the opportunity to be vaccinated and to reduce any uncertainty in the timing of vaccination and in the type of influenza vaccine received. These are described in greater detail in **Chapter 6**. Analyses were also restricted to those pregnancies that had complete information on potential confounding factors (**Section 4.6**).

**Potentially eligible pregnancies**

- Pregnancies ending between January 1, 2009 and March 31, 2016
- Pregnant women had to fulfil the following criteria: 'acceptable' status (as defined by CPRD), registered at an up-to-standard practice at least 6 months before the start of pregnancy, eligible for HES linkage.
- Any infants linked to live-birth pregnancies had to fulfil the following criteria: 'acceptable' status (as defined by CPRD), eligible for linkage to HES and ONS.

**Pregnancy-related exclusions**

- Multiple pregnancies
- Live-birth pregnancies with a discrepancy of >4 weeks between the delivery date & the infant's month/year of birth
- Stillbirth pregnancies with a linked infant
- Pregnancies with an implausible duration (live-births and stillbirths with a duration <18 or >46 weeks; miscarriages with a duration >28 weeks; late and third trimester deliveries with a duration <18 or >46 weeks)
- Outcome unknown pregnancies
- Overlapping pregnancies

**Congenital malformation exclusions**

- Pregnancies resulting in MCMs with known causes (e.g. chromosomal abnormalities).
- Pregnancies for which there was evidence of a congenital infection known to cause MCMs (Syphilis, HIV, varicella zoster, parvovirus, rubella, herpes simplex virus, cytomegalovirus, toxoplasmosis).

**Study-specific exclusions**

All studies were restricted to live-birth pregnancies with linked infant records (all other pregnancy outcomes were excluded).

**Objectives 3 & 4**

- Pregnancies ending after March 31, 2015.
- For prevalence comparisons with English EUROCAT registries, pregnancies were excluded if they ended after December 31, 2013 and if they occurred in regions that did not correspond to regions covered by the EUROCAT registries (**Objective 4 only)**.

**Objectives 5 & 6**

- Did not overlap with period of SIIV availability (defined as September 1$^{st}$ – March 31$^{st}$ from 2010-2016) (**Objective 5 only**).
- Did not overlap with a period of PIIV availability (October 21, 2009-March 31, 2010). (**Objective 6 only**).
- Pregnancies for which there was uncertainty in the timing or type of vaccine received.
- Pregnancies with missing data in confounder variables.

**Figure 4.4 – Summary of the criteria used to define study populations for the objectives of the thesis.** Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, Major congenital malformation.

## 4.6 Defining potential confounders in the study population

Factors associated with vaccine uptake and factors associated with MCMs were described in **Sections 1.4** and **1.7.2**, respectively. Factors for which there was evidence to suggest an association with both vaccine uptake and MCMs were considered and a conceptual framework was developed to identify confounders for vaccine safety analyses (**Figure 4.5**).

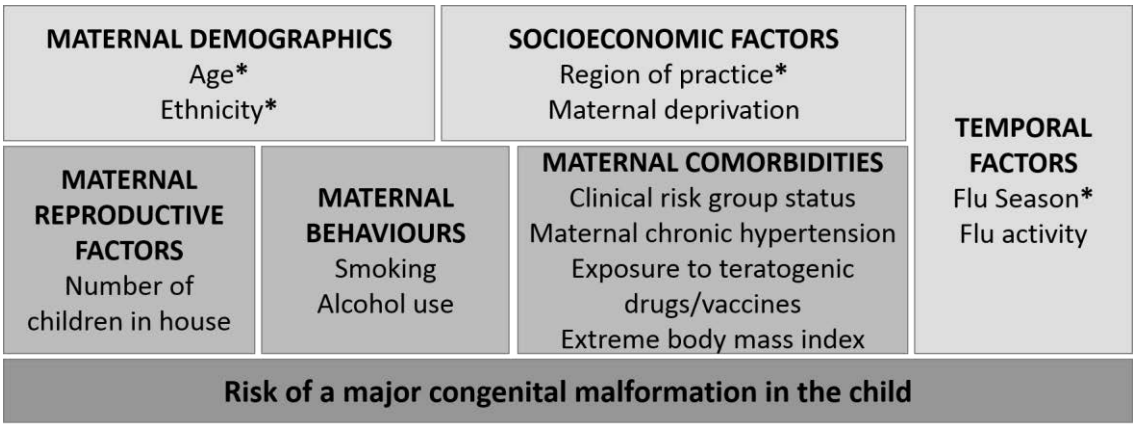



**Figure 4.5 – Conceptual framework used to identify potential confounders for vaccine safety analyses.** Distal factors included maternal demographics and socioeconomic factors. The effect of these factors was likely mediated, in part, through more proximal risk factors such as maternal reproductive factors, lifestyle behaviours and comorbidities. Separate to these were temporal risk factors related to the flu season and flu activity (i.e. the levels of influenza circulating in the community). *A priori confounders.

Potential confounders of interest were derived as follows:

**Maternal age (*a priori* confounder):** Maternal age at the end of each pregnancy was defined using information in the Pregnancy Register.

**Maternal ethnicity (*a priori* confounder):** Maternal ethnicity was derived using a previously published algorithm which incorporates information from both CPRD and HES.[251]

**Geographical region (*a priori* confounder):** The geographical region of the mother's general practice was identified from the CPRD practice file.

**The earliest influenza season a pregnancy overlapped with (*a priori* confounder):** Influenza seasons were defined as September, 1 - March, 31 each year. If a pregnancy overlapped with more than one season, the earliest was chosen.

**Household deprivation quintile (Index of Multiple Deprivation (IMD)):** Patient-level IMD quintiles were obtained through linkage with deprivation data where possible. Practice-level IMD data were used for the small proportion of pregnancies (<0.5%) where patient-level data were unavailable.

**Number of children in the maternal household:** The number of children aged ≤16 years and present in the maternal household at the start of each pregnancy was determined by identifying children registered at the mother's practice who had the same family number (a variable indicating individuals living in the same household) as the mother from CPRD patient files and practice files.

**Smoking status:** Maternal smoking records during pregnancy were identified from the clinical file and additional clinical details file in CPRD. Pregnancies were classified as belonging to a non-, ex- or current smoker. If there were multiple records during pregnancy then a current smoker record superseded all others whilst an ex-smoker record superseded a non-smoker record. If there were no records during pregnancy, the most recent record in the 10 years prior was identified and used. If there were multiple records on the same date the same rules were followed as above. If the most recent evidence indicated the woman was a non-smoker but she had evidence of smoking any time before this then she was reclassified as an ex-smoker. Pregnancies of women with unknown smoking status were excluded from analyses.

**Evidence of extreme BMI:** All available height and weight data for women in the study population were extracted from the additional clinical details file in CPRD and used to calculate BMI. BMI records that occurred from the start of the second trimester through to the end of the second month after pregnancy were excluded. The earliest BMI record in the first trimester was sought. If there was no record in the first trimester, the five years prior to the start of pregnancy were examined and the record closest to the pregnancy was used. If no records were available in the five years before the pregnancy, the year after the pregnancy was examined (excluding the first two months) and the record furthest from the end of pregnancy

was selected. If a BMI record had still not been identified, the most proximate BMI record before or after the pregnancy was used, within 10 years. Evidence of extreme BMI (<18 and ≥35) was of particular interest as a potential confounder in this study. Pregnancies of women with unknown BMI or a BMI between 18 and 34 were categorized as not having evidence of extreme BMI.

**Evidence woman belonged to at least one other clinical risk group for which influenza vaccination was recommended:** Identification of clinical risk group status in pregnant women was carried out by Dr Jemma Walker using CPRD clinical and therapy files. Women were considered to be part of a clinical risk group if they had evidence of a relevant condition at the start of the influenza season the pregnancy overlapped with. The following conditions were included: Chronic respiratory disease (including asthma), chronic heart disease, chronic kidney disease, diabetes mellitus, immunosuppression due to disease or treatment, chronic liver disease, chronic neurological disease, asplenia or dysfunction of the spleen. If a woman had evidence of the above but it was not clear at what point this had occurred then her pregnancy was considered to have unknown clinical risk group status and was excluded from analyses.

**Evidence of chronic hypertension:** Maternal clinical, referral and test files in CPRD were searched for evidence of a hypertension diagnosis. If this evidence occurred before a pregnancy, any subsequent pregnancy was classified as belonging to a woman with pre-existing hypertension. If this evidence first occurred during a pregnancy then further supportive evidence was required to rule out pregnancy-related hypertension; maternal records were searched for a further diagnosis record in the 6-12 months after the end of pregnancy or a prescription of an anti-hypertensive in the therapy file. If supportive evidence was available, the woman was considered to have hypertension (not pregnancy-related hypertension) at the time of her pregnancy.

**Evidence of hazardous drinking:** Maternal records relating to alcohol consumption were identified from the maternal clinical file and additional clinical details file in CPRD. Evidence of

hazardous drinking was defined as the consumption of ≥43 units/week or by the presence of a Read code indicating heavy drinking. Evidence of hazardous alcohol consumption was first searched for during each pregnancy. If there were no records during pregnancy, the most recent record in the 10 years prior was identified and used. If there were multiple records on the same day then the highest recorded level of alcohol consumption was used.

**Exposure to teratogenic drugs/live vaccines in the period before pregnancy and up to the end of the first trimester:** Identifying live vaccines given to women in the pregnancy period required the development of Read code lists (to search the maternal clinical file), product code lists (to search the maternal therapy file) and immunisation type code lists (to search the maternal immunisation file). To manage time constraints, the immunisation file for all women in the study population was examined to identify all live vaccines given in the pregnancy period. The MMR, yellow fever and BCG vaccines were the most commonly received whereas live typhoid, shingles and varicella vaccines were used in just <0.02% of women. Code lists were developed for MMR, yellow fever and BCG vaccines and evidence of vaccine receipt was identified from the 3 months before pregnancy until the end of the first trimester.

There is no definitive/comprehensive list of teratogenic drugs. A list of teratogenic drugs was decided based on an exploration of the related literature and cytotoxic drugs listed by the British National Formulary.[275, 276] Code lists for the following teratogenic medications were obtained from Sara Thomas: ACE inhibitors, Acitretin, Amiodarone, Azathioprine, Bexarotene, Carbamezepine, Cyclophosphamide, Dronedarone, Isotretinoin, Lithium, Methotrexate, Misoprostol, Mycophenolate, Phenobarbital, Phenyoin, Primidone, Propylthiouracil, Topiramate, Valproate, and Warfarin. A code list was not created for thalidomide as any prescription of thalidomide in the UK involves a negative pregnancy test before prescription and continuous negative tests throughout treatment.[277] Methimazole (or thiamazole, its alternative name) was also not included as this was not listed in the current or old version of

the British National Formulary, it was not in the CPRD data dictionary under any known trade name and it was suspected that it was not available in the UK during recent times.

The maternal therapy file in CPRD was examined from 6 months before the start of pregnancy through to the end of the first trimester for evidence of prescriptions. This larger window of time was chosen to account for prescriptions issued but not collected/utilized until a later date and the long length of some prescriptions for such drugs.

**Number of weeks that the first trimester overlapped with influenza activity above baseline levels:** This was calculated using weekly national influenza-like illness surveillance data from the Royal College of General Practitioners.[278] Data on the weeks in each year that had an influenza-like illness rate above the baseline threshold were provided by Public Health England. The total number of weeks in the first trimester that overlapped with a period in which the rate of influenza-like illness was above the baseline threshold was calculated for each pregnancy.

## 4.7 Chapter Summary

This chapter summarizes the criteria used to define study populations for the objectives in this thesis. The next methods chapter discusses the development of the algorithm used to identify MCMs. In the final methods chapter, the approach taken to identify vaccination during pregnancy is described in full and includes further detail on study-specific exclusion criteria related to vaccination.

# 5. Developing an algorithm to identify major congenital malformations

## 5.1 Introduction

Identifying congenital malformations in electronic health records poses a challenge due to the large and diverse number of these conditions. Distinguishing major from minor malformations and categorizing major malformations into anatomical subgroups can further complicate the process. A systematic review of the methods used to identify congenital malformations in UK electronic health records was carried out to inform the identification of MCMs in this thesis (**Chapter 2**). Of the 54 studies examined, 36 identified congenital malformations in stand-alone primary care data and 18 used secondary care data (with some using additional data such as death records). No study used linked primary care, hospital admissions and mortality data.

An objective of this thesis was to ascertain MCMs among live-born infants using linked CPRD primary care records, HES inpatient admissions and ONS mortality data and to establish the value of each data source in ascertaining these conditions, and their agreement (**Objective 3**). The prevalence of MCMs identified in stand-alone and linked data sources was then compared to prevalence estimates from external data sources (**Objective 4**) prior to analyses examining the safety of SIIV and PIIV (**Objectives 5-6**).

This chapter describes the algorithm developed to identify evidence of MCMs in these multiply-linked electronic health records. The key lessons from the systematic review that informed the approach used here are first summarized (**Section 5.2**). The use of EUROCAT guidelines and the development of initial code lists are then described (**Section 5.3**). After developing initial code lists, the methods to refine them are discussed (**Section 5.4**). The use of code lists to identify MCMs in infant records is then outlined (**Sections 5.5**). Finally, the identification of antenatal evidence for MCMs is detailed (**Section 5.6**).

## 5.2 Recapitulation of the methods used in other studies to identify congenital malformations in UK electronic health records

This section describes the three key lessons from the systematic review of the methods used to identify congenital malformations in UK electronic health records. These were used to inform the development of a comprehensive algorithm to identify MCMs in this thesis.

**1. Use of published guidelines to define congenital malformations.**

Studies identifying congenital malformations in primary care data frequently used published guidelines to: develop case definitions and code lists, distinguish between major and minor malformations, and classify MCMs into anatomical subgroups.[279, 280] EUROCAT guidelines were the most frequently used and were used for the same purposes here.

**2. Use of Read codes outside of the 'P' chapter on congenital malformations**

Both the Read and ICD-10 coding systems contain chapters of codes dedicated to congenital malformation diagnoses - the 'P' and 'Q' chapters, respectively. A key finding of the systematic review was that studies that identified congenital malformations in HES data using ICD-10 codes relied on the 'Q' chapter whilst studies using primary care data frequently used Read codes from both the 'P' chapter and other Read chapters.

Read codes from outside the 'P' chapter could be diagnostic in nature. For example, some studies used the Read code '*congenital mitral stenosis*' from the 'P' chapter as well as the code '*mitral stenosis*' from the 'G' chapter on circulatory system diseases which could also be non-congenital in origin.[281] Other codes from outside the 'P' chapter could relate to relevant procedures, observations, tests, medical history or administrative tasks. Examples of such codes used by studies in the systematic review included: '*personal history of congenital malformations*', '*repair of deformity of palate*', '*congenital heart condition monitoring*' and '*transfer of care from paediatric congenital heart services'*. Relying exclusively on Read codes from the 'P' chapter would likely under-ascertain MCMs and so relevant Read codes from other chapters were included in the code lists developed here.

**3. Use of criteria to decide on the inclusion of non-specific codes**

An examination of available code lists from studies included in the systematic review demonstrated that some codes used to identify congenital malformations were non-specific. Codes were considered non-specific (and are referred to as such throughout this thesis) if they could be used to encode:

1. **Congenital malformations or non-congenital conditions.**

   Example code: *'mitral stenosis'*.

2. **Major malformations or minor malformations.**

   Example code: *'other congenital heart anomalies'*.

3. **Malformations from different anatomical subgroups.**

   Example code: '*congenital anomaly not otherwise specified'.*

Studies identified in the systematic review did not provide details of the criteria used to decide on the inclusion of non-specific codes in code lists and/or their classification. In this work, the framework for deciding on the use of codes that could potentially relate to non-congenital conditions is described in **Section 5.4.1.** Codes that could relate to major or minor malformations are discussed in **Section 5.4.2** and codes that could refer to malformations of different anatomical subgroups are described in **Section 5.3.1.**

## 5.3 Use of EUROCAT guidelines to develop initial code lists

EUROCAT defines congenital malformations (major and minor) using ICD-10 codes that are modified by the British Paediatric Association (BPA) to include a fourth digit.[86] EUROCAT uses all the codes in the ICD-10 'Q' chapter to define congenital malformations as well as a small number of codes beyond this, including: D1810 (*'lymphangioma/cystic hygroma'*), D215 (*'benign neoplasm of the pelvis'*), D821 (*'DiGeorge syndrome'*), P350 (*'congenital rubella syndrome'*), P351 (*'congenital cytomegalovirus infection'*) and P371 (*'congenital toxoplasmosis'*). Codes P350, P351 and P371 related to congenital infections and so were not included in code lists developed to identify congenital malformations.

EUROCAT Guide 1.4 (published in 2016) was used to define congenital malformations for initial code lists and classify them into anatomical subgroups.[282] Guidelines were later used to refine these by defining codes related to:

1. **Conditions that could sometimes be a result of other non-congenital causes.**

   If such a code was present in the infant record then a decision was made as to whether the code represented an MCM or a condition with another cause.

2. **Minor malformations**.

   Codes that clearly related to minor malformations were removed from code lists. Codes that were ambiguous or needed to meet certain criteria to be classified as minor were considered separately.

3. **MCMs that were a result of known causes such as chromosomal anomalies**

   If such a code was present in the infant record or antenatally in the maternal record then the pregnancy was excluded.

### 5.3.1 Defining congenital malformations and anatomical subgroups using EUROCAT

Congenital malformation and their subgroups were defined according to EUROCAT guidelines (**Table 5.1**). At the time this work was carried out, EUROCAT guidelines categorized BPA-modified ICD-10 codes into the following 12 non-overlapping subgroups: 'nervous system malformations', 'eye malformations', 'ear, face and neck malformations', 'congenital heart defects', 'respiratory system malformations', 'orofacial clefts', 'abdominal wall defects', 'other malformations of the digestive system' (henceforth referred to as 'digestive system malformations'), 'genital system malformations', 'urinary system malformations', 'limb defects' and 'chromosomal anomalies'.[282] Codes in these subgroups could be categorized into even smaller and more specific subsets. Codes in the 'orofacial clefts' subgroup, for example, could be further categorized into subsets for 'cleft palate' and 'cleft lip with or without cleft palate'. However, in the work described here, subsets of malformations were not examined

due to the potential for data sparsity. Anatomical subgroups in this thesis were defined according to EUROCAT guidelines, with two deviations:

1. **Codes for conditions related to balanced rearrangements of chromosomes were grouped with chromosomal anomalies.** EUROCAT guidelines did not include ICD-10 codes for balanced chromosomal rearrangements (Q950-959) in the chromosomal anomalies subgroup. Because these codes related to chromosomal conditions that were later used to exclude pregnancies from analyses, they were included in the chromosomal anomalies subgroup in this thesis (**Table 5.1**).

**Table 5.1 – Congenital malformation case definitions in EUROCAT and in the initial code lists developed for this thesis**.

| Congenital malformation | BPA-modified ICD-10 codes used to define congenital malformations | |
|---|---|---|
| | EUROCAT | Thesis[a] |
| Any | Q chapter, D215, D821, D1810, P350, P351, P371 | Q chapter, D215, D821, D1810 |
| Nervous system | Q00-07 | Followed EUROCAT guidelines |
| Eye | Q10-15 | Followed EUROCAT guidelines |
| Ear, Face & Neck | Q16-18 | Followed EUROCAT guidelines |
| Congenital Heart Defects | Q20-26 | Followed EUROCAT guidelines |
| Respiratory | Q300, Q32-34 | Followed EUROCAT guidelines |
| Oro-facial clefts | Q35-37 | Followed EUROCAT guidelines |
| Digestive | Q38-45, Q790 | Followed EUROCAT guidelines |
| Abdominal Wall Defects | Q792, Q793, Q795 | Followed EUROCAT guidelines |
| Genital | Q50-52, Q54-56 | Followed EUROCAT guidelines |
| Urinary | Q60-64, Q794 | Followed EUROCAT guidelines |
| Limb | Q65-74 | Followed EUROCAT guidelines |
| Chromosomal | Q90-93, Q96-99 | Q90-93, Q95, Q96-99 |
| Other | D821, P350, P351, P371, Q0435, Q206, Q240, Q3381, Q411, Q412, Q418, Q4471, Q6190, Q710, Q712, Q713, Q720, Q722, Q723, Q730, Q7402, Q7484, Q750, Q751, Q754, Q7581, Q77, Q7800, Q782-Q788, Q793, Q795, Q7980, Q7982, Q80-Q82, Q86, Q87, Q890, Q893, Q894, Q936 | Q27, Q28, Q301-309, Q31, Q53, Q75-79 (except for Q790 and Q792-795 which were defined as digestive, abdominal wall and urinary malformations), Q80-89 |

[a]Minor malformations, malformations relating to prematurity, poorly-specified malformations and malformations with known causes were included in initial code lists. Code lists were later refined.

2. **Only codes that did not fall into one of the 12 main EUROCAT subgroups or that were non-specific were grouped into an 'other' subgroup.** EUROCAT guidelines defined an additional subgroup for 'other anomalies/syndromes' which covered a broad range of conditions.[282] Codes in this subgroup sometimes overlapped with codes in the 12 main subgroups described earlier. For example, the code Q793 for '*gastroschisis*' was part of both the 'abdominal wall defects' subgroup and 'other anomalies/syndromes' subgroup. Because of this overlap, guidelines for this subgroup were not followed and defining a directly equivalent subgroup for this thesis was not attempted. Instead, only those codes that did not come under any of the 12 main anatomical subgroups were classified as 'other' malformations. For example, codes Q270-279 and codes Q280-289, which refer to malformations of the peripheral vasculature, were not part of any subgroup and were therefore defined as 'other' malformations. In addition to the above, non-specific codes that could not be classified into a subgroup were defined as 'other malformations' (e.g. '*congenital anomaly not otherwise specified*') (**Table 5.1**).

### 5.3.2 Developing Read code lists

To develop Read code lists, EUROCAT BPA-modified ICD-10 codes in each subgroup were first used to create search terms of interest. For example, to identify Read codes for abdominal wall defects, the relevant BPA-modified ICD-10 codes used by EUROCAT were identified as being Q792, Q793 and Q795. The ICD-10 descriptions attached to these codes were then used to establish a list of search terms in free-text form, with wildcards used to account for any variation in the spelling or ordering of words (**Table 5.2**). The list of search terms was then used to search the Read code dictionary and relevant Read codes were retrieved. At this stage, all potentially relevant codes were retained regardless of what Read chapter they were from.

The hierarchical structure of the Read code system was utilized to increase the likelihood of capturing potentially relevant codes. When Read codes were identified through the use of search terms, they were examined and their common stems were noted. These stems were

then used to search for other codes in their vicinity. For example, a number of Read codes for omphalocele were identified which all began with 'J32'. The Read code dictionary was therefore searched for all codes with this stem to identify any others that might be relevant. Searches for 'J31', 'J33', 'J3' and 'J' were also be carried out to assess whether any relevant codes might be found in other areas of the same chapter.

After identifying Read codes using the above methods, they were checked against the full 'P' chapter in the Read dictionary. The vast majority of codes in the 'P' chapter had been captured through the above methods. The few that weren't were added to the code list. Finally, Read codes identified in this work were cross-checked with those used by the authors of studies included in the systematic review (described in **Chapter 2**). Potentially relevant Read codes that had been included by other authors but had not been identified in the search here were added to the code list.

**Table 5.2 - Defining search terms for Read codes based on EUROCAT BPA ICD-10 codes**

| BPA-modified ICD-10 code | ICD-10 description | Search terms created |
|---|---|---|
| Q792 | Exomphalos; Omphalocele | *exomphal*; *omphalo* |
| Q793 | Gastroschisis | *gastroschis* |
| Q795 | Other congenital malformations of abdominal wall | *congen*abdom*; *malf*abdom*; *anomal*abdom*; *abdom*defect*; *abdom*wall* |

### 5.3.2 Developing ICD-10 code lists

As EUROCAT defined malformations using ICD-10 (albeit a BPA-modified version), developing ICD-10 code lists was considerably more straightforward than developing Read code lists as the creation of search terms was not necessary to identify relevant codes. ICD-10 codes were selected from the ICD-10 dictionary and categorized into groups based on EUROCAT guidelines. However, because EUROCAT ICD-10 codes were modified to include an extra digit, it was sometimes not possible to identify an exact equivalent in the ICD-10 dictionary (**Table 5.3**).

**Table 5.3 - Identifying ICD-10 codes based on EUROCAT BPA-modified ICD-10 codes.**

| BPA-modified ICD-10 code | Description provided by EUROCAT | ICD-10 code | Description in the ICD-10 dictionary |
|---|---|---|---|
| Q254 | Other congenital malformations of aorta | Q254 | Other congenital malformations of aorta |
| Q2540 | Hypoplasia of aorta | No equivalent code | - |
| Q2541 | Persistent right aortic arch | No equivalent code | - |
| Q2542 | Overriding aorta | No equivalent code | - |
| Q2543 | Aneurysm of sinus of Valsalva | No equivalent code | - |
| Q2544 | Double aortic arch | No equivalent code | - |
| Q2545 | Congenital aneurysm of aorta | No equivalent code | - |
| Q255 | Atresia of pulmonary artery | Q255 | Atresia of pulmonary artery |

### 5.3.4 Developing OPCS-4 code lists

The OPCS-4 code system is divided into chapters based predominantly on organ systems. For each EUROCAT subgroup, the OPCS-4 chapter for the equivalent organ system was searched for potentially relevant codes by myself and Sara Thomas. For example, for congenital heart defects, relevant procedures were searched for in the 'K' chapter of the OPCS-4 code system which related specifically to heart procedures. Procedures known to be associated with congenital malformations were included in the code list.

## 5.4 Refining code lists

The first stages in the development of code lists for MCMs aimed to prioritize sensitivity in order to ensure that all potentially relevant codes were captured. Code lists were then reviewed by myself, Sara Thomas and Punam Mangtani (both of whom are clinical epidemiologists), and a consultant neonatologist (Steve Kempley). The following types of code were reviewed and discussed:

1. Codes that could relate to non-congenital conditions (**Section 5.4.1**)
2. Codes that could relate to minor or potentially minor malformations (**Section 5.4.2**)
3. Codes for which the classification of the subgroup was unclear (**Section 5.4.3**)
4. Codes relating to MCMs with known causes (**Section 5.4.4**)

### 5.4.1 Codes that could relate to non-congenital conditions.

Some of the codes in the initial code lists were from chapters outside of those dedicated to congenital malformations and could have been used by clinicians to encode non-congenital conditions. Other codes were from dedicated chapters for congenital malformations but were not always considered by EUROCAT to be 'true' malformations if they were associated with preterm birth or other circumstances.[282] The way such codes were treated is defined below.

**Codes from outside the dedicated chapters for congenital malformations**

All codes in the 'P' chapter of the Read code system and 'Q' chapter of ICD-10 relate to congenital malformation diagnoses. Therefore, only codes outside of these chapters were examined to determine whether they were likely to refer to non-congenital conditions. The following types of code were considered:

1. **Non-specific diagnostic Read codes from outside the 'P' chapter that referred to conditions that could result from multiple causes, including congenital causes:** These codes were retained in code lists if the most prevalent cause of the condition in the UK among this study population was likely to be congenital. If the condition was thought to have non-congenital causes more than 50% of the time then the code was removed from the code list. An example of such a condition was '*mitral stenosis*' from the 'G' chapter. Whilst mitral stenosis can occur following rheumatic fever, the consultant neonatologist advised that the prevalence of this was rare in the UK. The cause of mitral stenosis in the first few years of life was most likely to be congenital and so the code was retained.

2. **OPCS-4 codes and Read codes outside the 'P' chapter that referred to procedures, tests, monitoring of conditions, transfers of care and other administrative tasks:** These codes were included in the final code list if the procedure was known to be specific to a congenital malformation or if the procedure was likely to be carried out to correct a congenital malformation in the study population. For example '*correction of pectus excavatum*' was included as pectus excavatum is a known congenital malformation.

Conversely, '*insertion of prosthesis into chest wall*' was not included because this did not specifically refer to a congenital malformation and could be performed for other reasons in the study population (e.g. to correct disfigurement following an injury).

**Codes defined by EUROCAT as having other potential causes**

EUROCAT guidelines also defined conditions that could be considered MCMs but could, in some cases, be a result of preterm birth or some other cause (e.g. traumatic injury, intrauterine posture).[282] For some of these conditions, there were specific criteria that could be used to determine whether a condition in a particular individual was a "true" MCM or a result of another cause. For other conditions, no specific criteria were available. These were handled as follows:

1. **Conditions with specific criteria:** Patent ductus arteriosus and peripheral pulmonary artery stenosis were not considered MCMs when occurring in infants born before the 37$^{th}$ week of gestation (instead, their conditions were considered to be a result of prematurity).[282] Codes relating to such conditions were flagged and infants with such codes were then classified as having an MCM if they had a gestational age of ≥37 weeks.

2. **Conditions without specific criteria:** An example of such a condition was hydrocephaly. EUROCAT specifies that all cases should be investigated to determine if the condition could be a result of prematurity, but does not define specific criteria.[282] Furthermore, hydrocephalus may also be a result of traumatic injury or infection. Examining the entire medical record of all infants with such a code was not feasible and would not necessarily provide information about the cause of the condition. It was decided that codes from the 'P' chapter that described '*congenital hydrocephalus*' would be retained, conservatively. However, codes outside the P chapter that simply said '*hydrocephalus'* were excluded as they could be used to record hydrocephaly that was not congenital in origin.

### 5.4.2 Codes that could relate to minor or potentially minor malformations

Some of the codes in the initial code list related to minor malformations and could be removed from code lists. Others were only considered minor if certain criteria defined by EUROCAT were met and had to be considered on a case-by-case basis. Finally, there were also codes that were non-specific and could have been used to encode major or minor conditions. Criteria for the inclusion or exclusion of such codes were discussed and defined as follows:

1. **Clearly related to minor malformations.** Some codes were clearly defined as being minor in EUROCAT guidelines and therefore were flagged for exclusion from code lists. An example of such a code was '*tongue tie*'.
2. **Minor only if specific criteria were met. '***Hydronephrosis'*, for example, was only considered minor by EUROCAT when there was a pelvic dilatation of <10 millimetres but available codes did not provide this level of detail. Such codes were therefore considered based on the neonatologist's experience. If the majority of such conditions recorded in electronic health records in early childhood were likely to be major then the code was retained in the code list.
3. **Non-specific and could potentially be used to record MCMs. The** purpose of EUROCAT guidelines is to provide registries with a standardized framework to code and transmit data on MCMs to the central registry.[282] These guidelines have not been adopted in clinical practice, however, and so some of the ICD-10 codes defined by EUROCAT as relating to minor malformations may have been used to encode major or minor malformations in electronic health records. For example, EUROCAT specifies that the ICD-10 code '*other congenital deformities of skull, face and jaw*' should be used to encode minor malformations but this code may be used variably by clinicians to record major or minor malformations in hospital records. Such codes were discussed with the consultant neonatologist. It was agreed that clinicians were unlikely to be using these codes to refer

exclusively to minor conditions and that, to ensure that all MCMs were captured, such codes would be retained in code lists.

### 5.4.4 Codes relating to major malformations with known causes

As described in **Section 4.4.1**, pregnancies were excluded if they resulted in an MCM that had a known cause (i.e. a chromosomal abnormality, inherited genetic mutation or a specified exogenous cause such as exposure to a known teratogen like warfarin). As there was no complete guide to define codes for such MCMs, they were defined using a combination of EUROCAT guidelines and discussion with the consultant neonatologist.[283] Their presence in infant records or maternal records during the antenatal period was used to exclude pregnancies from analyses (**Appendix 4**).

All BPA-modified ICD-10 codes in the Q900-999 (*chromosomal anomalies*) subgroup were used to define major malformations with known causes as well as: Q800-809 (*congenital icthyosis*), Q810-819 (*epidermolysis bullosa*), D1810 (*lymphangioma*), D215 (*benign neoplasm of the pelvis*), D821 (*DiGeorge Syndrome*), Q860-868 (*congenital malformation syndromes due to exogenous causes, not elsewhere classified*), and the equivalent Read codes. Next, codes for syndromes with a known cause were considered. Syndromes are recognizable patterns of malformations that can be related to the same known cause such as a chromosomal abnormality, although not all syndromes fit this definition (e.g. Arnold-Chiari syndrome).[282] Remaining codes were identified if the consultant neonatologist advised that the majority of individuals with such a condition had a chromosomal aberration, inherited mutation or that the condition was known to be caused by a specified exogenous cause such as a particular teratogenic drug.

## 5.5 Use of code lists to identify congenital malformations in live-born infants

Following their development and refinement, code lists were used to search the records of eligible live-born infants for evidence of MCMs. The Read code list was used to search the clinical, referral and test files in CPRD. The ICD-10 code list was then used to search all

diagnoses in the HES episode file whilst the OPSC-4 code list was used to search all procedures in the HES procedures file. Finally, ICD-10 codes were also used to identify evidence from ONS mortality data; all causes of death were examined.

Each live-born infant could have multiple records from various data sources indicating evidence of an MCM. Each infant could be classified as having an MCM in more than one anatomical subgroup but was only counted once as having evidence of any MCM. Infants with an MCM with a known cause (or a congenital infection known to cause MCMs) were identified and the related pregnancies was excluded from analyses.

As congenital malformations arise *in utero*, it is not possible to know the date on which they occurred. The date on which they were recorded was used instead. For MCMs recorded in the CPRD, this was the 'event date' recorded by the GP. In HES data, the date on which a diagnosis is made is not provided. The 'episode start date' was therefore used as the earliest alternative when using HES data. For ONS mortality data, the ONS 'death date' was used.

Of the 53,582 records of MCMs among eligible infants, 2% (n=1,057) appeared to have a recording earlier than the pregnancy's estimated delivery date in the Pregnancy Register. In such cases, either the delivery date for the pregnancy was inaccurate (and actually occurred earlier) or the recording of the MCM was inaccurate (and actually occurred later). It was not possible to know with any certainty which of these was the case. Adjusting the pregnancy delivery date would have implications on how the start of pregnancy and trimester dates were defined. Furthermore, it would involve adjusting only those pregnancies that resulted in an MCM and could result in bias. Therefore, it was decided that the delivery date would remain the same. Instead, for these records, the date that the MCM was ascertained would be adjusted to be the same as the delivery date as this is the earliest that an MCM could be recorded in the live-born infant's records.

## 5.6 Identifying antenatal diagnoses of MCMs

Vaccine safety analyses were originally planned to include MCMs identified antenatally and postnatally. Antenatal evidence of MCMs would be identified by searching for evidence in maternal records during pregnancy. The limitations of this approach, and the potential to introduce bias, were assessed by examining antenatal diagnoses and vaccine uptake for those pregnancies that did not result in a live-birth with a linked infant (**Section 8.6**). Based on results from this assessment, safety analyses were restricted to MCMs diagnosed postnatally among live-births with linked infant records.

An initial set of Read and ICD-10 codes relating to MCMs detected antenatally was provided by Sara Thomas. This was then supplemented by examining codes from the 'L' chapter that covers obstetric care; relevant conditions were added to the code list. All codes were required to specify that they related to the foetus or the pregnancy in some way so as not to be confused with evidence of the mother having an MCM herself.

Codes relating to antenatal evidence of MCMs often lacked specificity. To aid in the interpretation of evidence, codes were classified as follows:

1. **Level 1 codes were the most specific**. They included terms which described the presence of a foetal malformation (e.g. '*Fetus with central nervous system malformation*').
2. **Level 2 codes were moderately specific**. They included terms which indicated that there was a suspected foetal malformation (e.g. '*Suspect fetal spina bifida'*).
3. **Level 3 codes were the least specific.** They described an abnormality that could relate to a malformation or could relate to some other abnormality of the pregnancy (e.g. '*Antenatal ultrasound scan abnormal*').

Evidence of an antenatal malformation was searched for anytime during the pregnancy and up to 8 weeks after estimated delivery date to account for any delayed recording (e.g. a GP noting

that there was antenatal evidence of a diagnosis that was then confirmed after delivery). Code lists to identify antenatal evidence of eligible MCMs in maternal records are provided in **Appendix 3**.

## 5.7 Chapter Summary

This chapter considered the key lessons from the systematic review of the methods used to identify congenital malformations in UK electronic health records. These were applied here to develop a comprehensive algorithm to identify MCMs from linked CPRD, HES and ONS mortality data. Unlike previous approaches, the methods described here include an overview of the rationale used when considering codes that are non-specific. Among Read codes, the greatest challenge was considering the inclusion/exclusion of codes that were from chapters not dedicated to congenital malformations, and which could therefore refer to non-congenital conditions. For ICD-10 codes, this was less of a challenge due to the fact that only codes from the dedicated 'Q' chapter were considered. Instead, for ICD-10 codes, the greatest challenge was the lack of granularity between codes. Unlike the EUROCAT BPA-modified ICD-10 codes, the ICD-10 codes used in HES have three digits. Furthermore, clinical coders do not follow these guidelines when coding congenital malformations. This meant that some codes could be used to record major or minor malformations. Decisions on how to handle these challenges and codes were made with the input of an experienced consultant neonatologist.

# 6. Identifying the influenza vaccination status of pregnant women

## 6.1 Introduction

This chapter describes how the influenza vaccination status was determined for each pregnancy using CPRD primary care data. The background to maternal influenza vaccination in the UK is described in **Section 1.5**. The CPRD database is described in **Section 3.1** and the general approach to data management in CPRD is described in **Section 3.7**. This chapter covers the availability of the influenza vaccine (**Section 6.2**) and the data used to identify evidence of vaccination (**Section 6.3**). Vaccination-related criteria used to exclude pregnancies from analyses on the safety of SIIV and PIIV are also described. Exclusions were grouped into those due to uncertainty in vaccination timing (**Section 6.4**) and those due to uncertainty in the type of influenza vaccine received (**Section 6.5**).

## 6.2 Annual availability of the influenza vaccine

UK guidelines for maternal influenza vaccination have varied over the last decade (**Figure 1.1**). Prior to the 2009/10 pandemic, only pregnant women in clinical risk groups were vaccinated against influenza. During the 2009/10 pandemic, all pregnant women were offered PIIV and those in clinical risk groups could also have been offered SIIV until PIIV became available.[12] In 2010/11, guidelines stated that all pregnant women should be offered SIIV, unless they had already received PIIV (which was available for use in the event of a shortage of SIIV).[13] From 2011/12 onwards, all pregnant women have been offered SIIV and PIIV has not been used.[4, 13]

To be eligible for inclusion in either the SIIV or PIIV safety analysis, pregnancies had to overlap with a period of influenza vaccine availability by at least one week. In the UK, SIIV becomes available as early as September each year in preparation for the seasonal influenza epidemic. Circulation of influenza can continue into March and SIIV may be offered as late as this.[284, 285] The period during which influenza vaccine was likely to be available (and eligible pregnancies

had to overlap with), referred to as the 'vaccination period,' was defined as follows for analyses on SIIV and PIIV:

1. **SIIV**: 1st September - 31st March for influenza seasons between 2010/2011 - 2015/16.
2. **PIIV**: 21st October 2009 (the date PIIV became available in the UK) - 31st March 2010.[12]

## 6.3 Evidence of vaccination in primary care records

**CPRD files containing vaccination evidence**

In CPRD, information on vaccinations can be found in the 'immunisation' file, 'therapy' file or 'clinical' file. In the immunisation file, immunisation type codes are used to record the vaccine type and can be used in conjunction with an immunisation status variable to determine whether the vaccine in question was given, refused or advised. In the therapy file, records are automatically created when prescriptions are generated and therefore vaccines can be assumed to have been administered when patients have a relevant product code in this file. In the clinical file, Read codes can also be used to record information about vaccination.

**Code lists used to identify vaccinations**

Initial immunisation type, product and Read code lists to identify records relating to influenza vaccination in maternal immunisation, therapy and clinical files were provided by Sara Thomas (a clinical epidemiologist) (**Appendix 6**). Codes were then classified by:

1. **Vaccine type**: SIIV, PIIV or unknown/unspecified type.
2. **Status**: received, refused, advised, contraindicated/not indicated, given elsewhere, adverse effects following administration.

Codes relating to the vaccine being advised or adverse effects of vaccination were not utilized because they were not necessarily indicative of the timing of vaccination. Using the above files and code lists, all vaccination records were identified for all eligible pregnant women at any time. For each woman, vaccination records were then divided into those that occurred within a vaccination period and those that occurred outside (April 1st – August 31st).

**Using evidence from the clinical file**

The clinical file is considered to be the least reliable file for identifying vaccinations. This is because, unlike the immunisation and therapy files, Read codes in the clinical file tend to be less specific about whether a vaccine was given. For example, in the clinical file, Read codes such as '*consent given for seasonal influenza vaccination*' could mean a patient consented to receiving the vaccine but does not necessarily mean the vaccine was administered.

The proportion of pregnant women for whom the clinical file was the sole source of evidence of vaccine receipt evidence across a particular vaccination period was very low (0.5%, n=550) (**Table 6.1**). An examination of the Read codes used among these women indicated that just 21.2% specified a vaccine had been given whilst the rest were non-specific (**Table 6.2**). However, because only a small proportion of women had evidence of vaccine receipt from just the clinical file, it was judged that the overall potential for misclassification of vaccination status by including these women was low.

**Table 6.1 - Source of vaccination receipt evidence for each woman and vaccination period.**

| File(s) from which vaccination receipt evidence was identified | Number of women (%) |
|---|---|
| Therapy file only | 727 (0.6) |
| Immunisation file only | 81,095 (67.4) |
| Clinical file only | 550 (0.5) |
| Therapy and immunisation files | 17,828 (14.8) |
| Therapy and clinical files | 234 (0.2) |
| Immunisation and clinical files | 15,278 (12.7) |
| Therapy, immunisation and clinical files | 4,559 (3.8) |

**Table 6.2 - Read terms used among women whose only evidence of vaccination receipt across a vaccination period came from the clinical file**.

| Read term | Number of women with Read code (%) |
|---|---|
| Consent given for pandemic influenza vaccination | 25 (4.2) |
| Consent given for seasonal influenza vaccination | 24 (4.1) |
| First pandemic influenza vaccination | 11 (1.9) |
| Influenza vacc consent given | 80 (13.6) |
| Influenza vaccination | 294 (49.8) |
| PANDEMRIX - first influenza A (H1N1v)2009 vaccination given* | 125 (21.2) |
| Seasonal influenza vaccination | 23 (3.9) |
| [V]Flu - influenza vaccination | 7 (1.2) |
| [V]Influenza vaccination | 1 (0.2) |

*The most specific vaccination receipt code. Remaining codes were non-specific in terms of whether or not the vaccine was received.

**Deciding on the use of evidence from multiple files**

Within a vaccination season, it was possible for a woman to have multiple records indicating a vaccine had been received and for these to occur on different days, in different files and relate to different types of influenza vaccine (**Table 6.3**). The earliest record of vaccination receipt within a vaccination period was considered the most accurate vaccination date for the woman, as subsequent records in the season could indicate re-recording of a previously received vaccine. However, if a woman's earliest evidence was recorded in the clinical file and was followed by a later record in the more reliable immunisation or therapy file, it was not clear which information should be used. As the gestational age at the time of vaccination was critical in the planned safety analyses, this was explored.

**Table 6.3 – Scenarios of conflicting influenza vaccination receipt records in pregnant women, within a single vaccination period.**

| Woman | Vaccination Period | Vaccination Date | Flu Vaccine Type | File | Summary of evidence for each woman, by vaccination season |
|---|---|---|---|---|---|
| 1 | 2010/11 | 01 Nov 2010 | Seasonal | Therapy | **Woman 1** has two vaccine receipt records in the **2010/11** period. They are both from the therapy file. The earliest record occurs in November 2010. Both records relate to SIIV. |
| 1 | 2010/11 | 01 Jan 2011 | Seasonal | Therapy | |
| 1 | 2011/12 | 01 Feb 2012 | Seasonal | Therapy | **Woman 1** has two vaccine receipt records in the **2011/12** period. They are from the therapy and immunisation files but occur on the same date. One record indicates an SIIV, the other record does not specify the vaccine type. |
| 1 | 2011/12 | 01 Feb 2012 | Unspecified | Immunisation | |
| 2 | 2013/14 | 15 Sept 2013 | Unspecified | Clinical | **Woman 2** has three vaccine receipt records in the **2013/14** period. The earliest comes from the clinical file but a month later she has two further records in the immunisation file. There is one record relating to an SIIV, the other two records do not specify the vaccine type. |
| 2 | 2013/14 | 15 Oct 2013 | Seasonal | Immunisation | |
| 2 | 2013/14 | 15 Oct 2013 | Unspecified | Immunisation | |
| 3 | 2010/11 | 01 Dec 2010 | Pandemic | Clinical | **Woman 3** had two vaccine receipt records in the **2010/11** period. They are both from the clinical file on the same day. One record specifies a PIIV, the other an SIIV. |
| 3 | 2010/11 | 01 Dec 2010 | Seasonal | Clinical | |
| 4 | 2010/11 | 01 Dec 2010 | Unspecified | Clinical | **Woman 4** has two vaccine receipt records in the **2010/11** period. They are both from the clinical file, with the earliest in December. Neither record specifies the type of vaccine used. |
| 4 | 2010/11 | 01 Jan 2011 | Unspecified | Clinical | |

**Records relating to vaccination were identified from maternal therapy, immunisation and clinical files. A woman could have multiple records indicating a vaccine was received on different dates and from different files. The influenza vaccine type could also be inconsistent across the vaccination period.**

Across a vaccination period, almost 13% of women had evidence of vaccine receipt in both the immunisation and clinical files (n=15,278) whilst fewer women had evidence in both the therapy and clinical file (0.2%; n=234) or all three files (3.8%; n=4,559) (**Table 6.1)**. However, very few of the women with vaccination evidence from multiple files had their earliest vaccination evidence from the clinical file. Among those with evidence in the immunisation and clinical files, 2.8% had their earliest evidence in the clinical file (n=432) and over 75% of these had specific Read codes that indicated a vaccine had been given (**Table 6.4 & 6.5**). Just 3.4% (n=8) of those with evidence in the therapy and clinical files had their earliest evidence in the clinical file and this was even lower for those with evidence from all three files (0.5%; n=23)(**Table 6.4**). These data demonstrated that the earliest evidence of vaccination was most likely to be recorded in the therapy or immunisation file and that few women had their earliest evidence in the clinical file. Treating all files equally and choosing the earliest evidence of vaccination was, therefore, unlikely to introduce considerable misclassification in vaccination timing.

**Table 6.4 - Source of the earliest evidence of vaccine receipt among women with evidence of receipt from multiple files.**

| **All files in which a woman had evidence of vaccine receipt** | **File(s) earliest evidence of vaccination receipt came from No. of women (%)** | | | | | | |
|---|---|---|---|---|---|---|---|
| | Therapy | Immunisation | Clinical | Therapy & Clinical | Therapy & Immunisation | Immunisation & Clinical | Therapy, Immunisation & Clinical |
| Therapy & immunisation (n=17,828) | 583 (3.3) | 177 (1.0) | - | - | 17,068 (95.7) | - | - |
| Therapy & clinical (n=234) | 63 (26.9) | - | 8 (3.4) | 163 (69.7) | - | - | - |
| Immunisation & clinical (n=15,278) | - | 956 (6.3) | 432 (2.8) | - | - | 13,890 (90.9) | - |
| Therapy, immunisation & clinical (n=4,559) | 72 (1.6) | 7 (0.2) | 23 (0.5) | 9 (0.2) | 115 (2.5) | 23 (0.5) | 4,310 (94.5) |

**Table 6.5: Read terms used among women with evidence of vaccination in the immunisation and clinical file but whose earliest evidence of vaccination receipt came from the clinical file**.

| Read term | Number of women with Read code (%) |
|---|---|
| Consent given for pandemic influenza vaccination | 3 (0.7) |
| Consent given for seasonal influenza vaccination | 6 (1.4) |
| First pandemic influenza vaccination | 19 (4.4) |
| Influenza vacc consent given | 11 (2.5) |
| Influenza vaccination | 56 (12.9) |
| PANDEMRIX - first influenza A (H1N1v)2009 vaccination given* | 334 (76.8) |
| PANDEMRIX - second influenza A (H1N1v) 2009 vaccination given* | 1 (0.2) |
| Seasonal influenza vaccination | 4 (0.9) |
| [V]Influenza vaccination | 1 (0.2) |

*Most specific evidence of vaccination

## 6.4 Exclusion criteria for pregnancies with uncertainty in vaccination timing.

Determining the trimester of vaccination was crucial for the work described in this thesis as most MCMs are likely to occur in the first trimester, when the majority of organogenesis occurs. In **Section 4.3**, a number of pregnancy-related exclusion criteria were described. The purpose of some of these was to minimize the potential for misclassification of the trimester of vaccination when pregnancy timings were uncertain. Here, exclusions to minimize the potential for misclassification when the timing of vaccination was uncertain are described.

**1. Vaccine refusal, contraindication or non-indication on the same date as the earliest evidence of vaccine receipt within a vaccination period.**

Within a vaccination period, all records relating to vaccination refusal, contraindication or non-indication were identified. If a woman's earliest record of vaccination receipt coincided with such a record it was impossible to know whether or not she had received the vaccine. Evidence of such a record before or after the earliest evidence of receipt did not constitute a conflict because a woman could accept or be given a vaccine at a later date or could decline vaccination if she had been vaccinated earlier in the season. Pregnancies belonging to women that had concurrent records of vaccination receipt and refusal, contraindication or non-indication were excluded.

**2. Vaccination evidence outside of the vaccination period.**

Records relating to vaccination between the 1st April and 31st August each year were identified. Evidence of vaccination between April and August was considered to be a retrospective recording of a vaccine that had been received in the prior vaccination season. Pregnancies were excluded if the only evidence of a vaccination occurred between vaccination periods because it was not possible to determine when the vaccination had occurred. If there was evidence of vaccination within the vaccination period and then further vaccination evidence between April and August, the pregnancy was not excluded and the earliest evidence of vaccination within the vaccination period was used.

**3. Evidence of vaccination given outside the practice.**

Evidence of the vaccine being given outside the practice was established using information in the immunisation and/or clinical files. Although GPs are required to record vaccinations occurring outside of the practice, it was not possible to know when these occurred.[73] For this reason, it was decided that if any such evidence occurred within the period of the pregnancy, the pregnancy would be excluded. It was considered possible that women with such evidence before their pregnancy could continue to receive their vaccinations elsewhere. Preliminary checks of the data indicated that among 1,222 pregnancies with such evidence anytime before their estimated start date, over 60% had this evidence in the 2 years prior. Excluding pregnancies with evidence anytime before the estimated start date would not significantly reduce the number of available pregnancies and so it was decided that a conservative approach would be taken and all such pregnancies excluded. Pregnancies with a record of vaccination given elsewhere in the year after the pregnancy had ended were also excluded to account for any retrospective recording by GPs.

**4. Vaccination receipt records before or after the pregnancy.**

It was possible for a woman's earliest evidence of vaccination within a vaccination period to occur before or after her pregnancy. Vaccination could occur before the pregnancy if the woman was in a clinical risk group or was a healthcare worker and was offered the vaccine

regardless of her pregnancy status. Alternatively, it was possible that the pregnancy start date was inaccurate and the pregnancy occurred earlier. Therefore, it was not possible to be certain that the vaccine hadn't been received during pregnancy and such pregnancies were excluded from analyses. To account for imprecision in the timing of the start of pregnancy and the fact that vaccination occurring shortly before pregnancy could have residual effects that lasted into the first trimester, pregnancies were included in a sensitivity analysis if a vaccine had been received in the 4 weeks prior to the pregnancy start date.

Vaccination could occur after a pregnancy if the woman had some other reason to be offered the vaccine such as being in a clinical risk group or being a healthcare worker. It was unclear why such women would not be offered the vaccine during their pregnancy, instead. Although the earliest vaccination receipt record in each season was used, it was also possible that a vaccination record occurring after pregnancy could be a retrospective recording of a vaccination that occurred during pregnancy. Again, because it was not possible to know whether and when such pregnancies were truly unvaccinated, they were excluded from analyses.

**5. Pregnancies that overlapped with two vaccination periods and received a vaccine in both.**
Pregnancies could overlap with two vaccination periods and have evidence of vaccination in both. Four scenarios were considered:

The first involved two vaccination records during pregnancy, one in each season (**Figure 6.1A**). Whilst it was possible that a vaccine was given in both seasons, it was also possible that the second vaccination was a retrospective recording by the GP. To account for the possibility that the pregnancy had been vaccinated twice, one strategy would be to examine effect modification between vaccinations in different trimesters. However, the number of such pregnancies was too low for this and so these pregnancies were excluded.

The second scenario involved a vaccination record before pregnancy in the first season and a further vaccination record during pregnancy in the second season (**Figure 6.1B**). The third

scenario related to those pregnancies that had a vaccine record during their pregnancy in the first season and another after the pregnancy in the second season (**Figure 6.1C**). The reasons for a vaccination record occurring before the start of a pregnancy or after the end of a pregnancy are described in the previous section. It was not possible to know whether such pregnancies had received two vaccines or not and so they were excluded.

The final scenario involved one vaccine being given in the first season before the pregnancy and one vaccine being given in the second season after the pregnancy (**Figure 6.1D**). The reasons for this occurrence were a combination of those described in the previous section. As it was not possible to be certain that such pregnancies were unvaccinated, they too were excluded.

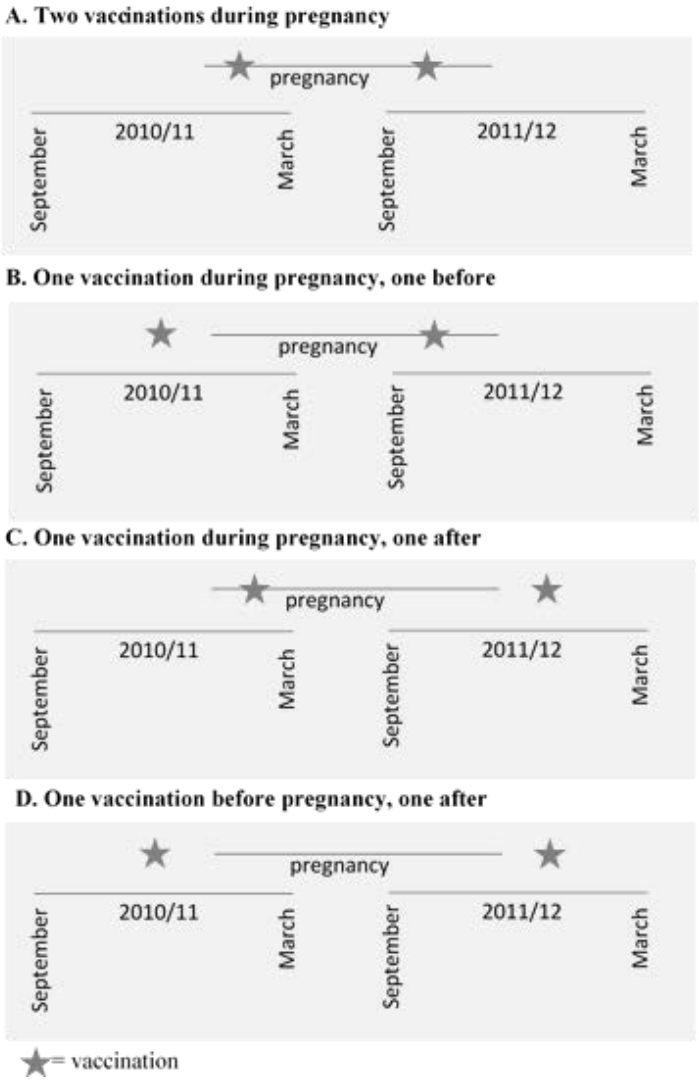



**Figure 6.1 – Scenarios for pregnancies overlapping with two vaccination periods, with vaccination receipt records in both**.

## 6.5 Exclusion criteria for pregnancies with uncertain vaccine type

As described in **Section 1.6.2**, one of the key limitations of the available safety evidence for maternal influenza vaccination with respect to MCMs was the small number of studies examining SIIV alone. To minimize the possibility that analyses examining SIIV included pregnant women who had received PIIV (and vice versa for the analysis on PIIV safety), pregnancies were excluded if there was any uncertainty in the type of influenza vaccine received.

Uncertainty in the type of influenza vaccine received could occur because of vaccination codes that did not specify whether the vaccine given was SIIV or PIIV. Furthermore, women could have multiple records within a vaccination period indicating a vaccine was received and the type of vaccine given was not always consistent (**Table 6.3**). Uncertainty about the vaccine type had to be considered in the context of the vaccines available and recommended for pregnancies in a particular vaccination period. The scenarios considered, and the exclusion criteria developed, are described below.

**1. Uncertainty around the type of influenza vaccine received for those pregnancies potentially eligible for the safety analysis of SIIV**

To be potentially eligible for the seasonal vaccine safety analyses, women had to be pregnant for at least one week in the 2010/11 vaccination period or a subsequent vaccination period.

In 2010/11, SIIV was offered to all pregnant women in any trimester but PIIV was still available and some may have received PIIV if stocks of SIIV were low (**Figure 1.1**).[12] Pregnancies were therefore excluded from this analysis if there was any evidence PIIV had been received or if there was only evidence of an unspecified vaccine type across the season (as it was not possible to know if the woman received PIIV).

In seasons after 2010/11, only SIIV was offered to pregnant women. A small number of pregnancies that had evidence of PIIV were excluded. It was thought these records could

relate to the GP re-recording that the woman had received PIIV during the pandemic or that these were data entry errors. Unspecified vaccine type in the years after 2010/11 was thought to relate to SIIV (as PIIV was no longer available) and was not used as an exclusion criterion.

**2. Uncertainty around the type of influenza vaccine received for those pregnancies potentially eligible for the safety analysis of PIIV**

To be potentially eligible for pandemic vaccine safety analyses, women had to be pregnant for at least one week in the 2009/10 vaccination period. During the 2009/10 pandemic, PIIV was available for all pregnant women but some women, such as those who were in clinical risk groups and healthcare workers, may also have been offered SIIV until PIIV became available (**Figure 1.1**).[12] Pregnancies were excluded from analyses of the safety of PIIV if there was any evidence SIIV had been received within the season or if there was only evidence of an unspecified vaccine type across the season (as it was not possible to know if this was SIIV).

**3. Uncertainty around the type of influenza vaccine received for those pregnancies potentially eligible for either SIIV or PIIV safety analyses**

Pregnancies that overlapped with both 2009/10 and 2010/11 vaccination periods by a week were potentially eligible for both the SIIV and PIIV safety analysis. In addition to following the exclusion criteria set out for pregnancies overlapping two vaccination periods (**Figure 6.1**), uncertainty in the type of vaccine received was also considered. Pregnancies that overlapped with both 2009/10 and 2010/11 were excluded from SIIV analyses if there was any evidence of a vaccine being received in the 2009/10 season (**Figure 6.2A**). Pregnancies overlapping both seasons were excluded from the PIIV analyses if there was any evidence of a vaccine being received in the subsequent 2010/11 season (**Figure 6.2B**). Pregnancies could be included in both analyses if there was no evidence of a vaccine being received in either (**Figure 6.2C**).

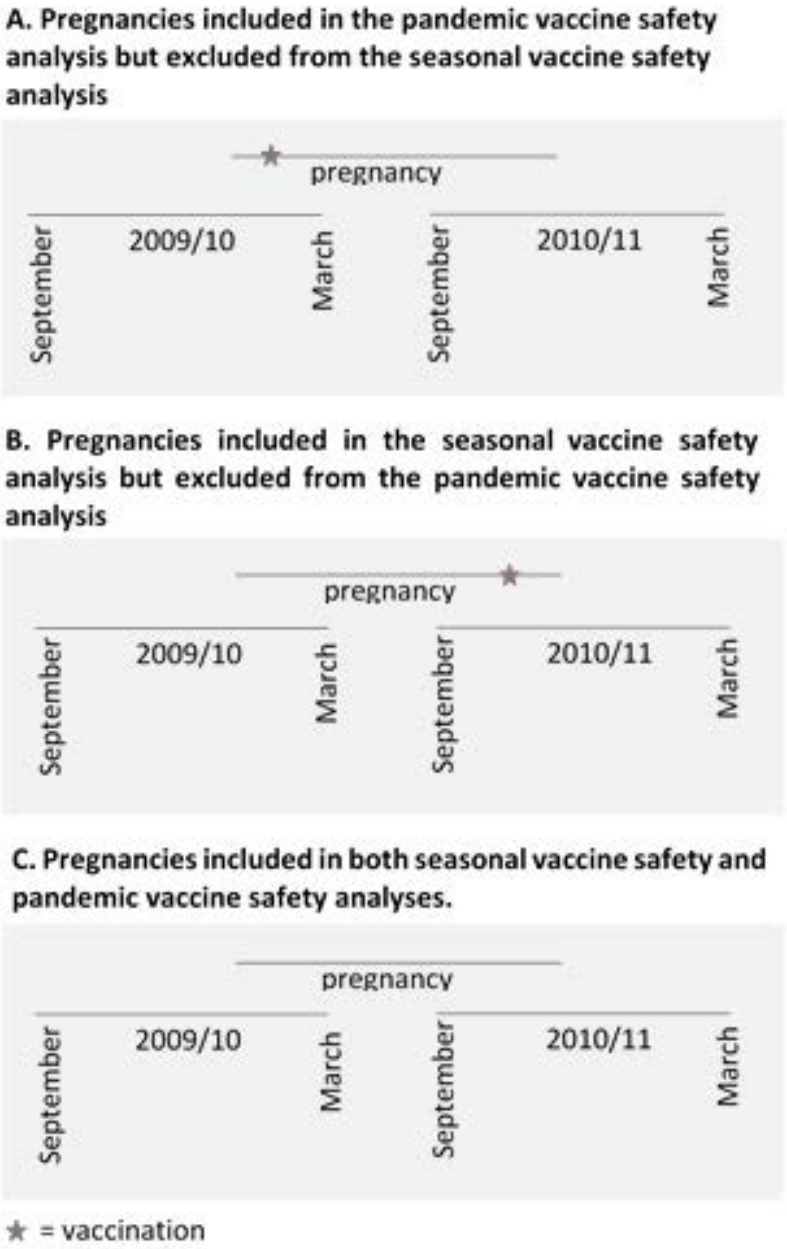



**Figure 6.2 – Additional exclusion criteria for pregnancies that overlapped with both the 2009/10 and 2010/11 seasons.** Pregnancies that overlapped with the 2009/10 and 2010/11 seasons were considered for pandemic vaccine safety analyses and seasonal vaccine safety analyses as described above. It should be noted that pregnancies where a vaccine was received before or after the start or end of pregnancy were excluded based on criteria described in **Section 6.4.5**.

## 6.6 Summary of vaccination exclusion criteria

In summary, pregnancies were excluded from vaccine safety analyses if:

1. They did not have at least one week of overlap with a period in which SIIV or PIIV was available.
2. The earliest evidence of vaccination receipt coincided with a record indicating non-receipt.
3. The only evidence of a vaccine being received occurred between April and August, after the vaccination period had ended.
4. There was evidence of the vaccine being given elsewhere anytime before the pregnancy, during the pregnancy, or in the year after the pregnancy.
5. There was evidence of a vaccination occurring within a vaccination period but before or after pregnancy.
6. The pregnancy overlapped with two vaccination periods and there was evidence that a vaccine had been received in both.
7. The pregnancy was potentially eligible for the pandemic analysis but had evidence of receiving SIIV or no information about the vaccine type received.
8. The pregnancy was potentially eligible for the seasonal analysis but had evidence of receiving PIIV or no information about the vaccine type received.

# Results Section

The findings of the work conducted in this thesis are presented in this section.

**Chapter 7** addresses **Objective 3** and examines the value of CPRD, HES and ONS data in identifying MCMs among live-born infants. It also addresses **Objective 4** and compares the prevalence of MCMs in these data with external data sources.

**Chapter 8** presents the results from a large, historical cohort study that examined the association between SIIV given during pregnancy and MCMs in the first year of life. Analyses are stratified by trimester. This chapter addresses **Objective 5.**

**Chapter 9** presents the results from a historical cohort study that examined the association between PIIV given during pregnancy and MCMs in the first year of life. Analyses are stratified by trimester. The chapter also describes the relationships observed between confounding factors, maternal influenza vaccination and MCMs in the context of what is known from the literature. This chapter addresses **Objective 6.**

# 7. The ascertainment of major congenital malformations in linked UK electronic health records

## 7.1 Introduction

A systematic review of the methods used to identify congenital malformations in UK electronic health records (**Chapter 2**) informed the development of an algorithm to identify MCMs in linked primary care records, hospital admissions and death certificates (**Chapter 5**). In this chapter, the algorithm was used to identify MCMs among live-born infants and **Objectives 3 & 4** were addressed.

The value of linked data in ascertaining individuals with MCMs was first assessed. The prevalence of MCMs in stand-alone and linked data sources was compared and the agreement between data sources, as well as their unique contribution, was examined (**Objective 3**). The prevalence of MCMs identified from the data sources used in this thesis was then compared with the prevalence from a published study using THIN (another population-based database of electronic primary care records in the UK) and English EUROCAT registries (**Objective 4**).

The chapter begins with an overview of the way in which the study population was derived in **Section 7.2**. In **Section 7.3**, which is presented in the form of a manuscript prepared for submission, the value of linked data in ascertaining individuals with MCMs is explored (**Objective 3**). In **Sections 7.4-7.5**, prevalence comparisons with external data sources are presented (**Objective 4**). Results from the chapter are summarized in **Section 7.6**.

## 7.2 Deriving the eligible study population

After applying the pregnancy exclusion criteria described in **Chapter 4,** there were 199,017 potentially eligible pregnancies that ended between January 1, 2009 and March 31, 2016. All infants delivered were eligible for HES and ONS linkage. For the studies described in this chapter, all infants were required to have the potential for a year of follow-up. Linked data were available until March 31, 2016 and so this was achieved by excluding pregnancies delivering after March 31, 2015. The study population was then restricted to live-birth pregnancies with a linked infant. Finally, to align with future exclusion criteria for vaccine safety studies, pregnancies were excluded if there was evidence of a congenital infection known to be associated with MCMs or evidence of an MCM with a known cause such as a chromosomal abnormality. The derivation of the study population is summarized in **Figure 7.1**.

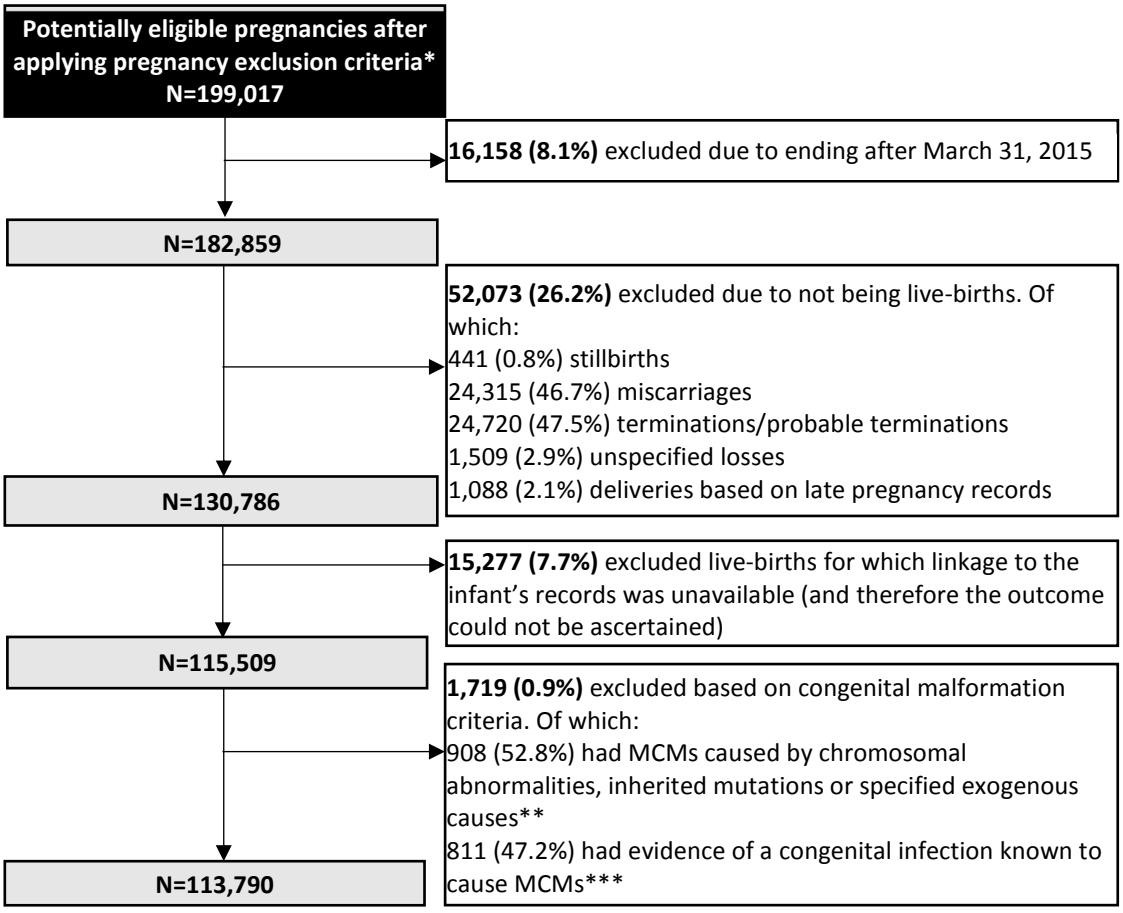



**Figure 7.1 - Deriving the study population to assess the ascertainment of MCMs in different data sources.** *The initial population of 199,017 pregnancies included those ending between January 1, 2009 and March 31, 2016. All live-born infants were eligible for linkage to HES and ONS. This flow diagram includes all potentially eligible pregnancies, in comparison to Figure 1 of the paper which presents only those pregnancies ending in live-births; **See Section 4.4.1; ***See Section 4.4.2. Abbreviations: MCM, Major Congenital Malformation; HES, Hospital Episode Statistics; ONS, Office for National Statistics.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

## SECTION A – Student Details

| | | | |
|---|---|---|---|
| **Student ID Number** | 1300677 | **Title** | Miss |
| **First Name(s)** | Maria | | |
| **Surname/Family Name** | Peppa | | |
| **Thesis Title** | The safety of influenza vaccination in pregnancy: Examining major congenital malformations as potential adverse outcomes using UK electronic health records | | |
| **Primary Supervisor** | Professor Punam Mangtani | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

## SECTION B – Paper already published

| | | | |
|---|---|---|---|
| Where was the work published? | | | |
| When was the work published? | | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | | | |
| Have you retained the copyright for the work?* | Choose an item. | Was the work subject to academic peer review? | Choose an item. |

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

## SECTION C – Prepared for publication, but not yet published

| | |
|---|---|
| Where is the work intended to be published? | Pharmacoepidemiology & Drug Safety |
| Please list the paper's authors in the intended authorship order: | Maria Peppa, Caroline Minassian, Punam Mangtani, Jemma L Walker, Stephen T Kempley, Nick J Andrews, Sara L Thomas |

| | |
|---|---|
| Stage of publication | **Not yet submitted** |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | This study was conceptualized and designed by P Mangtani, S Thomas, C Minassian and myself. I developed initial code-lists for MCMs and these were discussed and agreed with S Kempley, P Mangtani and S Thomas. I carried out the data management and analyses involved, with frequent discussion with co-authors to ensure agreement. I drafted the manuscript and revised it following comments from co-authors. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | Maria Peppa |
| **Date** | 19.03.2020 |

| | |
|---|---|
| **Supervisor Signature** | Punam Mangtani |
| **Date** | 20.03.2020 |

## 7.3 Paper 2: Identifying major congenital malformations in anonymised UK electronic health records: the value of primary care, hospital admissions and mortality data.

**Authors:** Maria Peppa[a*], Caroline Minassian[a], Punam Mangtani[a], Jemma L Walker[a,b], Stephen T Kempley[c], Nick J Andrews[b], Sara L Thomas[a].

[a]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London, United Kingdom

[b]Statistics, Modelling and Economics Department, Public Health England, Colindale Avenue, London, United Kingdom

[c]Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

*Corresponding author

## Abstract

**Purpose**

Anonymised UK electronic primary care data are increasingly used to identify major congenital malformations in post-licensure safety studies of drugs and vaccines given in pregnancy. However, these data may under-record major malformations identified during hospital admissions or after infant death. This study explored the value of different UK data sources in identifying congenital malformations.

**Methods**

Live-born singleton infants delivered between 2009 and 2015 and recorded in the UK Clinical Practice Research Datalink were selected. The prevalence of major malformations in the year after delivery was calculated using stand-alone and linked records from primary care, hospitalisations and death certificates. The proportion of infants with a recorded major malformation in multiple and single data sources was calculated to assess the agreement and contribution of each source.

**Results**

The study population included 113,790 infants of whom 7,931 (7%) had a major malformation recorded in at least one data source in the year after delivery. The prevalence of major malformations in the year after delivery was 265.7/10,000 person-years (95% CI, 256.0-275.8) in the primary care data and 745.8/10,000 person-years (95% CI, 729.6-762.4) in linked data. Among infants with a major malformation recorded in the year after delivery, 20% had evidence of their condition in both their primary care and hospitalisation records, 65% had evidence exclusively in hospitalisation data and 15% had evidence solely in their primary care records. Just 0.2% had evidence recorded on a death certificate.

**Conclusions**

Stand-alone Clinical Practice Research Datalink primary care data under-ascertain major congenital malformations. Linkage to hospitalisation data should be considered to maximize their ascertainment.

## Introduction

Anonymised electronic health records are frequently used to conduct post-marketing safety assessments of drugs and vaccines used during pregnancy.[175, 286] As they often cover large populations, they are well-suited to the examination of rare outcomes such as major congenital malformations (MCMs).[192, 215] The ability to link electronic health records from different health service settings further increases their potential to ascertain such conditions.[126, 177]

In the UK, safety studies examining MCMs as an outcome have relied on stand-alone primary care databases and linkage to hospitalisation or mortality data has not been explored. Whilst it is a requirement for information about hospitalisations and deaths to be transmitted to general practices, this can be delayed or incompletely recorded in the electronic primary care record which could result in the under-ascertainment of MCMs.[287] Indeed, several studies have demonstrated this to be the case for other clinical outcomes in stand-alone primary care data compared to hospitalisation data.[288-291] Under-ascertainment, if differential by exposure status, can bias effect measures and lead to incorrect conclusions about the safety of the drugs or vaccines examined. More broadly, under-ascertainment can result in underestimates of the burden of disease which can lead to insufficient commissioning of necessary health services.

This open cohort study used UK Clinical Practice Research Datalink (CPRD) primary care data linked to hospitalisation and mortality data to compare the prevalence of MCMs in stand-alone and linked data sources in the year after delivery. The agreement between data sources and the unique contribution of each was quantified. Finally, to establish the value of different follow-up periods in ascertainment, we examined the cumulative ascertainment of MCM records after delivery and until the end of the study period (which ran from January 1, 2009 – March 31, 2016) in stand-alone CPRD and stand-alone HES.

## Methods

### Data Sources

This study was conducted using anonymised, longitudinal primary care data from CPRD GOLD (referred to as CPRD) linked to hospitalisation data from the Hospital Episode Statistics (HES) database and Office for National Statistics (ONS) mortality data. The CPRD/London School of Hygiene and Tropical Medicine Pregnancy Register was used to identify the study population.[255]

At the time of the study, CPRD contained the medical records for 7% of the UK population registered with a general practice and was considered representative in terms of age, sex and ethnicity.[126] Upon joining a practice, data are captured until the patient dies, leaves the practice or the practice ends data collection for CPRD. Clinical data, including diagnoses and procedures, are recorded using Read codes based on consultations at the practice or information relayed from hospitals and specialist units.[126] Diagnostic validity has been shown to be good, including for MCMs.[180, 192, 194, 292, 293]

Of the English practices contributing primary care data to CPRD, 75% are linked to HES and ONS data.[126] Patients with linked data are considered to be broadly similar to those in the whole of CPRD.[253, 254] HES data include diagnoses and procedures, recorded using the International Classification of Diseases (ICD-10) and the Classification of Surgical Operations and Procedures (OPCS-4) coding, respectively.[177] ONS data contain the underlying and contributory causes of death, recorded using ICD-10. Follow-up in HES and ONS ends when the patient dies and is unaffected by the patient leaving the CPRD practice or the practice ending data collection.

The Pregnancy Register contains all pregnancy episodes identified in CPRD, and their outcomes, for women aged 11-49 years.[255] Pregnancies resulting in a live-birth delivery are linked to infant records for those infants registered at the same practice as their mother. Validation against

electronic maternity records in HES has shown most pregnancies to be well-captured in the Pregnancy Register.[255]

**Study Population**

We selected live-born singletons delivered between January 1, 2009 and March 31, 2015 and eligible for HES and ONS linkage. Infants had to be born to mothers registered at an up-to-standard practice (a research quality criterion defined by CPRD)[126] at least six months before the start of pregnancy. As the MCMs of interest in this study were those likely to be assessed in safety studies, infants were excluded if they had a malformation due to known causes (e.g. a chromosomal abnormality).

**Identifying MCMs**

The EUROCAT classification system was used to develop Read, ICD-10 and OPCS-4 code lists for MCMs which were subsequently reviewed by a consultant neonatologist (SK) (these are available at https://datacompass.lshtm.ac.uk/1630/).[86, 282] Codes which could be used to encode major or minor malformations (e.g. '*unspecified congenital malformation of limbs*') were retained to ensure all MCMs were captured. Codes that could potentially relate to non-congenital conditions (e.g. '*pulmonary valve disorders*') were retained if it was likely that they referred to an MCM in the majority of infants.

EUROCAT further classifies MCMs by the anatomical system affected.[86, 282] Subgroups were defined for heart, limb, genital, urinary, nervous system, respiratory, digestive, abdominal, orofacial, eye, and ear, face and neck malformations.[86, 282] MCMs that were not classified by EUROCAT as belonging to one of these subgroups, as well as undefined malformations (e.g. '*congenital anomaly not otherwise specified*'), were categorized as 'other' MCMs. Code lists were then used to search clinical, referral and test files in the CPRD data, episode and procedure files in HES, and all causes of death in ONS.

**Statistical analysis**

*Comparing MCM prevalence in stand-alone and linked data*

The number of infants with evidence of an MCM in the year after delivery was first ascertained in stand-alone CPRD, stand-alone HES and stand-alone ONS data. Prevalence calculations for stand-alone data sources were independent and follow-up was defined separately for each of these to reflect their maximum potential for ascertainment. Follow-up started at delivery and, for CPRD, ended at the earliest of: the date the infant left the practice or died, the date the practice last provided data to CPRD or one year after delivery. For stand-alone HES and stand-alone ONS, follow-up ended at the earliest of: the date the infant died or one year after delivery. Prevalence per 10,000 person-years was calculated alongside 95% confidence intervals. This was repeated for linked CPRD and HES (CPRD-HES) data as well as for linked CPRD, HES and ONS (CPRD-HES-ONS). Follow-up in linked data ended when the infant died or a year after delivery. Prevalence ratios (PRs) were then calculated to compare the prevalence in stand-alone HES with that in stand-alone CPRD and the prevalence in CPRD-HES-ONS with that in stand-alone CPRD and stand-alone HES.

*Assessing agreement and unique contributions of data sources in MCM ascertainment*

To assess agreement in the year after delivery, the proportion of infants with an MCM that had evidence in two or more data sources was calculated. The proportion of infants with evidence exclusively in CPRD, HES or ONS was then calculated to assess the unique contributions of individual data sources. For this analysis, to ensure the opportunity to ascertain MCMs was the same across all three data sources, the same follow-up criteria were used in each of them.

The start of follow-up was delivery and follow-up ended a year after or earlier if the patient died, left the practice or the practice ended data collection. To assess any changes in agreement over time, the analysis was repeated with follow-up extended up to the end of the study period (March 31, 2016).

*Assessing the proportion of infants with non-specific evidence of MCMs in different data sources: Non-specific limb malformation codes as an example.*

We noted that several Read and ICD-10 codes for limb malformations were non-specific and could potentially be used to record major limb malformations, minor limb malformations or even limb conditions that were not congenital in origin (Read and ICD-10 codes considered to be non-specific are detailed in **Supplementary Tables 1-2**). We used the major limb malformation subgroup as an example to assess the extent to which infants only had non-specific evidence of their condition in the different data sources.

All Read and ICD-10 codes for limb malformations, recorded in the year after delivery, were identified in the study population. Follow-up was standardized across data sources as described earlier. The proportion of infants that only had non-specific limb malformation codes and no additional specific codes for major limb malformations was calculated for those that had evidence of their condition exclusively in HES, exclusively in CPRD, or in both.

*Assessing the cumulative ascertainment of MCM from delivery*

For each infant with an MCM, we identified the earliest recording of an MCM in stand-alone CPRD and stand-alone HES during the study period (January 1, 2009 – March 31, 2016). For each data source, we established the cumulative ascertainment of MCMs over the course of the study period as well as the proportion of diagnoses that were identified at delivery and by one year of age.

**Ethics**

Approval for the study protocol was received from the Independent Scientific Advisory Committee of the Medicines & Healthcare Products Regulatory Agency (reference 17_040RA) and made available to the reviewers. Institutional ethical approval was also received (reference 13720). In accordance with CPRD guidelines, results were suppressed when fewer than five patients were described in order to prevent deductive disclosure of patient identities.

## Results

### Study Population

We identified 113,790 eligible live-born singleton infants for inclusion in the study (**Figure 1**). The majority of infants were male (51.4%) and of white ethnicity (82.9%) (**Table 1**). Available follow-up time varied by data source. In stand-alone CPRD, 86% of infants had a full year of follow-up compared to 99.9% in stand-alone HES and linked data. In total, 7% (n=7,931) of infants had an MCM recorded in at least one data source in the year after delivery.

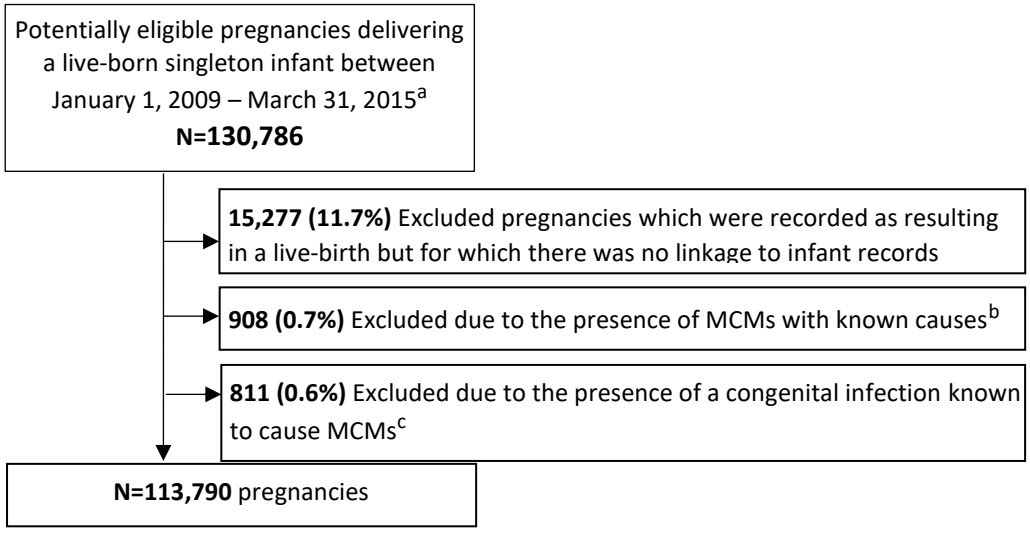



**Figure 1 - Identifying the eligible study population.** [a]Live-born infants were born to mothers registered at up-to-standard practices at least six months before the start of pregnancy. Infants were eligible for HES and ONS linkage. [b]Chromosomal anomalies (e.g. Down syndrome), heritable conditions (e.g. polycystic kidney disease), or specified exogenous causes (e.g. foetal alcohol syndrome). [c]Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Parvovirus, Varicella-zoster, Syphilis, HIV.

**Table 1 - Characteristics of infants in the study population.**

| | All infants N=113,790 (column %) | Infants with evidence of an MCM in at least one data source in the year after delivery N=7,931 (row %) |
|---|---|---|
| **Sex of infant** | | |
| Male | 58,447 (51.4) | 4,144 (7.1) |
| Female | 55,343 (48.6) | 3,787 (6.8) |
| **Ethnicity of infant** | | |
| White | 94,364 (82.9) | 6,446 (6.8) |
| South Asian | 6,880 (6.1) | 617 (9.0) |
| Black | 3,372 (3.0) | 259 (7.7) |
| Other | 1,994 (1.8) | 146 (7.3) |
| Mixed | 4,192 (3.7) | 336 (8.0) |
| Unknown | 2,988 (2.6) | 127 (4.3) |
| **Index of Multiple Deprivation quintile[a]** | | |
| 1 (Least deprived) | 24,053 (21.1) | 1,746 (7.3) |
| 2 | 22,227 (19.5) | 1,614 (7.3) |
| 3 | 22,035 (19.4) | 1,503 (6.8) |
| 4 | 23,088 (20.3) | 1,500 (6.5) |
| 5 (Most deprived) | 22,387 (19.7) | 1,568 (7.0) |
| **Geographic region** | | |
| North East | 2,801 (2.5) | 197 (7.0) |
| North West | 17,112 (15.0) | 1,330 (7.8) |
| Yorkshire & The Humber | 2,601 (2.3) | 165 (6.3) |
| East Midlands | 1,999 (1.8) | 84 (4.2) |
| West Midlands | 12,646 (11.1) | 1,258 (10.0) |
| East of England | 12,156 (10.7) | 877 (7.2) |
| South West | 14,358 (12.6) | 857 (6.0) |
| South Central | 17,083 (15.0) | 1,153 (6.8) |
| London | 17,572 (15.4) | 992 (5.7) |
| South East Coast | 15,462 (13.6) | 1,018 (6.6) |
| **Year of birth** | | |
| 2009 | 19,946 (17.5) | 1,180 (5.9) |
| 2010 | 20,281 (17.8) | 1,384 (6.8) |
| 2011 | 19,739 (17.4) | 1,353 (6.9) |
| 2012 | 19,592 (17.2) | 1,361 (7.0) |
| 2013 | 16,892 (14.8) | 1,291 (7.6) |
| 2014 | 14,320 (12.6) | 1,128 (7.9) |
| 2015 | 3,020 (2.7) | 234 (7.8) |

[a]Deprivation at the maternal household level was used except for 0.07% (n=76) of infants where this was unavailable and practice-level deprivation was used. Abbreviations: MCM, major congenital malformation.

**Prevalence comparisons between stand-alone and linked data**

*HES and CPRD*

The prevalence of MCMs in HES data in the year after delivery was 630 per 10,000 person-years (95% CI, 615.2-645.2) whereas in stand-alone CPRD it was 265.7 (95% CI, 256.0-275.8), a prevalence ratio (PR) of 2.4 (95% CI, 2.3-2.5) (**Table 2**). Almost all MCM subgroups had a higher prevalence in HES compared to CPRD (**Table 2**). The most notable increases were seen for limb (PR, 2.9; 95% CI 2.7-3.1), nervous system (PR, 2.0; 95% CI, 1.5-2.6), ear, face and neck (PR, 2.5; 95% CI, 1.4-4.7) and other malformations (PR, 10.7; 95% CI: 9.2-12.5). The only exceptions were for eye malformations, which were twice as prevalent in CPRD, and abdominal, heart and orofacial malformations which displayed similar prevalence in both data sources (**Table 2**).

*CPRD-HES-ONS and CPRD*

In linked CPRD-HES-ONS data, the prevalence of MCMs was almost three-fold that in stand-alone CPRD (PR, 2.8; 95% CI, 2.7-2.9) (**Table 2**). This increase was mainly due to additional cases identified in HES; few additional cases were identified from ONS. The prevalence of all subgroups was higher in CPRD-HES-ONS compared to stand-alone CPRD with the exception of abdominal, orofacial and eye malformations which were similar. Two-fold or greater increases in prevalence were observed for limb, genital, nervous system, respiratory, digestive, ear, face and neck, and other malformations (**Table 2**).

*CPRD-HES-ONS and HES*

Linked CPRD-HES-ONS data showed an increased prevalence of MCMs compared to stand-alone HES (PR, 1.2; 95% CI, 1.1-1.2), though this was less than the increase seen in comparison to CPRD (**Table 2**). Among the subgroups, an increase compared to stand-alone HES was seen for limb, heart, genital, urinary and eye malformations. Remaining subgroups showed similar prevalence.

**Table 2 - Prevalence of MCMs in the year after delivery, by data source.**

| Type of MCM | Stand-alone CPRD | | Stand-alone HES | | CPRD-HES[a] | CPRD-HES-ONS[a,b] | Prevalence Ratios (95% CI) | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | Prevalence per 10,000 person-years (95% CI) | n | Prevalence per 10,000 person-years (95% CI) | Prevalence per 10,000 person-years (95% CI) | Prevalence per 10,000 person-years (95% CI) | HES vs CPRD | CPRD-HES-ONS vs CPRD | CPRD-HES-ONS vs HES |
| Any | 2780 | 265.7 (256.0-275.8) | 6757 | 630.0 (615.2-645.2) | 745.3 (729.1-761.9) | 745.8 (729.6-762.4) | 2.4 (2.3-2.5) | 2.8 (2.7-2.9) | 1.2 (1.1-1.2) |
| Limb | 904 | 85.3 (79.9-91.0) | 2721 | 245.1 (236.1-254.5) | 290.5 (280.7-300.7) | 290.5 (280.7-300.7) | 2.9 (2.7-3.1) | 3.4 (3.2-3.7) | 1.2 (1.1-1.2) |
| Heart | 685 | 64.5 (59.8-69.5) | 803 | 71.1 (66.3-76.2) | 94.2 (88.7-100.0) | 94.3 (88.8-100.1) | 1.1 (1.0-1.2) | 1.5 (1.3-1.6) | 1.3 (1.2-1.5) |
| Genital | 300 | 28.2 (25.2-31.6) | 489 | 43.2 (39.5-47.2) | 53.9 (49.8-58.4) | 53.9 (49.8-58.4) | 1.5 (1.3-1.8) | 1.9 (1.7-2.2) | 1.2 (1.1-1.4) |
| Urinary | 318 | 29.9 (26.8-33.3) | 445 | 39.3 (35.8-43.1) | 49.7 (45.7-54.0) | 49.8 (45.8-54.0) | 1.3 (1.1-1.5) | 1.7 (1.4-1.9) | 1.3 (1.1-1.4) |
| Nervous system | 80 | 7.5 (6.0-9.3) | 168 | 14.8 (12.7-17.2) | 18.2 (15.8-20.8) | 18.2 (15.9-20.9) | 2.0 (1.5-2.6) | 2.4 (1.9-3.2) | 1.2 (1.0-1.5) |
| Respiratory | 48 | 4.5 (3.4-6.0) | 80 | 7.0 (5.7-8.8) | 8.9 (7.3-10.8) | 9.0 (7.4-10.9) | 1.6 (1.1-2.3) | 2.0 (1.4-2.9) | 1.3 (0.9-1.7) |
| Digestive | 121 | 11.3 (9.5-13.6) | 225 | 19.8 (17.4-22.6) | 21.5 (19.0-24.4) | 21.7 (19.1-24.6) | 1.7 (1.4-2.2) | 1.9 (1.5-2.4) | 1.1 (0.9-1.3) |
| Abdominal | 34 | 3.2 (2.3-4.5) | 55 | 4.8 (3.7-6.3) | 4.8 (3.7-6.3) | 4.8 (3.7-6.3) | 1.5 (1.0-2.4) | 1.5 (1.0-2.4) | 1.0 (0.7-1.5) |
| Orofacial | 129 | 12.1 (10.2-14.4) | 141 | 12.4 (10.5-14.6) | 12.8 (10.9-15.0) | 12.8 (10.9-15.0) | 1.0 (0.8-1.3) | 1.1 (0.8-1.3) | 1.0 (0.8-1.3) |
| Eye | 105 | 9.8 (8.1-11.9) | 52 | 4.6 (3.5-6.0) | 12.0 (10.1-14.2) | 12.0 (10.1-14.2) | 0.5 (0.3-0.7) | 1.2 (0.9-1.6) | 2.6 (1.9-3.7) |
| Ear, Face & Neck | 17 | 1.6 (1.0-2.6) | 46 | 4.0 (3.0-5.4) | 5.2 (4.0-6.7) | 5.2 (4.0-6.7) | 2.5 (1.4-4.7) | 3.3 (1.9-6.0) | 1.3 (0.9-1.9) |
| Other | 187 | 17.5 (15.2-20.2) | 2092 | 187.4 (179.5-195.6) | 201.1 (192.9-209.6) | 201.1 (192.9-209.6) | 10.7 (9.2-12.5) | 11.5 (9.9-13.4) | 1.1 (1.0-1.1) |

[a]The number of infants with MCMs in CPRD-HES and CPRD-HES-ONS are suppressed to prevent deductive disclosure of identities in accordance with CPRD guidelines; [b]Prevalence estimates in CPRD-HES-ONS were sometimes the same as those in CPRD-HES as very few or no additional cases were identified in ONS data. Abbreviations: 95% CI, 95% confidence interval; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data; MCM, major congenital malformation.

**Agreement and contribution of data sources**

After standardizing follow-up across data sources, the proportion of infants with a recorded MCM in the year after delivery remained similar to that described earlier (6.9%; n=7,901) (**Figure 2**). After extending standardized follow-up to the end of the study period, 64% of infants had >2 years of follow-up and a further 679 infants with an MCM were identified **(Supplementary Tables 3-4).**

*Agreement between data sources*

Of the infants with a recorded MCM in the year after delivery, 20.3% had evidence of their condition in both CPRD and HES (**Figure 2**). Orofacial and abdominal malformations were the only subgroups for which the majority of infants, 85.5% and 61.8% respectively, had agreement in CPRD and in HES. For remaining subgroups, the proportion of infants with evidence of their condition in both data sources varied. Infants with digestive or heart malformations had approximately 40% agreement, followed by infants with urinary (35.9%), genital (29.5%), respiratory (26%) and nervous system malformations (20.7%). Agreement between CPRD and HES was lower for infants with eye (15.7%), limb (12.8%), ear, face and neck malformations (6.8%) and those with other malformations (1.6%).

In general, the proportion of infants that had agreement between both data sources did not increase considerably when followed up to the end of the study period. The greatest increase in agreement were seen for genital malformations (29.5% to 37.3%) (**Supplementary Table 4**).

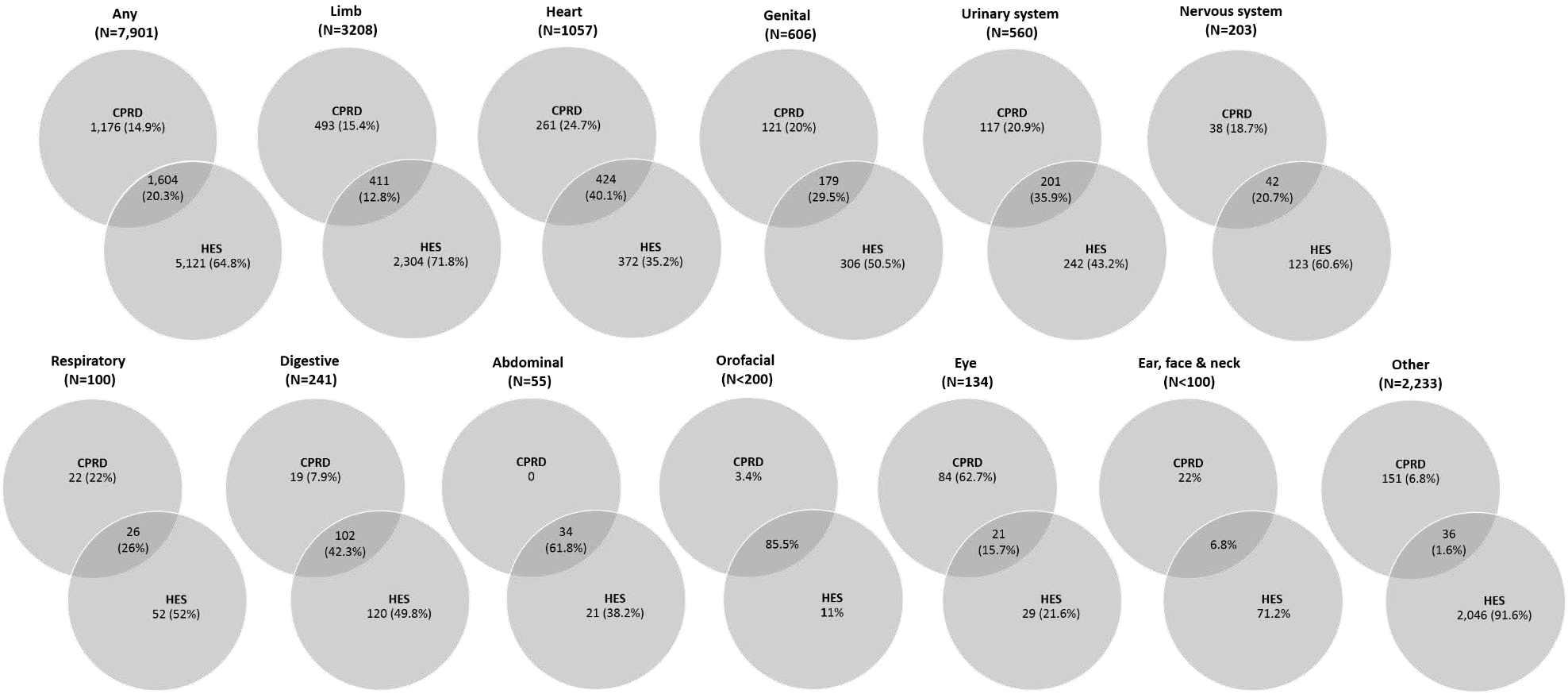



**Figure 2 – Number and proportion of infants with evidence of an MCM in the year after delivery, by data source.** The number and proportion of infants with an MCM identified from death certificates is not shown to prevent deductive disclosure of patient identities. Similarly, for some subgroups with small numbers of infants only the proportions are shown and denominators are suppressed. Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, major congenital malformation.

*Ascertainment of MCMs in individual data sources*

The majority of the 7,901 infants with an MCM were identified exclusively from evidence in HES (64.8%) (**Figure 2**). This was also the case for infants that had limb (71.8%), ear, face and neck (71.2%), nervous system (60.6%), genital (50.5%) or respiratory malformations (52%), as well as those that had 'other' malformations (91.6%). Although the majority of infants with an MCM only had evidence of their condition in HES, the proportion of infants with evidence solely in CPRD remained substantial (14.9%) (**Figure 2**). This was also observed for all subgroups except for infants with orofacial and abdominal malformations, for which few or none had evidence of their condition exclusively in CPRD. Eye malformations were the only conditions for which the majority of infants were identified from evidence in CPRD alone (62.7%).

Of the 7,901 infants with any type of MCM, 28.3% (n=2,233) had evidence of an 'other' MCM. Due to the unexpectedly high proportion of infants in this category that were identified exclusively in HES (91.6%), we carried out a further exploratory analysis. Of the 2,233 infants with an 'other' MCM code in their records, 349 (15.6%) had at least one additional MCM code elsewhere in their records that could be classified into one of the 11 MCM subgroups. Among the remaining 1,884 infants who had no evidence to suggest they belonged to another MCM subgroup, 57% (n=1,064) had an ICD-10 code Q825 for '*congenital non-neoplastic naevus*', and 30% (n=566) had an ICD-10 code Q828 for '*other specified congenital malformations of skin*'. We excluded all 1,884 infants with solely an 'other' MCM code and re-ran the analysis for any MCM. The preponderance of any MCM recorded only in HES remained, with 56% of infants having an MCM code in HES alone (**Supplementary Figure 1**).

Neither ONS mortality data nor HES procedures were useful in ascertaining MCMs. Just 0.2% (n=14) of infants with an MCM had evidence of their condition in ONS. Subgroups with such evidence included heart, urinary, nervous system, respiratory, digestive and other MCMs. Similarly, few infants with an MCM were identified through HES procedure codes alone; the

majority of infants with an OPCS-4 procedure code had an additional ICD-10 code in HES or Read code in CPRD. Extending follow-up time to the end of the study period did not alter the contribution of ONS or HES procedure data. To prevent deductive disclosure of patient identities due to small numbers, further details are not presented.

**Non-specific limb malformation codes**

Among the 2,304 infants that had a limb malformation identified exclusively in HES, 91.9% only had a non-specific ICD-10 code without additional specific evidence. This was considerably higher than for the 493 infants with a limb malformation identified exclusively in CPRD, for which 52.7% only had a non-specific Read code. For those 411 infants that had evidence of their condition in both data sources, 51.3% had a non-specific code without a more specific Read or ICD-10 code.

**Cumulative ascertainment of MCM recordings over time in stand-alone and linked data**

Extending follow-up time to the end of the study period and comparing the cumulative ascertainment of the earliest MCM recordings in stand-alone CPRD and HES indicated that longer follow-up was required for the ascertainment of MCMs in CPRD. At delivery, just 9% of MCM cases recorded in CPRD had been identified, compared to 56% in HES. By one year, 84% of cases in CPRD had been identified compared to 93% of those in HES (**Figure 3**).

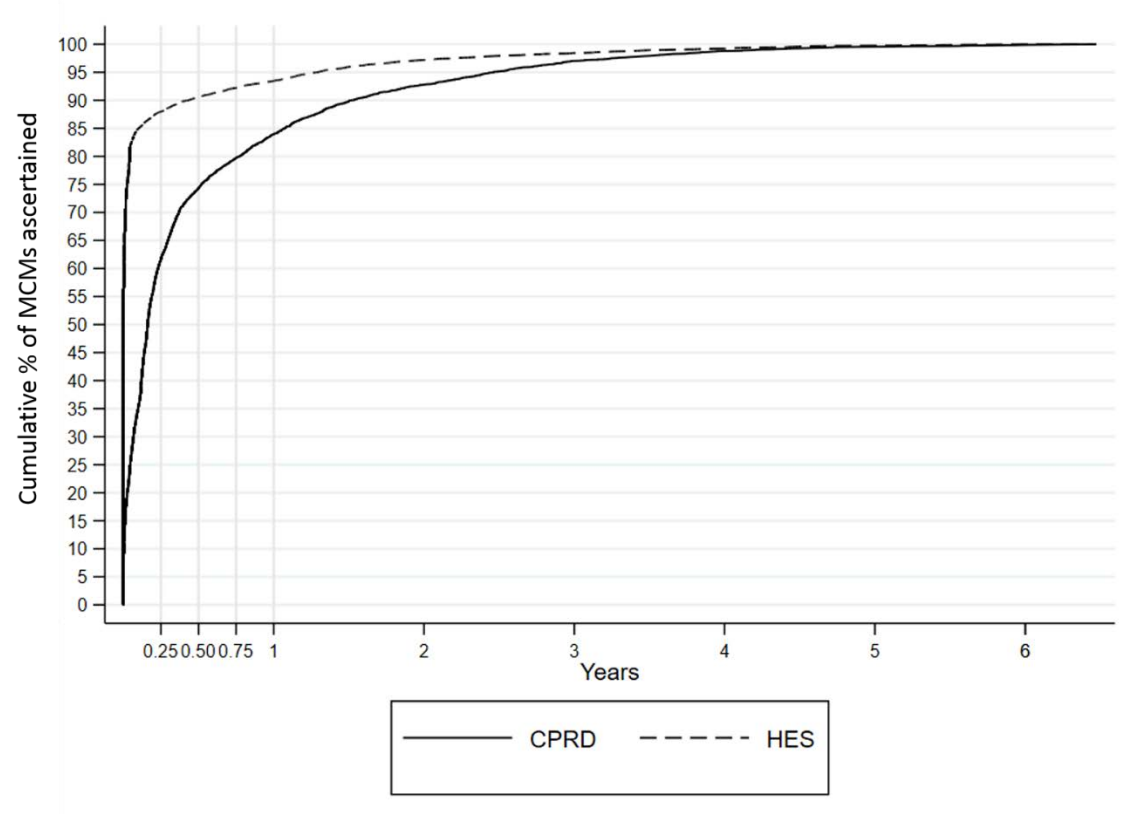



**Figure 3 – Distribution of MCM records from delivery until the end of the study period in stand-alone CPRD and stand-alone HES.** Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, major congenital malformation.

## Discussion

This study compared the ascertainment of MCMs among live-born infants in CPRD, HES and ONS data between January 1, 2009 and March 31, 2016. Both CPRD and HES were important sources of information for the identification of such conditions and linked CPRD-HES data maximized ascertainment, whilst further linkage to ONS data made little difference. Almost two thirds of infants had evidence of an MCM exclusively in HES and would not have had their condition identified in another data source, with similar results seen for most MCM subgroups. Furthermore, infants with a diagnosis in HES were identified earlier than those with a diagnosis in CPRD, with more than half identified at delivery. Nevertheless, 15% of MCM cases were only identified in CPRD; this proportion was higher for some subgroups, most notably for eye malformations for which more than half of cases were identified through CPRD. We found that despite the severity and often life-long implications of MCMs, just 20% of infants with any such condition had evidence in both CPRD and HES. Agreement varied for MCM subgroups but was generally low and did not improve appreciably with increased follow-up time.

There are a number of potential reasons for the higher ascertainment of MCMs in HES compared to CPRD. First, whilst hospitalisations and deaths are required to be communicated to general practice, communications may be delayed or may not be encoded in the patient's electronic primary care record.[287] Instead, the general practitioner may scan the hospital letter or enter information from the letter as free-text, both of which are unavailable to investigators as part of CPRD.[291]

Second, it is possible that some of the diagnoses recorded in HES did not actually relate to MCMs. Whilst EUROCAT offers a framework for defining MCMs, health professionals do not use the guidelines to encode diagnoses, and so some identified codes could have been used by clinicians to record minor malformations or even other conditions. This might apply in particular to the non-specific MCM codes; our examination of non-specific limb malformation

codes revealed a particularly high proportion of infants with exclusively non-specific codes among those with evidence solely in HES.

It is also notable that 'other' MCM codes were recorded far more frequently in HES compared to CPRD, and that the majority of these were due to two ICD-10 codes for congenital malformations of the skin, namely Q825 and Q828. In EUROCAT, ICD-10 codes are modified to include a fourth digit.[86] At the time of the study period, EUROCAT considered all 4-digit versions of Q828 ('*other specified congenital malformations of the skin*') to be major malformations except for Q82.80 ('*simple/abmormal palmar crease*').[86] Q825 codes (*'congenital non-neoplastic naevus*') are further classified by EUROCAT into Q8250 – Q8252 (considered minor malformations) and Q82.58 (considered a major malformation).[86] In HES, this level of granularity is not available and so all Q825 and Q828 ICD-10 codes were considered conservatively to relate to MCMs in this study. Conversely, in Read, codes equivalent to Q8250-8252 and Q8280 are available and could therefore (if used by primary care physicians) be classified as minor and excluded from our analyses. This could partially explain the high proportion of infants with evidence of an 'other' MCM exclusively in HES and could contribute to the similar results seen for any MCM. However, even after excluding the infants with only an 'other' MCM, some of whom may have had a minor skin malformation, 56% of infants still had evidence of 'any' MCM exclusively in HES. In addition, it is important to note that clinical coders considered these malformations of sufficient importance to document in the infants' inpatient records. Studies examining the validity of MCM codes in HES have not been undertaken to date, although a government audit estimated the positive predictive value (PPV) of primary diagnoses in HES was 96% (IQR 89-96%) in 2011.[181] Validation studies of MCM diagnoses in HES would help to clarify the PPV of both specific and non-specific MCM codes.

Similarly, recording of MCMs in CPRD but not in HES might be due in part to general practitioners choosing MCM codes to record non-MCM conditions, or reflecting tentative diagnoses made before referring infants to specialists. A few validation studies of MCM

diagnoses in CPRD have been performed, showing generally good PPV for major cardiac (94%; 95% CI, 91-97) and neural tube (71%; 95% CI, 64-77) malformations as well as for MCMs overall (85%; 95% CI, 79-89).[192, 194, 209, 292] Alternatively, as the HES data comprised only hospitalisations (not hospital outpatient visits), the CPRD data may have captured true MCMs that were not diagnosed in hospital at delivery, and for which the young child did not receive inpatient care during the follow-up period.

Our prevalence rates in stand-alone CPRD were found to be higher or consistent with those found in a previous study using The Health Improvement Network, a different UK electronic primary care dataset, with the exception of nervous system malformations which had a slightly lower prevalence in our study.[201] Our prevalence of congenital heart defects in stand-alone CPRD was also consistent with that estimated by another study using CPRD data between 2001-2003.[218] Studies of other conditions have also shown, as we have for MCMs, the agreement between CPRD and HES to be low. Agreement for poisonings, upper gastrointestinal bleeds and bleeds occurring in hospitalised patients using anticoagulants was similar to the low agreement we found for MCMs, at approximately 20%.[288-290] Some conditions such as burns and fractures had even lower agreement, whilst myocardial infarctions had higher levels (51%).[288, 291]

**Strengths & Limitations**

This study has a number of strengths. First, we included a large number of live-born infants which allowed for a thorough exploration of MCMs and rarer subgroups. Second, we went beyond linkage of CPRD and HES diagnoses, including ONS data to identify any diagnoses recorded following the infant's death and searching HES procedures using OPCS-4 codes. With this new approach we demonstrated that neither of these contributed many additional cases. Third, we maximised ascertainment of MCMs by drawing up a rigorous MCM diagnostic code list based on the EUROCAT framework, with the input of a consultant neonatologist. Fourth, whilst we examined MCMs recorded in the year after delivery, we also followed infants up

beyond a year when possible; almost two thirds of infants had two or more years of available follow-up. The value of this is demonstrated by the fact that 8% of all MCMs identified over the course of the study period were recorded more than a year after delivery.

Despite the above, inherent limitations of the data meant that complete ascertainment of cases was not possible. As described earlier, free-text in CPRD (a potential source of feedback from inpatient and outpatient secondary care) is no longer available to investigators. Furthermore, we did not use outpatient HES data due to the very low proportion of records with diagnostic codes.[261] Our use of the Pregnancy Register enabled identification of 11.7% of potentially eligible pregnancies during the study period recorded as resulting in a live-birth but with no linked infant. Lack of linkage could arise if the mother left the practice or the practice stopped collecting data shortly after the infant's birth. However, it could also occur if infants died shortly after birth or had a prolonged hospitalisation that prevented or delayed registration with a practice, which could include some infants with severe MCMs. Thus, the generalisability of our findings is restricted to infants who were registered with their mother's general practice at some point during the study period.

**Conclusion**

This first study of the completeness of recording of MCMs in UK electronic health data adds to the growing body of evidence that the use of stand-alone primary care data can under-ascertain outcomes of interest. Linkage of CPRD to diagnostic data from hospitalisations markedly increases MCM ascertainment whilst linkage to hospitalisation procedure and mortality data identifies few additional cases. Use of linked data has the potential to maximize the ascertainment of MCMs and may allow for earlier ascertainment of diagnoses, although there is still value in long-term follow-up of infants beyond the first year of life. Our findings highlight the need for further research on the validity of MCM codes in HES and in CPRD data, notably the PPV of non-specific MCM codes. The recent availability of additional linked primary care data (CPRD Aurum) will increase sample sizes further but the different coding structure of

these data will necessitate separate assessment of data completeness. Likely improvements to diagnostic coding in outpatient HES data over time should also allow further ascertainment of MCMs in future studies using linked UK electronic health data.

## Acknowledgements

See research paper cover sheet.

## Funding

This research is funded by the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Immunisation at the London School of Hygiene and Tropical Medicine in partnership with Public Health England. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

## References

References are included as part of the main reference list at the end of the thesis.

## Paper 2: Supplementary material

**Supplementary Table 1 – Non-specific Read codes for limb malformations.**

| Read Term | Read Code |
|---|---|
| correction of congenital deformity of hand | 7l0f.00 |
| correction of congenital deformity of hand nos | 7l0fz00 |
| correction of congenital deformity of hip | 7l0g.00 |
| primary correction of congenital deformity of foot | 7l0j.00 |
| primary correction of club foot | 7l0j.11 |
| primary correction of talipes | 7l0j.12 |
| other correction of congenital deformity of foot | 7l0k.00 |
| other operations for club foot | 7l0k.11 |
| other correction of talipes | 7l0k.12 |
| skull, face and jaw congenital deformities | PE0..00 |
| skull congenital deformities | pe0..13 |
| congenital spine deformity | pe2..00 |
| congenital postural scoliosis | PE22.00 |
| congenital talipes varus | pe50.00 |
| congenital clubfoot - varus | pe50.12 |
| congenital talipes equinovarus | pe51.00 |
| other deformities of feet | pe7..00 |
| talipes, unspecified | pe70.00 |
| clubfoot nos | pe70.11 |
| congenital talipes equinus | pe7y200 |
| feet deformities nos | pe7z.00 |
| other congenital limb anomalies | pf...00 |
| syndactyly - webbing of digits | pf1..00 |
| syndactyly of toes without bone fusion | pf13.00 |
| webbed toes | pf13.11 |
| fused toes | pf14.11 |
| conjoined toes | pf14.12 |
| syndactyly nos | pf1z.00 |
| upper limb anomaly, unspecified | pf50.00 |
| other congenital anomalies of fingers | pf5r.00 |
| other anomaly of fingers nos | pf5rz00 |
| lower limb anomaly, unspecified | pf60.00 |
| other congenital hip joint deformity | pf63.00 |
| congenital deformity of hip, unspecified | pf63x00 |
| other congenital hip joint deformity nos | pf63z00 |
| other congenital anomalies of toe | pf66.00 |
| skull and face bone anomalies | pg0..00 |
| anomalies of spine | pg1..00 |
| other anomaly of spine | pg1y.00 |
| anomalies of spine nos | pg1z.00 |

These were codes that could potentially be used to record major limb malformations, minor limb malformations or limb conditions that were not congenital in origin. For example, EUROCAT considered syndactyly of the 2nd and 3rd toes to be a minor malformation but Read codes for syndactyly did not specify the affected toes and could also have been used for major malformations. These non-specific codes were retained but some infants with these codes may not have had a major limb malformation.

**Supplementary Table 2 – Non-specific ICD-10 codes for limb malformations**.

| ICD-10 Description | ICD-10 Code |
|---|---|
| **other congenital deformities of hip** | Q658 |
| **congenital deformity of hip, unspecified** | Q659 |
| **talipes equinovarus** | Q660 |
| **other congenital varus deformities of feet** | Q663 |
| **other congenital deformities of feet** | Q668 |
| **congenital deformity of feet, unspecified** | Q669 |
| **other congenital deformities of skull, face and jaw** | Q674 |
| **congenital deformity of spine** | Q675 |
| **congenital deformity of hand** | Q681 |
| **congenital deformity of knee** | Q682 |
| **other specified congenital musculoskeletal deformities** | Q688 |
| **fused toes** | Q702 |
| **webbed toes** | Q703 |
| **syndactyly, unspecified** | Q709 |
| **oth cong malformation of upper limb(s) inc shoulder girdle** | Q740 |
| **congenital malformation of knee** | Q741 |
| **other cong malformation of lower limb(s) incl pelvic girdle** | Q742 |
| **other specified congenital malformations of limb(s)** | Q748 |
| **unspecified congenital malformation of limb(s)** | Q749 |
| **other congenital deformities of hip** | Q658 |

These were ICD-10 codes that could potentially be used to record major limb malformations, minor limb malformations or limb conditions that were not congenital in origin. For example, EUROCAT considered syndactyly of the 2$^{nd}$ and 3$^{rd}$ toes to be a minor malformation but ICD-10 codes for syndactyly did not specify the affected toes and could also have been used for major malformations. These non-specific codes were retained but some infants with these codes may not have had a major limb malformation. Abbreviations: ICD-10, International Classification of Diseases version 10.

**Supplementary Table 3 – Total follow-up time for infants in linked CPRD-HES-ONS after standardizing follow-up across all data sources.**

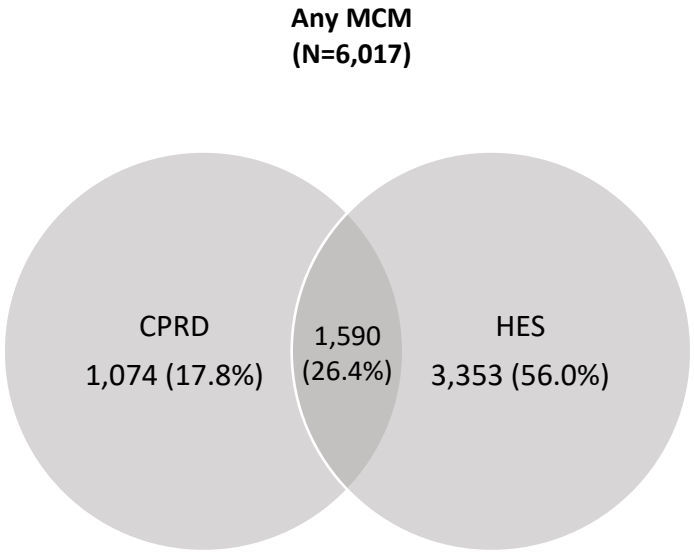
| Follow-up time (years) | Number of infants (%) N=113,790 |
|---|---|
| ≤1 | 16017 (14.1) |
| 1-2 | 24711 (21.7) |
| 2-3 | 20565 (18.1) |
| 3-4 | 17601 (15.5) |
| 4-5 | 14246 (12.5) |
| 5-6 | 11268 (9.9) |
| 6-7 | 8008 (7.0) |
| >7 | 1374 (1.2) |

Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data.

**Supplementary Table 4 - Number and proportion of infants with evidence of an MCM in CPRD, HES or both in the year after delivery or anytime in the study period.**

| Type of MCM | Total number of infants with evidence in CPRD or HES | | Number and proportion of infants with evidence only in CPRD | | | | Number and proportion of infants with evidence only in HES | | | | Number and proportion of infants with agreement in CPRD & HES | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Year after delivery | Anytime in the study period | Year after delivery | | Anytime in study period | | Year after delivery | | Anytime in study period | | Year after delivery | | Anytime in study period | |
| | | | n | % (95% CI) | n | % (95% CI) | n | % (95% CI) | N | % (95% CI) | n | % (95% CI) | n | % (95% CI) |
| **Any** | 7901 | 8580 | 1176 | 14.9 (14.1-15.7) | 1383 | 16.1 (15.3-16.9) | 5121 | 64.8 (63.7-65.9) | 5269 | 61.4 (60.4-62.4) | 1604 | 20.3 (19.4-21.2) | 1928 | 22.5 (21.6-23.4) |
| **Limb** | 3208 | 3403 | 493 | 15.4 (14.1-16.7) | 586 | 17.2 (16.0-18.5) | 2304 | 71.8 (70.2-73.4) | 2333 | 68.6 (67.0-70.1) | 411 | 12.8 (11.7-14.0) | 484 | 14.2 (13.1-15.4) |
| **Heart** | 1057 | 1165 | 261 | 24.7 (22.1-27.4) | 293 | 25.2 (22.7-27.7) | 372 | 35.2 (32.3-38.2) | 396 | 34.0 (31.3-36.8) | 424 | 40.1 (37.1-43.1) | 476 | 40.9 (38.0-43.7) |
| **Genital** | 606 | 732 | 121 | 20.0 (16.9-23.4) | 102 | 13.9 (11.5-16.7) | 306 | 50.5 (46.4-54.5) | 357 | 48.8 (45.1-52.5) | 179 | 29.5 (25.9-33.3) | 273 | 37.3 (33.8-40.9) |
| **Urinary** | 560 | 605 | 117 | 20.9 (17.6-24.5) | 132 | 21.8 (18.6-25.3) | 242 | 43.2 (39.1-47.4) | 251 | 41.5 (37.5-45.5) | 201 | 35.9 (31.9-40.0) | 222 | 36.7 (32.8-40.7) |
| **Nervous system** | 203 | 280 | 38 | 18.7 (13.6-24.8) | 74 | 26.4 (21.4-32.0) | 123 | 60.6 (53.5-67.4) | 142 | 50.7 (44.7-56.7) | 42 | 20.7 (15.3-26.9) | 64 | 22.9 (18.1-28.2) |
| **Respiratory** | 100 | 109 | 22 | 22.0 (14.3-31.4) | 22 | 20.2 (13.1-28.9) | 52 | 52.0 (41.8-62.1) | 58 | 53.2 (43.4-62.8) | 26 | 26.0 (17.7-35.7) | 29 | 26.6 (18.6-35.9) |
| **Digestive** | 241 | 275 | 19 | 7.9 (4.8-12.0) | 28 | 10.2 (6.9-14.4) | 120 | 49.8 (43.3-56.3) | 139 | 50.5 (44.5-56.6) | 102 | 42.3 (36.0-48.8) | 108 | 39.3 (33.5-45.3) |
| **Abdominal** | 55 | 56 | 0 | - | 0 | - | 21 | 38.2 (25.4-52.3) | 22 | 39.3 (26.5-53.2) | 34 | 61.8 (47.7-74.6) | 34 | 60.7 (46.8-73.5) |
| **Orofacial**[a] | <200 | <200 | - | 3.4 | - | 5.0 | - | 11.0 | - | 11.3 | - | 85.5 | - | 83.6 |
| **Eye** | 134 | 172 | 84 | 62.7 (53.9-70.9) | 97 | 56.4 (48.6-63.9) | 29 | 21.6 (15.0-29.6) | 39 | 22.7 (16.6-29.7) | 21 | 15.7 (10.0-23.0) | 36 | 20.9 (15.1-27.8) |
| **Ear, Face & Neck**[a] | <100 | <100 | - | 22.0 | - | 23.9 | - | 71.2 | - | 68.7 | - | 6.8 | - | 7.5 |
| **Other** | 2233 | 2394 | 151 | 6.8 (5.8-7.9) | 207 | 8.6 (7.6-9.8) | 2046 | 91.6 (90.4-92.7) | 2124 | 88.7 (87.4-90.0) | 36 | 1.6 (1.1-2.2) | 63 | 2.6 (2.0-3.4) |

[a]Number of infants and confidence intervals suppressed to prevent deductive disclosure in accordance with CPRD guidelines. Abbreviations: 95% CI, 95% confidence interval; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, major congenital malformation.




**Supplementary Figure 1 – Number and proportion of infants with evidence of an MCM in the year after delivery, by data source.** These data exclude 1,884 infants with an 'other' MCM but no evidence of an MCM in another subgroup. Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; MCM, major congenital malformation.

## 7.4 External validation of MCMs identified in CPRD with published THIN data

The discussion section of Paper 2 (**Section 7.3**) noted that the prevalence of any MCMs and MCM subgroups in stand-alone CPRD were found to be higher or consistent with those from a previous study using THIN, a different UK electronic primary care dataset (**Table 1.7**).[201] This section provides the details of this comparison. The study population in CPRD included 113,790 infants delivered in England between 2009 and 2015, as described earlier (**Figure 7.1**). The THIN study included 794,209 live-births delivered in the UK between 1990 and 2009.[201] In both data sources, follow-up started at delivery and ended a year later or earlier if the practice stopped collecting data or the infant left the practice or died.

### 7.4.1 Results of prevalence comparisons between CPRD & THIN

In stand-alone CPRD, the prevalence of MCMs was 1.2 times (95% CI, 1.2-1.3) that in THIN in the year after delivery (**Table 7.1**).[201] Most MCM subgroups had similar prevalence rates in both data sources. However, prevalence rates in CPRD were higher for limb (Prevalence Ratio (PR), 2.1; 95% CI, 2.0-2.3), digestive (PR, 1.3; 95% CI, 1.1-1.6), urinary (PR, 1.6; 95% CI, 1.4-1.8), and eye malformations (PR, 1.6; 95% CI, 1.3-1.9) (**Table 7.1**). Only nervous system malformations had a lower prevalence in CPRD (PR, 0.7; 95% CI, 0.6-0.9).

**Table 7.3 - Prevalence of MCMs in stand-alone CPRD and published THIN data in the year after delivery.**

| | **Stand-alone CPRD (N=113,790)** | | **Published THIN Data (N=794,209)** | | **Prevalence Ratios (95% CI)** |
|---|---|---|---|---|---|
| | n | Prevalence per 10,000 live-births (95% CI) | n | Prevalence per 10,000 live-births (95% CI) | CPRD vs. THIN |
| Any MCM | 2780 | 244.3 (235.5-253.4) | 15,741 | 198.0 (195.0-201.0) | 1.2 (1.2-1.3)* |
| Limb | 904 | 79.4 (74.5-84.8) | 2,970 | 37.4 (36.1-38.8) | 2.1 (2.0-2.3)* |
| Heart | 685 | 60.2 (55.9-64.9) | 4,778 | 60.2 (58.5-61.9) | 1.0 (0.9-1.1) |
| Genital | 300 | 26.4 (23.5-29.5) | 1,970 | 24.8 (23.7-25.9) | 1.1 (0.9-1.2) |
| Urinary | 318 | 27.9 (25.0-31.2) | 1,362 | 17.1 (16.3-18.1) | 1.6 (1.4-1.8)* |
| Nervous | 80 | 7.0 (5.7-8.7) | 759 | 9.6 (8.9-10.3) | 0.7 (0.6-0.9)** |
| Respiratory | 48 | 4.2 (3.2-5.6) | 419 | 5.3 (4.8-5.8) | 0.8 (0.6-1.1) |
| Digestive | 121 | 10.6 (8.9-12.7) | 637 | 8.0 (7.4-8.7) | 1.3 (1.1-1.6)* |
| Abdominal | 34 | 3.0 (2.1-4.2) | 208 | 2.6 (2.3-3.0) | 1.1 (0.8-1.6) |
| Orofacial | 129 | 11.3 (9.5-13.5) | 978 | 12.3 (11.6-13.1) | 0.9 (0.8-1.1) |
| Eye | 105 | 9.2 (7.6-11.2) | 469 | 5.9 (5.4-6.5) | 1.6 (1.3-1.9)* |
| Ear, Face & Neck | 17 | 1.5 (0.9-2.4) | 84 | 1.1 (0.8-1.3) | 1.4 (0.8-2.4) |

*Prevalence higher in CPRD than THIN; **Prevalence higher in THIN than in CPRD. Abbreviations: CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; 95% CI, 95% confidence interval; MCM, major congenital malformation.

### 7.4.2 Could differences in Read code lists used to identify MCMs explain the higher prevalence of limb, digestive, urinary and eye malformations in CPRD compared to THIN?

The Read code list developed in **Chapter 5** of this thesis to identify MCMs in CPRD included 3,209 codes. Of these codes, 2,587 (80.6%) were also part of the Read code list used in the published THIN study to identify MCMs (**Figure 7.2)**. These are referred to as "mutual codes". The remaining 622 codes that were part of the Read code list developed to identify MCMs in CPRD but were not part of the Read code list used in the THIN study are referred to as "CPRD-only codes" (**Figure 7.2)**. The majority of infants in CPRD with limb, digestive, urinary and eye malformations were identified from mutual codes but some were identified from CPRD-only codes. The use of these codes could result in the increased prevalence in CPRD compared to THIN if they usefully captured MCMs that were not captured in the THIN study. Increased prevalence in CPRD could also occur if CPRD-only codes were non-specific and resulted in the identification of individuals who did not have an MCM.

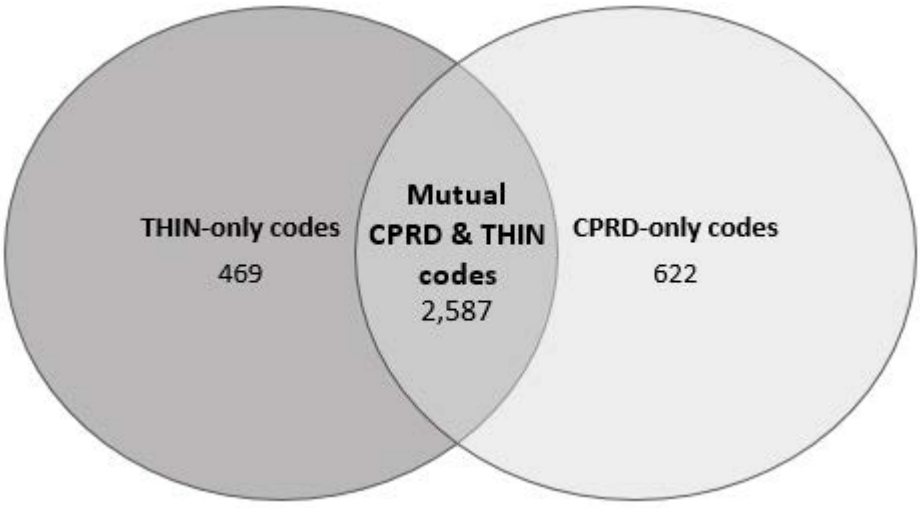



**Figure 7.4 - Distribution of codes used to identify MCMs in the CPRD study and published THIN study.** Abbreviations: CPRD, Clinical Practice Research Datalink; THIN, The Health Improvement Network; MCM, major congenital malformation.

Limb malformations

Only 0.6% of those with limb malformations in CPRD were identified from CPRD-only codes (the rest were identified from mutual codes); the higher prevalence of these conditions in the CPRD study compared to the THIN study could therefore not be explained by the use of CPRD-only codes.

Digestive malformations

In total, 16.5% of those in CPRD with a digestive malformation were identified from CPRD-only codes. An examination of the CPRD-only codes in the records of these infants showed that these codes usefully ascertained additional infants with diaphragmatic hernias and tracheo-oesophageal fistulas that were not captured through the use of mutual codes (**Table 7.2**). If CPRD-only codes had not been used, and these infants were not identified as having a digestive malformation, the prevalence rate in CPRD would be slightly lower (9.3 per 10,000 live-births; 95% CI, 7.6-11.3) and similar to that in THIN (8.0 per 10,000 live-births; 95% CI, 7.4-8.7).[201]

Urinary malformations

In total, 40.3% of those in CPRD with a urinary malformation were identified from CPRD-only codes. Most of these infants were identified from a CPRD-only code for hydronephrosis – a malformation defined by EUROCAT as being minor when associated with a pelvis dilatation of <10 mm **(Table 7.2)**.[86] As it was not possible to know whether an infant had major or minor hydronephrosis, such codes were conservatively treated as being major across all studies described in this thesis. However, if all hydronephrosis codes were treated as minor malformations and excluded, the prevalence rate of urinary malformations in CPRD decreased to 18.1 per 10,000 live-births (95% CI, 15.7-20.7), similar to the prevalence rate observed in THIN (17.1 per 10,000 live-births; 95% CI, 16.3-18.1).[201]

Eye malformations

In total, 31.4% of those with eye malformations in CPRD were identified from CPRD-only codes. Most of these infants had a CPRD-only code for anisocoria **(Table 7.2)**. During the period in which the studies described in this thesis were conducted, anisocoria was not classified by EUROCAT as a minor malformation and so such records were treated as evidence of an MCM.[86] However, treating anisocoria as a minor malformation (in line with the most recent EUROCAT guidelines) reduced the prevalence of eye malformations to 6.9 per 10,000 live-births (95% CI, 5.5-8.7), similar to that in THIN (5.9 per 10,000 live-births; 95% CI, 5.4-6.5).[201]

**Table 7.2 - Number of infants whose only evidence of an MCM was from a CPRD-only code, by subgroup.**

| MCM subgroup | % infants identified exclusively from a CPRD-only Read code (%) | Read code description (Read code) | No. of infants with Read code |
|---|---|---|---|
| Limb | 0.6 (≤5) | Arthrogryposis (N233000) | ≤5 |
| Urinary | 40.3 (128) | Bifid kidney (PD3F.00) | ≤5 |
| Urinary | | Closure of exstrophy of bladder (7B23400) | ≤5 |
| Urinary | | Congenital abnormality of the kidney (PD8..00) | ≤5 |
| Urinary | | Duplex kidney (PD80.00) | ≤5 |
| Urinary | | Endoscopic dilatation of ureteric orifice (7B1D400) | ≤5 |
| Urinary | | Endoscopic incision of ureterocele (7B1D300) | ≤5 |
| Urinary | | Endoscopic incision of ureterocele (7B1D600) | ≤5 |
| Urinary | | Heminephrectomy for duplex kidney (7B02000) | ≤5 |
| Urinary | | Hydronephrosis (K11..00) | 113 |
| Urinary | | Hydronephrosis nos (K11Z.00) | ≤5 |
| Urinary | | Hydronephrosis with pelviureteric junction obstruction (K113.11) | ≤5 |
| Urinary | | Hydronephrosis with ureteropelvic junction obstruction (K113.00) | ≤5 |
| Urinary | | Hydroureteronephrosis (K111.00) | ≤5 |
| Urinary | | Open excision of ureterocele (7B16000) | ≤5 |
| Urinary | | Small kidney of unknown cause (K09..00) | ≤5 |
| Urinary | | Stricture of pelviureteric junction (K133100) | ≤5 |
| Digestive | 16.5 (20) | Diaphragmatic hernia (J34..00) | ≤5 |
| Digestive | | Duhamel hirschsprung abdoperin (7726Y11) | ≤5 |
| Digestive | | Freeing of adhesions of tongue (7523200) | ≤5 |
| Digestive | | Repair of diaphragmatic hernia (760K.00) | 14 |
| Digestive | | Stenosis of intestine nos (J50Z200) | ≤5 |
| Digestive | | Tracheo-oesophageal fistula (J10Y200) | ≤5 |
| Eye | 31.4 (33) | Anisocoria - unequal pupil diameter (F4K4100) | 26 |
| Eye | | Aphakia (F4K3000) | ≤5 |
| Eye | | Coloboma of optic disc (F4H2200) | ≤5 |
| Eye | | Corneal scar or opacity nos (F4B0Z00) | ≤5 |
| Eye | | Glaucoma (F45..00) | ≤5 |
| Eye | | H/O: glaucoma (1482) | ≤5 |

Numbers suppressed to prevent deductive disclosure. Abbreviations: MCM, major congenital malformation; CPRD, Clinical Practice Research Datalink.

### 7.4.3 Could Read codes used to identify MCMs in the THIN study but not in CPRD explain the lower prevalence of nervous system malformations in CPRD?

In total, 469 codes were used in the THIN study that were not included in the code list developed for CPRD (referred to as "THIN-only codes") (**Figure 7.2**). It was possible that by not including these codes, the prevalence of nervous system malformations in CPRD could be under-ascertained.

The majority of the 469 THIN-only Read codes were not included because they had been retired from the Read dictionary when the code list for the work described in this thesis was developed (86.8%; n=407). Once retired, Read codes are no longer used to encode clinical data and retired codes present in patient records are replaced with newer versions. It is therefore unlikely that the use of these codes by the THIN study could explain the difference in prevalence. As these codes were no longer part of the Read dictionary, it was not possible to examine their descriptions and explore differences further.

The remaining 62 THIN-only Read codes were not included in the CPRD study either because the conditions they referred to did not fit inclusion criteria (7.7%; n=36) or because they were not identified during the development of the code lists (5.5%; n=26) (**Appendix 7**). Among the 113,790 infants in the study population, just a single infant had one of these latter codes in their infant record. The code related to the procedure '*freeing of spinal tether*'which could indicate the infant had spina bifida, a nervous system malformation. This was not enough, however, to explain the lower prevalence of these malformations in CPRD.

### 7.4.4 Could differences in the study periods explain differences in the prevalence rates between CPRD & THIN?

Another potential reason for differences in prevalence was that rates were calculated for different study periods. Infants in the THIN study were born between 1990-2009 whereas infants included in this CPRD study were born between 2009-2015.[201] English registry data from EUROCAT showed that annual prevalence rates among live-births fluctuated between

1990 and 2016 but average prevalence rates before and after 2009 were similar for the MCM subgroups for which differences were seen.[294] Therefore, it is unlikely that the reason for the differences observed between the two data sources is a result of MCM prevalence increasing or decreasing although it is possible that recording of conditions changed over time.

### 7.4.5 Could differences in the criteria used to define study populations explain differences in the prevalence rates between CPRD & THIN?

Different criteria to define study populations were also considered as a possible reason for differences. In the THIN study, infants were required to be registered with a general practice in the first year of life.[201] In the work described in this thesis, no such requirement was placed on the study population as it was thought that this could potentially exclude infants with severe MCMs that were delayed in registering at the practice. However, this seemed unlikely to explain the differences in prevalence as just 0.6% of infants in the CPRD study registered with a practice more than 12 months after delivery and excluding them made no difference to the overall prevalence of MCMs.

## 7.5 External validation of MCMs identified in CPRD, HES and linked data with data from English EUROCAT registries

This section describes a comparison of the prevalence of MCMs among live-born infants in the year after delivery between stand-alone and linked CPRD, HES and ONS data with English EUROCAT data. To make the study populations as comparable as possible, the 113,790 infants identified in **Figure 7.1** were further restricted to those delivered between 2009-2013 (prior to the transfer of UK EUROCAT registries to the National Congenital Anomaly and Rare Disease Registration Service which could have disrupted data collection) and registered at a practice in a similar geographic region to the included registries. After restrictions, there were 45,601 infants in the study population (**Figure 7.3**). In comparison, English EUROCAT registries had a study population of over 1 million infants.[294]

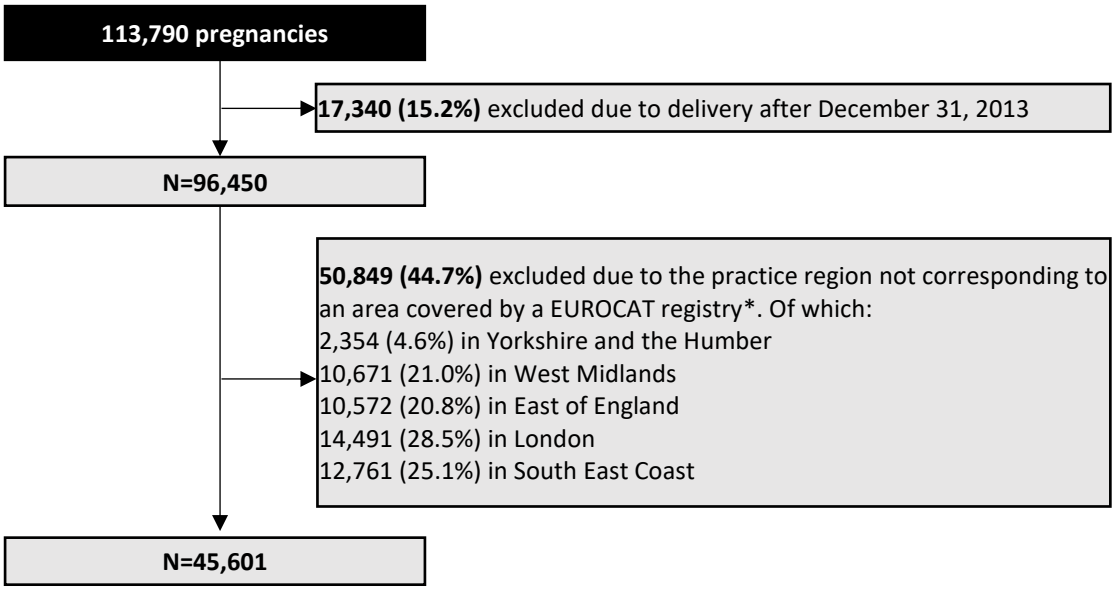



**Figure 7.3 - Derivation of pregnancies included in the comparison of MCM prevalence rates with English EUROCAT data.** *Between 2009 and 2013, EUROCAT received data from the following registries in England: NorCAS, EMSYCAR, CAROBB, WANDA and SWCAR. The most closely corresponding CPRD practice regions were: North East and North West (corresponding to NorCAS), East Midlands (corresponding to EMSYCAR), South Central (corresponding to CAROBB and WANDA) and South West (corresponding to SWCAR). Pregnancies in any other CPRD region were excluded.

### 7.5.1 Results of prevalence comparisons with English EUROCAT registries

CPRD and EUROCAT

Overall, the prevalence of MCMs in CPRD was 1.7 times higher (95% CI, 1.6-1.8) than that in EUROCAT (**Table 7.3**).[294] Prevalence was higher in CPRD than in EUROCAT for limb (PR, 3.2; 95% CI, 2.9-3.6), heart (PR, 1.4; 95% CI, 1.2-1.6), genital (PR, 1.4; 95% CI, 1.2-1.7) and eye malformations (PR, 5.3; 95% CI, 3.8-7.3) but was similar for other subgroups. This was in line with results from a study by Sokal *et al.*, which demonstrated a higher prevalence in THIN compared to UK EUROCAT registries for the same subgroups.[201] Results were also consistent with a study by Wurst *et al.* which examined heart defects and found them to be more prevalent in CPRD compared to UK registries.[218]

*HES and EUROCAT*

The prevalence of MCMs in HES was over three times that in EUROCAT (PR, 3.6; 95% CI, 3.5-3.8) (**Table 7.3**).[294] All MCM subgroups had higher prevalence rates in HES with the exception of abdominal and orofacial malformations which had similar prevalence rates to those seen in EUROCAT. Of all subgroups, limb defects had the greatest difference in prevalence with EUROCAT data (PR, 8.3; 95% CI, 7.7-8.9).

*CPRD-HES-ONS and EUROCAT*

The prevalence of MCMs in linked CPRD-HES-ONS data was more than four times that in EUROCAT (PR, 4.3; 95% CI, 4.1-4.5).[294] As with HES, similar prevalence rates for orofacial and abdominal malformations were seen between CPRD-HES-ONS and EUROCAT whilst all other subgroups had a higher prevalence in CPRD-HES-ONS. Limb defects, eye malformations and malformations of the ear, neck and face had the highest increases in prevalence compared to EUROCAT.

**Table 7.3 - The prevalence of MCMs in stand-alone CPRD, stand-alone HES, linked CPRD-HES-ONS and English EUROCAT registries.** Abbreviations: CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data; 95% CI, 95% confidence interval; MCM, major congenital malformation.

| | Stand-alone CPRD (N=45,601) | | Stand-alone HES (N=45,601) | | CPRD-HES-ONS (N=45,601) | | EUROCAT (N=1,034,278) | | Prevalence Ratios (95% CI) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Prevalence per 10,000 live-births (95% CI) | N | Prevalence per 10,000 live-births (95% CI) | n | Prevalence per 10,000 live-births (95% CI) | n | Prevalence per 10,000 live-births (95% CI) | CPRD vs. EUROCAT | HES vs. EUROCAT | CPRD-HES-ONS vs. EUROCAT |
| Any MCM | 1,176 | 257.9 (243.7-272.8) | 2,535 | 555.9 (535.3-577.3) | 3,033 | 665.1 (642.6-688.4) | 15,967 | 154.4 (152.0-156.8) | 1.7 (1.6-1.8) | 3.6 (3.5-3.8) | 4.3 (4.1-4.5) |
| Limb | 400 | 87.7 (79.6-96.7) | 1,034 | 226.7 (213.5-240.8) | 1,255 | 275.2 (260.6-290.6) | 2,831 | 27.4 (26.4-28.4) | 3.2 (2.9-3.6) | 8.3 (7.7-8.9) | 10.1 (9.4-10.7) |
| Heart | 288 | 63.2 (56.3-70.9) | 327 | 71.7 (64.4-79.9) | 437 | 95.8 (87.3-105.2) | 4,691 | 45.4 (44.1-46.7) | 1.4 (1.2-1.6) | 1.6 (1.4-1.8) | 2.1 (1.9-2.3) |
| Genital | 121 | 26.5 (22.2-31.7) | 172 | 37.7 (32.5-43.8) | 220 | 48.2 (42.3-55.0) | 1,910 | 18.5 (17.7-19.3) | 1.4 (1.2-1.7) | 2.0 (1.7-2.4) | 2.6 (2.3-3.0) |
| Urinary | 122 | 26.8 (22.4-31.9) | 166 | 36.4 (31.3-42.4) | 209 | 45.8 (40.0-52.5) | 2,216 | 21.4 (20.5-22.3) | 1.2 (1.0-1.5) | 1.7 (1.4-2.0) | 2.1 (1.8-2.5) |
| Nervous | 28 | 6.1 (4.2-8.9) | 68 | 14.9 (11.8-18.9) | 81 | 17.8 (14.3-22.1) | 943 | 9.1 (8.6-9.7) | 0.7 (0.4-1.0) | 1.6 (1.3-2.1) | 1.9 (1.5-2.4) |
| Respiratory | 19 | 4.2 (2.7-6.5) | 30 | 6.6 (4.6-9.4) | 39 | 8.6 (6.3-11.7) | 388 | 3.8 (3.4-4.1) | 1.1 (0.7-1.8) | 1.8 (1.2-2.5) | 2.3 (1.6-3.2) |
| Digestive | 57 | 12.5 (9.7-16.2) | 94 | 20.6 (16.8-25.2) | 107 | 23.5 (19.4-28.3) | 1,447 | 14.0 (13.3-14.7) | 0.9 (0.7-1.2) | 1.5 (1.2-1.8) | 1.7 (1.4-2.0) |
| Abdominal | 20 | 4.4 (2.8-6.8) | 28 | 6.1 (4.2-8.9) | 28 | 6.1 (4.2-8.9) | 551 | 5.3 (4.9-5.8) | 0.8 (0.5-1.3) | 1.2 (0.8-1.7) | 1.2 (0.8-1.7) |
| Orofacial | 56 | 12.3 (9.5-15.9) | 65 | 14.3 (11.2-18.2) | 66 | 14.5 (11.4-18.4) | 1,281 | 12.4 (11.7-13.1) | 1.0 (0.7-1.3) | 1.2 (0.9-1.5) | 1.2 (0.9-1.5) |
| Eye | 46 | 10.1 (7.6-13.5) | 22 | 4.8 (3.2-7.3) | 57 | 12.5 (9.7-16.2) | 197 | 1.9 (1.7-2.2) | 5.3 (3.8-7.3) | 2.5 (1.6-3.9) | 6.6 (4.8-8.9) |
| Ear, Face & Neck | 6 | 1.3 (0.6-2.9) | 20 | 4.4 (2.8-6.8) | 25 | 5.5 (3.7-8.1) | 92 | 0.9 (0.7-1.1) | 1.5 (0.5-3.3) | 4.9 (2.9-8.1) | 6.2 (3.8-9.7) |

### 7.5.2 Could limited follow-up in some English registries explain differences in prevalence rates?

As described in **Section 1.7.1**, English registries receive notifications from multiple sources to ascertain MCMs and also conduct active case ascertainment.[118, 119] This approach enhances the completeness of data and also provides opportunities for quality control. Together with the standardized manner by which data on MCMs are collected (i.e. the use of common coding guidelines), these strengths have established EUROCAT as a reliable source on the prevalence of these conditions and have resulted in registry data being used extensively for research.

Individual registries may, however, differ in their ascertainment of MCMs. Notification of cases is not compulsory by law and active case ascertainment may be limited by available resources and access to data sources.[118] For example, although registries strive to ascertain MCMs throughout the first year of life, this is not always possible in practice (Judith Rankin, personal communication). Indeed, some registries caution that although ascertainment is high for MCMs identified in the antenatal period, data can be more limited for diagnoses made postnatally.[120, 121, 124]

Variation in full reporting of MCMs throughout the first year of life could partly explain the higher prevalence of MCMs in electronic health records compared to UK EUROCAT registries. A EUROCAT report on the data quality of all contributing European registries between 2011 and 2015, which roughly corresponded to the study period, examined the prevalence rate of six MCMs likely to be diagnosed after the neonatal period.[295] The report showed that the total congenital anomaly prevalence for these conditions was lower in four of the five English registries compared to the average rate from all registries contributing to EUROCAT.[295] These results suggested potentially lower levels of notifications from paediatric, surgical and other units during this period.

This explanation is supported by findings that abdominal and orofacial malformations, both of which represent a small number of conditions that are apparent at birth and require corrective

procedures immediately or shortly thereafter, had similar prevalence rates in electronic health records used in this thesis and in registry data. Other MCM subgroups generally captured broader spectra of conditions, some of which might only be detected after prolonged investigation or may not require immediate treatment. These conditions had lower prevalence rates in registry data than in HES or linked data, suggesting that differences in prevalence may sometimes occur when longer follow-up is needed to ascertain conditions.

### 7.5.3 Could limitations of clinical coding systems and practices in UK electronic health records explain differences in prevalence rates?

The higher prevalence of MCMs in electronic health records could be explained by the inherent limitations of clinical coding systems and practices. Whilst EUROCAT publishes detailed guidelines on how MCMs should be coded by registries, these guidelines have not been adopted as part of clinical coding practice in the UK.[283] Clinicians have flexibility in the codes they use to record MCMs. As discussed in **Section 5.4**, this flexibility in coding choice was accounted for when developing code-lists for the work described in this thesis, but may have led to the inflation of prevalence rates in electronic health records. Clinicians may:

**1. Use non-specific codes from chapters outside of the dedicated Read 'P' or ICD-10 'Q' chapters for congenital malformation diagnoses.** These non-specific codes could refer to congenital or non-congenital conditions (e.g. mitral stenosis which could be congenital or could have other causes). Such codes were included in code-lists used to search patient records if they were thought to relate to MCMs in the majority of the study population during the study period. However, because such codes may also be used by clinicians to encode non-congenital conditions, the possibility that some individuals were classified as having an MCM when they had a non-congenital condition could not be discounted.

**2. Use non-specific Read or ICD-10 codes from the dedicated chapters for congenital malformation diagnoses.** These non-specific codes could refer to major or minor malformations (e.g. '*unspecified congenital malformation of limbs*') or conditions that require

additional information to be classified as true MCMs (e.g. congenital hydronephrosis is only considered a true MCM if there is a pelvis dilatation of >10mm).[283] Although the inclusion of such non-specific codes in code-lists used to search patient records were carefully considered together with a consultant neonatologist, there was a possibility that some individuals were classified as having an MCM when they had a minor malformation or did not meet the necessary criteria to be defined as a true MCM.

These limitations may have been further exacerbated by the difference in the BPA-modified ICD-10 coding system used by EUROCAT and the ICD-10 coding system used in HES. The BPA-modified coding system adds an extra digit to the ICD-10 codes which allows for additional granularity and allows generic diagnostic codes to be split into more specific diagnostic codes that can then be defined as major or minor. For example, in EUROCAT, code Q825 for '*congenital non-neoplastic naevus*' is further split into codes Q8251, Q8252 and Q8258 which are then separately defined as major (Q8258) and minor (Q8250-8252).[283]

The prevalence rate of limb malformations appeared to be particularly elevated in routine data compared to EUROCAT registries, particularly among data from HES. It was thought that this was likely a result of non-specific ICD-10 codes that could be used to encode both major and minor malformations or other conditions, thereby inflating prevalence estimates. For example, the ICD-10 code '*other congenital deformities of feet*' could be used to refer to a number of conditions, such as: syndactyly of the 2nd and 3rd toes (defined as a minor malformation by EUROCAT), talipes equinovarus of postural origin (described by EUROCAT as not being a true MCM), talipes equinovarus of congenital origin (defined as an MCM by EUROCAT) or talipes calcaneovarus (defined as an MCM by EUROCAT).[283] Indeed, among infants whose only evidence of a limb malformation was in HES, the proportion that had an ICD-10 code that could be considered non-specific was >90% (described in **Section 7.3**). This could explain why the prevalence of these conditions was so high when HES data were used. To a lesser extent but likely for the same reasons, the prevalence of limb malformations was also elevated in

CPRD.

**3. Have a lower threshold for coding diagnoses than registries.** For example, clinicians may routinely use the code '*patent ductus arteriosus*' regardless of whether the opening in the heart was a result of preterm birth and resolved in its own time or whether the infant had a severe patent ductus arteriosus. Conversely, EUROCAT has robust and standardized coding guidelines that emphasize the need to only encode patent ductus arteriosus that is not associated with prematurity. [283]

**4. Encode tentative diagnoses.** Clinicians, particularly in primary care, may encode suspected diagnoses which require further investigation. It is possible that a proportion of MCMs recorded in primary care relate to other conditions. Tentative coding is less likely to occur in secondary care where clinical coding is related to reimbursement.[261]

The above examples are likely to explain the higher prevalence of MCMs in electronic health records compared to registry data. These are expanded upon further in **Chapter 11.**

## 7.6 Chapter summary and conclusions

Using the algorithm developed to identify MCMs in **Chapter 5**, this chapter demonstrated that the proportion of infants with an MCM that had coded evidence of their condition in both CPRD and HES was just 20%. Previous studies examining vaccine and drug safety in pregnancy have relied on stand-alone primary care data **(Chapter 2)**. However, the study in this chapter found that 65% of infants with an MCM had evidence of their condition exclusively in HES and that reliance on primary care data would tend to under-ascertain these conditions. Prevalence rates in CPRD were generally similar to or higher than those in equivalent primary care records from THIN. Prevalence rates in CPRD, HES and CPRD-HES-ONS were also similar to or higher than those in EUROCAT. Elevated prevalence rates of some MCM subgroups could potentially be explained by the use of non-specific Read and ICD-10 codes which could be used to record minor malformations or non-congenital conditions as well as MCMs.

# 8. Examining seasonal influenza vaccination during pregnancy and major congenital malformations

## 8.1 Introduction

This results chapter addresses **Objective 5**. It contains the results of a large, population-based cohort study used to assess the safety of SIIV receipt during pregnancy, with MCMs as the outcome of interest. The chapter builds on previous work, including the systematic review of the identification of MCMs in UK electronic health records (**Chapter 2**), the development of an algorithm to identify such conditions (**Chapter 5**) and the exploration of the value of different data sources in their ascertainment (**Chapter 7**). It is followed by **Chapter 9** which examines the safety of PIIV during pregnancy, with MCMs as the outcome of interest (**Objective 6**).

In this chapter, **Section 8.2** summarizes the derivation of the final study population for SIIV safety analyses. **Section 8.3** presents results from the analysis in the form of a submitted manuscript along with supplementary material. **Section 8.4** describes the prevalence of ICD-10 coded MCM subgroups and conditions by vaccination status. **Section 8.5** explains why analyses examined vaccination in each trimester and **Section 8.6** provides the rationale for restricting analyses to live-births. **Section 8.7** and **Section 8.8** consider whether the exclusion of terminations due to foetal anomaly and other pregnancy outcomes could have biased results.

## 8.2 Deriving the final study population for analyses on SIIV safety

The methods used to identify potentially eligible pregnancies are described in **Chapter 4**. After applying these criteria, 199,017 potentially eligible pregnancies were identified. **Figure 8.1** shows how the final study population for the examination of the safety of SIIV was derived after applying study-specific exclusion criteria (**Section 4.5**). A total of 116,661 pregnancies were identified, of which 78,150 were live-births with linked infant records and went on to be used in the main analysis described in **Section 8.3.** Reasons for excluding other pregnancy types are described in **Section 8.6**.

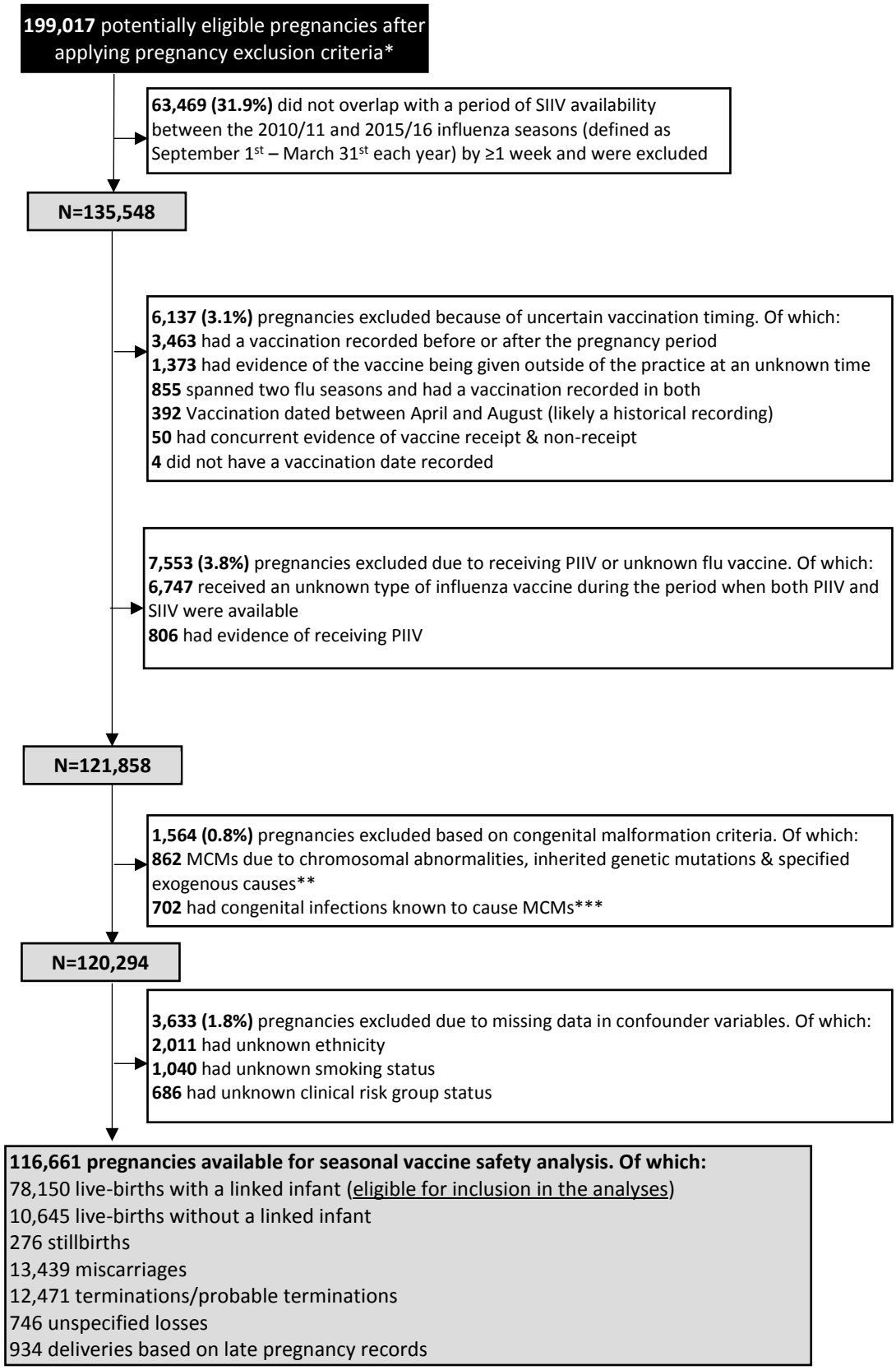



**Figure 8.1 – Deriving the study population for seasonal influenza vaccine safety analyses. ***The initial population of 199,017 pregnancies included those ending between January 1, 2009 and March 31, 2016. All live-born infants were eligible for linkage to HES and ONS. The identification of the 199,017 potentially eligible pregnancies is described in Sections 4.2-4.3. This flow diagram includes all potentially eligible pregnancies, in comparison to Figure 1 of the submitted paper which presents only those pregnancies ending in live-births. **See Section 4.4.1; ***See Section 4.4.2.

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

# RESEARCH PAPER COVER SHEET

**Please note that a cover sheet must be completed for each research paper included within a thesis.**

## SECTION A – Student Details

| | | | |
|---|---|---|---|
| **Student ID Number** | 1300677 | **Title** | Miss |
| **First Name(s)** | Maria | | |
| **Surname/Family Name** | Peppa | | |
| **Thesis Title** | The safety of influenza vaccination in pregnancy: Examining major congenital malformations as potential adverse outcomes using UK electronic health records | | |
| **Primary Supervisor** | Professor Punam Mangtani | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

## SECTION B – Paper already published

| | | | |
|---|---|---|---|
| Where was the work published? | | | |
| When was the work published? | | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | | | |
| Have you retained the copyright for the work?* | Choose an item. | Was the work subject to academic peer review? | Choose an item. |

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

## SECTION C – Prepared for publication, but not yet published

| | |
|---|---|
| Where is the work intended to be published? | Clinical Infectious Diseases |
| Please list the paper's authors in the intended authorship order: | Maria Peppa, Sara L Thomas, Caroline Minassian, Jemma L Walker, Helen I McDonald, Nick J Andrews, Stephen T Kempley, Punam Mangtani |

| | |
|---|---|
| Stage of publication | **Undergoing revision** |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | This study was conceptualized by P Mangtani and designed by P Mangtani, S Thomas, C Minassian, J Walker, N Andrews and myself. I developed initial code-lists for MCMs and these were discussed and agreed with S Kempley, P Mangtani and S Thomas. Code-lists for vaccines had been previously developed by S Thomas. J Walker contributed code-lists for clinical risk groups. I developed code-lists and algorithms for remaining covariates and carried out data management and analyses. These were discussed with co-authors to ensure agreement. I drafted the manuscript and revised it following comments from co-authors. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | Maria Peppa |
| **Date** | 19.03.2020 |

| | |
|---|---|
| **Supervisor Signature** | Punam Mangtani |
| **Date** | 20.03.2020 |

## 8.3 Submitted Paper: Seasonal influenza vaccination during pregnancy and the risk of major congenital malformations in live-born infants

**Authors:** Maria Peppa*[a], Sara L Thomas[a], Caroline Minassian[a], Jemma L Walker[a,b], Helen I McDonald[a] , Nick J Andrews[b], Stephen T Kempley[c], Punam Mangtani[a]

[a]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom

[b]Statistics, Modelling and Economics Department, Public Health England, London, United Kingdom

[c]Blizard Institute, Queen Mary University of London, London, United Kingdom

*Corresponding author

## Abstract

**Background:** Available evidence indicates that seasonal inactivated influenza vaccination during pregnancy protects both the mother and her newborn, and is safe. Nevertheless, ongoing safety assessments are important in sustaining vaccine uptake. Few studies have explored safety in relation to major congenital malformations, particularly in the first trimester when most organogenesis occurs.

**Methods:** Anonymised UK primary care data (the Clinical Practice Research Datalink), including a recently developed Pregnancy Register, were used to identify live-born singletons delivered between 2010 and 2016. Maternal influenza vaccination was determined using primary care records and stratified by trimester. Ascertainment of major malformations from infant primary care records was maximized by linkage to hospitalisation data and death certificates. The relationship between vaccination and major malformations recorded in the year after delivery and in early childhood was then assessed using multivariable Cox regression.

**Results:** A total of 78,150 live-birth pregnancies were identified: 6,872 (8.8%) were vaccinated in the first trimester, 11,678 (14.9%) in the second and 12,931 (16.5%) in the third. Overall, 5,707 live-births resulted in an infant with a major malformation recorded in the year after delivery and the adjusted hazard ratio when comparing first-trimester vaccination to no vaccination was 1.06 (99%CI, 0.94-1.19; p=0.2). Results were similar for second and third-trimester vaccination and for analyses considering major malformations recorded beyond the first birthday.

**Conclusions:** In this large, population-based historical cohort study there was no evidence to suggest that seasonal influenza vaccine was associated with major malformations when given in the first trimester or subsequently in pregnancy.

## Introduction

Pregnant women and newborn infants are at increased risk of complications following influenza infection.[37, 296] Seasonal influenza vaccination (SIV) during pregnancy has been shown to provide good protection to both groups.[63, 297, 298] The World Health Organization recommended SIV for all pregnant women, regardless of trimester, in 2012.[299] Women, however, are concerned about the safety of vaccination during pregnancy for their child.[16, 300]

Several studies have demonstrated the safety of the 2009/10 monovalent pandemic vaccine with respect to major congenital malformations (MCMs), but few have assessed SIV.[20-23] Those that have examined SIV, and have stratified by trimester of vaccination, have generally been limited by low numbers of first-trimester vaccinations and inadequate infant follow-up which could result in under-ascertainment of MCMs.[20-23] To date, there has only been one large US study of first-trimester vaccination with adequate infant follow-up.[103]

We examined the association between SIV administered in the first and subsequent trimesters, and the risk of MCMs in a different setting by using a large UK cohort, with ascertainment of malformations using long-term follow-up in linked primary care, hospitalisation and mortality datasets.

## Methods

### Data Sources

This study utilized the Clinical Practice Research Datalink (CPRD), the CPRD/London School of Hygiene and Tropical Medicine (LSHTM) Pregnancy Register, hospital admissions data from the Hospital Episode Statistics database (HES), Office for National Statistics (ONS) death certificate data, deprivation quintiles linked to household post-codes, and data on influenza activity from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre.

The CPRD contains anonymised, electronic primary care records for 7% of the UK population registered at a general practice. It includes diagnoses and procedures recorded using Read codes, vaccination records and prescriptions.[126] The CPRD has been shown to be broadly representative of the UK population and diagnostic validity is high.[126, 180]

The Pregnancy Register lists all pregnancies identified in CPRD, for women aged 11-49 years.[255] It includes pregnancy outcomes and estimates of pregnancy timings derived from all available pregnancy data in CPRD including estimated delivery dates, last menstrual period dates, ultrasound dating scans and prematurity records. The first, second and third trimesters are defined as the pregnancy start through week 13, week 14 through 26 and week 27 through the pregnancy end, respectively. Live-birth deliveries are linked to records of infants registered at the same practice as their mother. Validation of the Pregnancy Register against linked electronic maternity records in HES has indicated overall good agreement, suggesting most pregnancies are well-captured in the Register.[255]

Patient data in CPRD can be linked to the HES and ONS data for 75% of English practices.[126] Linked HES data include information on diagnoses and procedures, recorded using the International Classification of Diseases (ICD-10) and the Classification of Surgical Operations and Procedures (OPCS-4), respectively. ONS death certificate data include primary and

contributory causes of death recorded using ICD-10. Deprivation quintiles are derived from the 2015 Index of Multiple Deprivation (IMD) for Lower Super Output Areas.[269]

Weekly general practice consultation rates for influenza-like illness from the RCGP were used to identify periods of influenza circulation above baseline levels for each season. The validity of these data has been confirmed through microbiological surveillance.[278]

This study received approval from the Independent Scientific Advisory Committee of the Medicines & Healthcare Products Regulatory Agency (reference 17_040RA); the approved protocol was made available to the reviewers. Approval was also received from LSHTM's ethics committee (reference 13720).

**Study design**

This historical cohort study compared live-birth pregnancies that received SIV, stratified by trimester of vaccination, to those unvaccinated. The primary outcome was the presence of any MCMs among infants in the year after delivery. Secondary outcomes examined any MCMs, major limb malformations and congenital heart defects recorded after delivery and anytime in the study period between September 1, 2010 and March 31, 2016 (the latest date for which all linked data were available).

**Study population**

Pregnancies resulting in a live-born singleton during the study period were identified from the Pregnancy Register. Pregnant women had to be registered at an up-to-standard practice (a quality standard set by CPRD to indicate continuous recording of data within the practice)[126] for at least 6 months before the start of pregnancy to enable the ascertainment of pre-conception exposures. Live-born infants had to be eligible for HES and ONS linkage. Finally, pregnancies were required to overlap with a period of influenza vaccine availability (1st September to 31st March, annually) by at least one week.

**Identifying vaccinations**

In the UK, pregnant women are offered SIV in any trimester.[5] The earliest vaccination record in each influenza season was identified in CPRD from immunisation records, prescriptions or Read codes, and used to determine the trimester of vaccination. Pregnancies were excluded if the timing or nature of vaccination was uncertain (e.g. if there was a possibility that SIV was received outside of the practice at an unknown time or a possibility that pandemic vaccine was received) (**Figure 1**).

**Identifying MCMs**

Code lists for MCMs were developed with a consultant neonatologist (SK), following EUROCAT guidelines.[283] MCMs were then ascertained from infant records in CPRD, HES data for diagnoses and procedures, and ONS. Pregnancies were excluded if there was an antenatal or infant record indicating a chromosomal or heritable anomaly, a malformation due to a known teratogen (e.g. foetal alcohol syndrome), or a congenital infection associated with malformations. Infants were followed-up from delivery for a year or until the end of the study period. Follow-up ended earlier if they died, left the practice or the practice stopped collecting data for CPRD.

**Potential confounders**

We considered *a priori* confounders to be maternal age and ethnicity, geographical region (due to variation in vaccine uptake and MCM ascertainment) and the earliest influenza season a pregnancy overlapped with. Other potential confounders included: household deprivation quintile (IMD), number of children in the household, maternal smoking, hazardous drinking, extreme body mass index (BMI) of <18 or ≥35, belonging to another clinical risk group for which vaccination was recommended during the study period,[5] non-pregnancy related chronic hypertension, exposure to teratogenic drugs or live vaccines, and number of weeks the first

trimester overlapped with influenza activity above baseline levels (see **Supplementary Table 1** for details of how these were derived).

**Statistical analyses**

Baseline pregnancy characteristics were described by vaccination status. Logistic regression was used initially to model the univariable relationship between vaccination and MCMs recorded in the year after delivery and assess confounding. After *a priori* confounders, remaining potential confounders were added individually to the logistic regression model and assessed for a ≥5% change in the odds ratios between first-trimester vaccination or vaccination anytime and MCMs. Multicollinearity was monitored between IMD, ethnicity and region and between the number of children in the household and maternal age. Finally, random effects models were used to assess clustering by mother and practice. Once confounders had been identified using logistic regression models, all final analyses were conducted using Cox proportional hazards models to account for improved ascertainment of the outcome among infants with longer follow-up time. Results were compared to those from logistic regression. To account for multiple analyses, 99% confidence intervals (CIs) were calculated. All models were complete case analyses.

Three sensitivity analyses were conducted. First, we included pregnancies that received SIV in the 4 weeks prior to their start to account for any imprecision in the estimated pregnancy start dates. Second, we included MCMs recorded in HES or ONS after follow-up in CPRD had ended because the infant left the practice or the practice ended data collection. In the main analyses, pregnancies of women with unknown BMI or a BMI between 18 and 34 were combined in a single category as they had comparable associations with MCMs. The third sensitivity analysis excluded pregnancies of women with unknown BMI.

STATA version 14.2 was used for all analyses.

## Results

### Characteristics of the eligible study cohort

We identified 103,742 potentially eligible pregnancies resulting in live-born singletons during the study period. After exclusions were applied, the final cohort included 78,150 pregnancies among 71,124 women (**Figure 1**). Most pregnancies were of white women (85.5%), aged 25-34 (58.9%) years (**Table 1**).

Vaccine uptake was 40.3% (n=31,481): 8.8% (n=6,872) in the first trimester, 14.9% (n=11,678) in the second and 16.5% (n=12,931) in the third. Vaccination in the first trimester or anytime in pregnancy was less likely if the woman was: young, of Black ethnicity, living in a more deprived area, not part of a clinical risk group for which vaccination was recommended,[5] unexposed to teratogenic medications and/or live vaccines, a current smoker or part of a household with children (**Table 1; Supplementary Table 2**). Vaccination also varied by region and the earliest influenza season the pregnancy overlapped with.

Of the 78,150 pregnancies, 7.3% (n=5,707) resulted in an infant with an MCM recorded in the year after delivery, whilst 7.7% (n=6,029) had an MCM recorded after delivery and anytime in the study period. Most MCMs were recorded early in life, with 51% recorded at delivery and 87.2% in the following three months (**Supplementary Figure 1**). Most infants had at least one year of follow-up (73.5%) and almost half had at least two (48.9%) (**Supplementary Table 3**).

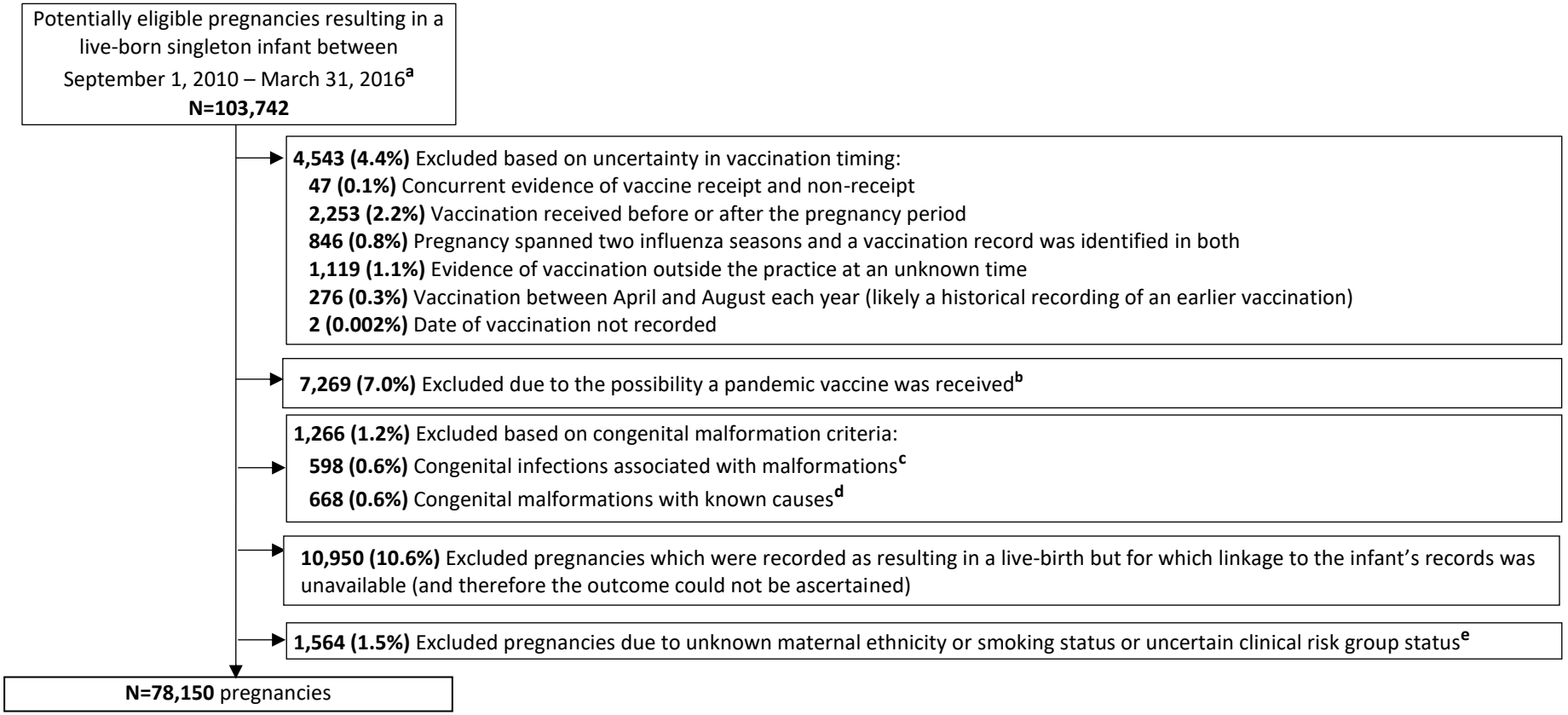



**Figure 5 - Derivation of pregnancies used in analyses. [a]At least one week of the pregnancy had to occur when influenza vaccine was available**. All infants had to be eligible for linkage to HES and ONS data. [b]Pandemic vaccine was available alongside SIV in 2009/10 and 2010/11. Pregnant women could be offered the pandemic vaccine in 2010/11, or in 2009/10 if their pregnancy ended after September 1, 2010 but started in the prior influenza season. Pregnancies that received pandemic vaccine or an unspecified influenza vaccine in 2009/10 or 2010/11 were excluded. [c]Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Parvovirus, Varicella-zoster, Syphillis, HIV. [d]Chromosomal anomalies, heritable conditions, or malformations due to a known teratogen. [e]Among pregnancies for which linkage to the infant record was available, 720 had unknown maternal ethnicity, 403 had unknown maternal smoking status and 449 had an uncertain maternal clinical risk group status.

**Table 5 - Characteristics of eligible pregnancies included in analyses, by vaccination status.**

| | No. pregnancies (%) N=78,150 | No. pregnancies unvaccinated (%) n=46,669 | No. pregnancies vaccinated in trimester 1 (%) n=6,872 | No. pregnancies vaccinated anytime (%) n=31,481 |
|---|---|---|---|---|
| **Maternal age (years)** | | | | |
| <18 | 719 (0.9) | 458 (63.7) | 33 (4.6) | 261 (36.3) |
| 18-24 | 13,243 (17.0) | 8,451 (63.8) | 982 (7.4) | 4,792 (36.2) |
| 25-34 | 46,030 (58.9) | 27,138 (59.0) | 4,150 (9.0) | 18,892 (41.0) |
| ≥35 | 18,158 (23.2) | 10,622 (58.5) | 1,707 (9.4) | 7,536 (41.5) |
| **Maternal ethnicity** | | | | |
| White | 66,849 (85.5) | 39,618 (59.3) | 5,939 (8.9) | 27,231 (40.7) |
| South Asian | 5,501 (7.0) | 3,272 (59.5) | 507 (9.2) | 2,229 (40.5) |
| Black | 2,881 (3.7) | 1,953 (67.8) | 196 (6.8) | 928 (32.2) |
| Other | 1,850 (2.4) | 1,171 (63.3) | 146 (7.9) | 679 (36.7) |
| Mixed | 1,069 (1.4) | 655 (61.3) | 84 (7.9) | 414 (38.7) |
| **Maternal IMD status[a]** | | | | |
| 1=least deprived | 15,847 (20.3) | 8,730 (55.1) | 1,579 (10.0) | 7,117 (44.9) |
| 2 | 14,905 (19.1) | 8,569 (57.5) | 1,345 (9.0) | 6,336 (42.5) |
| 3 | 15,144 (19.4) | 8,880 (58.6) | 1,406 (9.3) | 6,264 (41.4) |
| 4 | 16,064 (20.6) | 10,015 (62.3) | 1,304 (8.1) | 6,049 (37.7) |
| 5=most deprived | 16,190 (20.7) | 10,475 (64.7) | 1,238 (7.7) | 5,715 (35.3) |
| **Region** | | | | |
| London | 12,922 (16.5) | 8,295 (64.2) | 991 (7.7) | 4,627 (35.8) |
| North East | 1,811 (2.3) | 1,203 (66.4) | 113 (6.2) | 608 (33.6) |
| North West | 11,636 (14.9) | 6,771 (58.2) | 1,133 (9.7) | 4,865 (41.8) |
| Yorkshire & The Humber | 1,453 (1.9) | 922 (63.5) | 123 (8.5) | 531 (36.6) |
| East Midlands | 780 (1.0) | 549 (70.4) | 45 (5.8) | 231 (29.6) |
| West Midlands | 8,545 (10.9) | 4,561 (53.4) | 997 (11.7) | 3,984 (46.6) |
| East of England | 7,862 (10.1) | 4,463 (56.8) | 741 (9.4) | 3,399 (43.2) |
| South West | 9,974 (12.8) | 5,936 (59.5) | 777 (7.8) | 4,038 (40.5) |
| South Central | 11,670 (14.9) | 6,710 (57.5) | 1,157 (9.9) | 4,960 (42.5) |
| South East Coast | 11,497 (14.7) | 7,259 (63.1) | 795 (6.9) | 4,238 (36.9) |
| **Mother was part of a clinical risk group[b]** | | | | |
| No | 73,804 (94.4) | 44,513 (60.3) | 6,230 (8.4) | 29,291 (39.7) |
| Yes | 4,346 (5.6) | 2,156 (49.6) | 642 (14.8) | 2,190 (50.4) |
| **Maternal smoking status** | | | | |
| Non | 41,081 (52.6) | 23,922 (58.2) | 3,729 (9.1) | 17,159 (41.8) |
| Current | 17,687 (22.6) | 11,630 (65.8) | 1,278 (7.2) | 6,057 (34.3) |
| Ex | 19,382 (24.8) | 11,117 (57.4) | 1,865 (9.6) | 8,265 (42.6) |
| **Maternal hazardous drinking** | | | | |
| No | 77,502 (99.2) | 46,308 (59.8) | 6,811 (8.8) | 31,194 (40.3) |
| Yes | 648 (0.8) | 361 (55.7) | 61 (9.4) | 287 (44.3) |
| **Extreme maternal BMI** | | | | |
| No | 71,335 (91.3) | 42,560 (59.7) | 6,235 (8.7) | 28,775 (40.3) |
| Underweight (<18) | 1,656 (2.1) | 1,042 (62.9) | 147 (8.9) | 614 (37.1) |
| Obese (≥35) | 5,159 (6.6) | 3,067 (59.5) | 490 (9.5) | 2,092 (40.6) |
| **Maternal chronic hypertension (non-pregnancy related)** | | | | |
| No | 77,097 (98.7) | 46,074 (59.8) | 6,760 (8.8) | 31,023 (40.2) |
| Yes | 1,053 (1.4) | 595 (56.5) | 112 (10.6) | 458 (43.5) |
| **Maternal exposure to teratogenic medication(s)[c] or live vaccines[d]** | | | | |
| No | 73,370 (93.9) | 43,928 (59.9) | 6,386 (8.7) | 29,442 (40.1) |
| Yes | 4,780 (6.1) | 2,741 (57.3) | 486 (10.2) | 2,039 (42.7) |
| **Earliest influenza season a pregnancy overlapped with** | | | | |

| | No. pregnancies (%) N=78,150 | No. pregnancies unvaccinated (%) n=46,669 | No. pregnancies vaccinated in trimester 1 (%) n=6,872 | No. pregnancies vaccinated anytime (%) n=31,481 |
|---|---|---|---|---|
| 2009/10 | 5,234 (6.7) | 5,171 (98.8) | 0 (0.0) | 63 (1.2) |
| 2010/11 | 13,040 (16.7) | 10,135 (77.7) | 425 (3.3) | 2,905 (22.3) |
| 2011/12 | 18,468 (23.6) | 11,254 (60.9) | 1,607 (8.7) | 7,214 (39.1) |
| 2012/13 | 15,910 (20.4) | 7,833 (49.2) | 2,067 (13.0) | 8,077 (50.8) |
| 2013/14 | 13,383 (17.1) | 6,906 (51.6) | 1,503 (11.2) | 6,477 (48.4) |
| 2014/15 | 9,987 (12.8) | 4,715 (47.2) | 1,251 (12.5) | 5,272 (52.8) |
| 2015/16 | 2,128 (2.7) | 655 (30.8) | 19 (0.9) | 1,473 (69.2) |
| **No. of weeks the first trimester overlapped with influenza activity above baseline levels** | | | | |
| None | 63,145 (80.8) | 35,467 (56.2) | 4,813 (7.6) | 27,678 (43.8) |
| 0-2 | 6,556 (8.4) | 4,649 (70.9) | 1,091 (16.6) | 1,907 (29.1) |
| 2-4 | 1,668 (2.1) | 1,200 (71.9) | 154 (9.2) | 468 (28.1) |
| 4-6 | 2,059 (2.6) | 1,525 (74.1) | 260 (12.6) | 534 (25.9) |
| 6-8 | 2,954 (3.8) | 2,377 (80.5) | 346 (11.7) | 577 (19.5) |
| 8-10 | 703 (0.9) | 541 (77.0) | 88 (12.5) | 162 (23.0) |
| 10-12 | 1,065 (1.4) | 910 (85.5) | 120 (11.3) | 155 (14.6) |
| **No. of children in the maternal household** | | | | |
| None | 27,868 (35.7) | 15,211 (54.6) | 2,833 (10.2) | 12,657 (45.4) |
| 1-2 | 42,911 (54.9) | 26,419 (61.6) | 3,565 (8.3) | 16,492 (38.4) |
| ≥3 | 7,371 (9.4) | 5,039 (68.4) | 474 (6.4) | 2,332 (31.6) |

[a]For 46 (0.06%) pregnancies, maternal household IMD was unavailable and practice-level IMD was used. [b]Chronic respiratory, heart, kidney, liver or neurological disease, diabetes, immunosuppression due to disease or treatment, asplenia or dysfunction of the spleen. [c]Exposure from six months before pregnancy start until the end of the first trimester. [d]Exposure from three months before pregnancy start until the end of the first trimester. Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index.

**Primary analyses**

The univariable Cox regression analysis showed evidence for a crude association between vaccination anytime in pregnancy and MCMs recorded in the year after delivery; results were similar for first and second-trimester vaccination (**Table 2**). However, all associations were eliminated following adjustment for *a priori* confounders: maternal age and ethnicity, region and the earliest influenza season a pregnancy overlapped with (**Table 2**). The most important of these appeared to be region and season; hazard ratios (HRs) remained similar upon the addition of age and ethnicity **(Supplementary Tables 4-5)**. Both region and season were associated with age and ethnicity ($\chi^2$ $p<0.001$), suggesting that adjustment for the former likely resulted in partial adjustment for the latter.

Of the remaining potential confounders, only maternal IMD and number of children in the household were associated with both vaccination and MCMs in univariable analyses

(**Supplementary Tables 2 and 6**). However, upon addition to the model, neither these nor any others altered HRs by ≥5% (**Supplementary Tables 4 and 5**). Fully-adjusted models showed no evidence of an association between vaccination anytime (HR, 1.02; 99% CI, 0.94-1.10; p=0.54), vaccination in the first trimester (HR, 1.06; 99% CI, 0.94-1.19; p=0.23) or the second (HR, 1.02; 99% CI, 0.92-1.13; p=0.63) and MCMs recorded in the year after delivery (**Table 2**). The logistic regression models used to investigate confounding gave very similar results to our final Cox regression models (**Supplementary Tables 4 and 5**).

**Secondary analyses**

Results from analyses in which follow-up was extended to include any MCMs ascertained from delivery until the end of the study period were almost identical (**Table 2**). Unadjusted models examining major limb malformations showed a crude association with vaccination in all trimesters (**Table 3**). However, adjusting for *a priori* or all potential confounders removed any associations. For congenital heart defects, no association was seen with vaccination in any model.

**Sensitivity analyses**

Sensitivity analyses that included 216 additional pregnancies for which vaccination occurred four weeks prior to their estimated start, or allowed for follow-up in HES and ONS data to continue after follow-up in CPRD had ended, or excluded 8,093 pregnancies of women with unknown BMI did not differ substantially from main analyses (**Table 4**).

**Table 2 – Examining the association between vaccination and MCMs.**

| Vaccination (No. pregnancies) | No. MCMs/person-years (rate per 100 person-years) | HR, unadjusted (99% CI) | *P* value | HR, adjusted for *a priori* confounders (99% CI) | *P* value | HR, adjusted for all potential confounders (99% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| **Models including MCMs ascertained in the year after delivery (N=5,707 MCMs)** | | | | | | | |
| **Never** (46,669) | 3,289/38,898 (8.5) | 1.00 | | 1.00 | | 1.00 | |
| **Any trimester** (31,481) | 2,418/24,827 (9.7) | 1.10 (1.03-1.18) | <0.001 | 1.03 (0.96-1.11) | 0.33 | 1.02 (0.94-1.10) | 0.54 |
| **Trimester 1** (6,872) | 565/5,560 (10.2) | 1.17 (1.04-1.32) | <0.001 | 1.08 (0.96-1.22) | 0.11 | 1.06 (0.94-1.19) | 0.23 |
| **Trimester 2** (11,678) | 902/9,153 (9.9) | 1.11 (1.01-1.22) | 0.006 | 1.03 (0.93-1.14) | 0.45 | 1.02 (0.92-1.13) | 0.63 |
| **Trimester 3** (12,931) | 951/10,115 (9.4) | 1.05 (0.96-1.16) | 0.17 | 1.00 (0.91-1.10) | >0.99 | 0.99 (0.90-1.10) | 0.86 |
| **Models including MCMs ascertained after delivery and anytime in the study period (N=6,029 MCMs)** | | | | | | | |
| **Never** (46,669) | 3,505/102,311 (3.4) | 1.00 | | 1.00 | | 1.00 | |
| **Any trimester** (31,481) | 2,524/54,389 (4.6) | 1.09 (1.02-1.17) | 0.001 | 1.03 (0.96-1.10) | 0.36 | 1.02 (0.94-1.09) | 0.56 |
| **Trimester 1** (6,872) | 594/11,648 (5.1) | 1.18 (1.05-1.32) | <0.001 | 1.09 (0.97-1.22) | 0.07 | 1.07 (0.95-1.20) | 0.16 |
| **Trimester 2** (11,678) | 941/20,203 (4.7) | 1.10 (1.00-1.21) | 0.008 | 1.03 (0.93-1.13) | 0.48 | 1.02 (0.92-1.13) | 0.65 |
| **Trimester 3** (12,931) | 989/22,539 (4.4) | 1.04 (0.95-1.14) | 0.27 | 0.99 (0.90-1.09) | 0.85 | 0.99 (0.90-1.09) | 0.73 |

A priori confounders were maternal age, maternal ethnicity, region and the earliest influenza season a pregnancy overlapped with. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. Abbreviations: MCM, major congenital malformations; IMD, Index of Multiple Deprivation; BMI, body mass index; HR, Hazard Ratio; CI, Confidence Interval.

**Table 3 - Examining the association between vaccination, major limb malformations and congenital heart defects.**

| Vaccination (No. pregnancies) | No. MCMs/person-years (rate per 100 person-years) | HR, unadjusted (99% CI) | *P* value | HR, adjusted for *a priori* confounders (99% CI) | *P* value | HR, adjusted for all potential confounders (99% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| **Models including limb malformations ascertained after delivery and anytime in the study period (N=2,425 limb malformations)** | | | | | | | |
| **Never** (46,669) | 1,350/107,080 (1.3) | 1.00 | | 1.00 | | 1.00 | |
| **Any trimester** (31,481) | 1,075/56,940 (1.9) | 1.20 (1.08-1.33) | <0.001 | 1.10 (0.99-1.23) | 0.03 | 1.07 (0.96-1.21) | 0.11 |
| **Trimester 1** (6,872) | 235/12,259 (1.9) | 1.20 (1.00-1.44) | 0.01 | 1.07 (0.89-1.29) | 0.34 | 1.03 (0.86-1.25) | 0.66 |
| **Trimester 2** (11,678) | 405/21,145 (1.9) | 1.22 (1.06-1.41) | <0.001 | 1.11 (0.96-1.29) | 0.07 | 1.09 (0.93-1.27) | 0.17 |
| **Trimester 3** (12,931) | 435/23,536 (1.9) | 1.18 (1.02-1.36) | 0.003 | 1.11 (0.96-1.28) | 0.07 | 1.09 (0.94-1.26) | 0.14 |
| **Models including congenital heart defects ascertained after delivery and anytime in the study period (N=789 heart defects)** | | | | | | | |
| **Never** (46,669) | 479/109,133 (0.4) | 1.00 | | 1.00 | | 1.00 | |
| **Any trimester** (31,481) | 310/58,303 (0.5) | 0.99 (0.82-1.20) | 0.90 | 0.96 (0.79-1.17) | 0.58 | 0.93 (0.76-1.15) | 0.39 |
| **Trimester 1** (6,872) | 67/12,568 (0.5) | 0.97 (0.69-1.36) | 0.82 | 0.93 (0.66-1.31) | 0.58 | 0.91 (0.64-1.29) | 0.49 |
| **Trimester 2** (11,678) | 129/21,621 (0.6) | 1.12 (0.87-1.44) | 0.26 | 1.08 (0.83-1.41) | 0.45 | 1.04 (0.79-1.37) | 0.68 |
| **Trimester 3** (12,931) | 114/24,114 (0.5) | 0.89 (0.68-1.16) | 0.25 | 0.87 (0.66-1.14) | 0.18 | 0.85 (0.65-1.13) | 0.14 |

A priori confounders were maternal age, maternal ethnicity, region and the earliest influenza season a pregnancy overlapped with. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. Abbreviations: MCM, major congenital malformations; IMD, Index of Multiple Deprivation; BMI, body mass index; HR, Hazard Ratio; CI, Confidence Interval.

**Table 4 - Examining the association between first-trimester vaccination and MCMs in sensitivity analyses.**

| Models | HR, unadjusted (99% CI) | *P* value | HR, adjusted for *a priori* confounders (99% CI) | *P* value | HR, adjusted for all potential confounders (99% CI) | *P* value |
|---|---|---|---|---|---|---|
| **Models including MCMs diagnosed in the year after delivery** | | | | | | |
| **Main model** | **1.17 (1.04-1.32)** | **<0.001** | **1.08 (0.96-1.22)** | **0.11** | **1.06 (0.94-1.19)** | **0.23** |
| Including pregnancies vaccinated in the 4 weeks prior to the start[a] | 1.19 (1.06-1.33) | <0.001 | 1.09 (0.97-1.23) | 0.06 | 1.07 (0.95-1.21) | 0.14 |
| Including diagnoses made beyond truncation of follow-up in CPRD[b] | 1.17 (1.04-1.32) | <0.001 | 1.08 (0.96-1.22) | 0.11 | 1.06 (0.94-1.19) | 0.23 |
| Excluding pregnancies with unknown BMI[c] | 1.18 (1.05-1.33) | <0.001 | 1.09 (0.96-1.23) | 0.09 | 1.07 (0.94-1.21) | 0.19 |
| **Models including MCMs diagnosed after delivery and anytime in the study period** | | | | | | |
| **Main model** | **1.18 (1.05-1.32)** | **<0.001** | **1.09 (0.97-1.22)** | **0.07** | **1.07 (0.95-1.20)** | **0.16** |
| Including pregnancies vaccinated in the 4 weeks prior to the start[a] | 1.19 (1.07-1.33) | <0.001 | 1.10 (0.98-1.24) | 0.03 | 1.08 (0.96-1.21) | 0.09 |
| Including diagnoses made beyond truncation of follow-up in CPRD[d] | 1.17 (1.05-1.31) | <0.001 | 1.09 (0.97-1.22) | 0.06 | 1.07 (0.95-1.20) | 0.14 |
| Excluding pregnancies with unknown BMI[c] | 1.18 (1.05-1.33) | <0.001 | 1.09 (0.96-1.23) | 0.08 | 1.07 (0.95-1.21) | 0.16 |

A priori confounders were maternal age, maternal ethnicity, region and the earliest influenza season a pregnancy overlapped with. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. [a]This model included an additional 216 pregnancies with a vaccination in the 4 weeks before the pregnancy start. [b]There were 22 infants with an MCM recorded in HES or ONS after follow-up in CPRD had ended. [c]This model excluded 8,093 pregnancies that belonged to women with unknown BMI. [d]There were 110 infants with an MCM recorded in HES or ONS after follow-up in CPRD had ended. Abbreviations: MCM, major congenital malformations; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics death certificate data; BMI, body mass index; IMD, Index of Multiple Deprivation; HR, Hazard Ratio; CI, Confidence Interval.

## Discussion

This UK-based historical cohort study examined the association between SIV during pregnancy and MCMs in live-born infants, between the 2010/11 and 2015/16 influenza seasons. Based on 6,872 pregnancies vaccinated in the first trimester, there was no evidence for an association with MCMs recorded in the year after delivery (adjusted HR, 1.06; 99% CI, 0.94-1.19; p=0.2). No evidence of an association was seen in analyses assessing subsequent trimesters or pregnancy overall, or analyses including MCMs recorded after delivery and anytime in the study period. Analyses of major limb and congenital heart defects adjusted for confounding also showed no evidence for an association with first-trimester or later vaccination.

**Strengths**

Reviews examining the safety of influenza vaccination with respect to MCMs have highlighted the limited number of studies examining first-trimester vaccination with SIV. Among the few such studies, further limitations such as the low number of pregnancies vaccinated in the first trimester and short follow-up time of infants have prompted calls for further safety evidence.[20-23]

The utilization of the Pregnancy Register, which includes information on trimester dates, allowed for the identification of a large number of pregnancies vaccinated in the first trimester. Follow-up in most studies has been limited to the immediate period around delivery.[50, 90, 104] Whilst a few studies have attempted follow-up for the year after delivery,[101, 103] extending follow-up beyond a year has been shown to still increase the prevalence of recorded MCMs in CPRD.[201, 218, 301] The majority of infants in our cohort had at least one year of follow-up and almost half had at least two. The value of longer follow-up is demonstrated by the fact that 12.8% of MCMs in our cohort were identified after 3 months and 5.3% after a year.

A further strength of this study was the linkage of CPRD data to HES and ONS to maximize MCM ascertainment. Previous research suggests that reliance on sole data sources can lead to significant under-ascertainment of conditions.[302] This may be particularly true for MCMs, many of which are likely to be identified in hospital and communicated in letters not available to researchers in the electronic primary care record unless encoded, which may be incomplete or delayed. Linkage to ONS further serves to ascertain those cases that may have been detected following the infant's death. For completeness, we also examined MCM recordings made in HES or ONS after follow-up in CPRD had ended, but this made minimal difference.

**Limitations**

Whilst our study had a number of strengths, there were also limitations. Coding algorithms to identify MCMs were developed in accordance with EUROCAT guidelines and with a consultant neonatologist. The few studies that have assessed the positive predictive value of MCMs recorded in CPRD have found this to be good overall (78-86%), with results for congenital heart defects being above 90%.[192, 194, 292, 293] However, validation of diagnoses in HES have not been undertaken.

The estimate of gestation at the time of vaccination is based on the Pregnancy Register's use of a wide range of information recorded in primary care which is thought to give rise to increased accuracy. However, any imprecision in the estimated pregnancy start date could result in misclassification of the timing of vaccination during pregnancy. Sensitivity analyses including pregnancies that received SIV in the 4 weeks prior to their start went some way in addressing this and did not reveal evidence for an association with MCMs. In addition to the above, whilst general practitioners are required to document vaccinations received outside of the surgery and the maternal influenza vaccination programme was delivered almost entirely through general practices over the study period, misclassification of vaccination could potentially occur if women were vaccinated elsewhere and practitioners were not notified.[73]

We adjusted for a number of potential confounders but were not always able to determine maternal smoking, hazardous drinking or BMI at the start of pregnancy and sometimes had to rely on the most proximate record. Although in our main analyses women with unknown BMI were categorized as not having any evidence of extreme BMI, our sensitivity analyses excluding these pregnancies yielded similar results. We cannot discount the possibility of residual confounding from other risk factors for MCMs that may also be associated with vaccine uptake in pregnancy and that are likely to be poorly recorded in CPRD, such as religion.[303]

This study only examined live-birth pregnancies with linked infant records, excluding 10.6% of pregnancies because they lacked linkage. There are many reasons for non-linkage, including the practice stopping contributing to CPRD or mothers moving away. It is possible that severe malformations resulting in the death or prolonged hospitalisation of neonates could also prevent linkage, but it seems unlikely that this incomplete ascertainment would depend on maternal vaccination status. This study also did not explore any potential role of malformations on the causal pathway between vaccination and pregnancy losses. However, studies thus far have found no evidence for an association between vaccination and such outcomes.[18-20]

**Comparison with other studies**

Our results are consistent with those from other studies that have examined SIV receipt during pregnancy and have shown no association with MCMs; this includes analyses of first-trimester vaccination for which point estimates from other studies ranged between 0.67 and 1.91, with confidence intervals including the null.[90, 101, 103, 104] Reassuringly, our point estimates for MCMs following first-trimester vaccination are in line with those from the largest study to date, which examined SIV receipt between 2004-2013 in the US (adjusted prevalence ratio, 1.02; 95% CI, 0.94-1.10; p=0.55).[103] Ours is the next largest study and provides further evidence on the safety of SIV during pregnancy in another setting and for subsequent years, using a recently-

developed Pregnancy Register that considers all available data in CPRD to estimate gestation at the time of vaccination as well as maximizing ascertainment of MCMs through long-term follow-up in linked data.

The lack of an association between first-trimester vaccination and congenital heart defects in our study was consistent with results from two other studies, including the large US study.[103, 104] Whilst other studies have examined limb malformations and not found any association with vaccination, they have grouped these with defects in other organ systems or examined a limited selection of particular diagnoses such as talipes equinovarus (clubfoot).[103, 104] This study assessed all major limb malformations as a stand-alone subgroup and confirmed the lack of association with SIV.

**Conclusions**

The findings from this large cohort study, in which the majority of infants were followed-up for at least one year, provide further evidence on the safety profile of influenza vaccination in pregnancy. There was no evidence for an association between first-trimester vaccination and MCMs, limb malformations or congenital heart defects after controlling for confounding. This study shows ongoing monitoring of the safety of first-trimester vaccination is possible using CPRD and could usefully include additional MCM subgroups when sufficient numbers become available.

## Acknowledgements

See research paper cover sheet.

## Funding

This research is funded by the National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Immunisation at the London School of Hygiene and Tropical Medicine

in partnership with Public Health England. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

## References

References are included as part of the main reference list at the end of the thesis.

## Submitted Paper: Supplementary Material

**Supplementary Table 1** - **See Section 4.6** for details of how potential confounders were defined.

**Supplementary Table 2** - Examination of the association between all potential confounders and vaccination.

**Supplementary Table 3** - Follow-up time among eligible infants.

**Supplementary Table 4** - Logistic and Cox regression models examining the relative odds and hazards of major malformations diagnosed in the year after delivery for those pregnancies vaccinated in the first trimester.

**Supplementary Table 5** - Logistic and Cox regression models examining the relative odds and hazards of major malformations diagnosed in the year after delivery for those pregnancies vaccinated anytime.

**Supplementary Table 6** - Examination of the association between all potential confounders and major malformations recorded in the first year of life.

**Supplementary Figure 1** - Distribution of the timing of major malformation recordings in the study period.

**Supplementary Table 6 - Examination of the association between all potential confounders and vaccination.**

| | No. pregnancies unvaccinated (%) n=47,661 | No. pregnancies vaccinated anytime in pregnancy (%) n=32,053 | No. pregnancies vaccinated in 1st trimester (%) n=7,009 | Odds ratio for vaccination anytime (99% CI) | *P* value | Odds ratio for vaccination in the 1st trimester (99% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| **Maternal age (years)** | | | | | | | |
| <18 | 531 (65.7) | 277 (34.3) | 35 (4.3) | 0.75 (0.62-0.91) | <0.0001 | 0.43 (0.27-0.67) | <0.0001 |
| 18-24 | 8,661 (63.8) | 4,910 (36.2) | 1,009 (7.4) | 0.81 (0.77-0.86) | | 0.76 (0.69-0.84) | |
| 25-34 | 27,598 (59.0) | 19,217 (41.1) | 4,235 (9.1) | 1.00 | | 1.00 | |
| ≥35 | 10,871 (58.7) | 7,649 (41.3) | 1,730 (9.3) | 1.01 (0.97-1.06) | | 1.04 (0.96-1.12) | |
| **Maternal ethnicity** | | | | | | | |
| White | 40,106 (59.3) | 27,493 (40.7) | 6,001 (8.9) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| South Asian | 3,303 (59.5) | 2,246 (40.5) | 511 (9.2) | 0.99 (0.92-1.07) | | 1.03 (0.91-1.17) | |
| Black | 1,965 (67.7) | 936 (32.3) | 198 (6.8) | 0.69 (0.63-0.77) | | 0.67 (0.55-0.82) | |
| Other | 1,182 (63.3) | 684 (36.7) | 148 (7.9) | 0.84 (0.74-0.96) | | 0.84 (0.67-1.05) | |
| Mixed | 664 (61.5) | 415 (38.5) | 84 (7.8) | 0.91 (0.78-1.07) | | 0.85 (0.63-1.14) | |
| Unknown | 441 (61.3) | 279 (38.8) | 67 (9.3) | - | | - | |
| **Maternal IMD status** | | | | | | | |
| 1=least deprived | 8,958 (55.2) | 7,258 (44.8) | 1,620 (10.0) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| 2 | 8,746 (57.5) | 6,456 (42.5) | 1,371 (9.0) | 0.91 (0.86-0.97) | | 0.87 (0.78-0.96) | |
| 3 | 9,079 (58.6) | 6,403 (41.4) | 1,443 (9.3) | 0.87 (0.82-0.92) | | 0.88 (0.79-0.97) | |
| 4 | 10,198 (62.4) | 6,143 (37.6) | 1,319 (8.1) | 0.74 (0.70-0.79) | | 0.72 (0.65-0.79) | |
| 5=most deprived | 10,680 (64.8) | 5,793 (35.2) | 1,256 (7.6) | 0.67 (0.63-0.71) | | 0.65 (0.59-0.72) | |
| **Region** | | | | | | | |
| London | 8,415 (64.2) | 4,697 (35.8) | 1,008 (7.7) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| North East | 1,232 (66.8) | 612 (33.2) | 113 (6.1) | 0.89 (0.78-1.02) | | 0.77 (0.59-1.00) | |
| North West | 6,879 (58.2) | 4,932 (41.8) | 1,147 (9.7) | 1.28(1.20-1.37) | | 1.39 (1.24-1.57) | |
| Yorkshire & The Humber | 934 (63.6) | 535 (36.4) | 125 (8.5) | 1.03 (0.89-1.19) | | 1.12 (0.86-1.45) | |
| East Midlands | 570 (71.0) | 233 (29.0) | 46 (5.7) | 0.73 (0.60-0.90) | | 0.67 (0.45-1.01) | |
| West Midlands | 4,663 (53.4) | 4,065 (46.6) | 1,025 (11.7) | 1.56 (1.45-1.68) | | 1.84 (1.62-2.08) | |
| East of England | 4,588 (57.0) | 3,459 (43.0) | 759 (9.4) | 1.35 (1.25-1.46) | | 1.38 (1.21-1.58) | |
| South West | 6,026 (59.5) | 4,099 (40.5) | 788 (7.8) | 1.22 (1.14-1.31) | | 1.09 (0.96-1.24) | |
| South Central | 6,850 (57.5) | 5,074 (42.6) | 1,188 (10.0) | 1.33 (1.24-1.42) | | 1.45 (1.29-1.63) | |
| South East Coast | 7,504 (63.3) | 4,347 (36.7) | 810 (6.8) | 1.04 (0.97-1.11) | | 0.90 (0.79-1.02) | |

| | No. pregnancies unvaccinated (%) n=47,661 | No. pregnancies vaccinated anytime in pregnancy (%) n=32,053 | No. pregnancies vaccinated in 1st trimester (%) n=7,009 | Odds ratio for vaccination anytime (99% CI) | *P* value | Odds ratio for vaccination in the 1st trimester (99% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| **Mother was part of a clinical risk group** | | | | | | | |
| No | 45,240 (60.4) | 29,659 (39.6) | 6,312 (8.4) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| Yes | 2,172 (49.8) | 2,194 (50.3) | 643 (14.7) | 1.54 (1.42-1.67) | | 2.12 (1.88-2.39) | |
| Unknown | 249 (55.5) | 200 (44.5) | 54 (12.0) | - | | - | |
| **Maternal smoking status** | | | | | | | |
| Non | 24,280 (58.2) | 17,433 (41.8) | 3,801 (9.1) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| Current | 11,784 (65.8) | 6,136 (34.2) | 1,296 (7.2) | 0.73 (0.69-0.76) | | 0.70 (0.64-0.77) | |
| Ex | 11,289 (57.4) | 8,389 (42.6) | 1,896 (9.6) | 1.03 (0.99-1.08) | | 1.07 (0.99-1.16) | |
| Unknown | 308 (76.4) | 95 (23.6) | 16 (4.0) | - | | - | |
| **Maternal hazardous drinking** | | | | | | | |
| No | 47,289 (59.8) | 31,764 (40.2) | 6,947 (8.8) | 1.00 | 0.07 | 1.00 | 0.37 |
| Yes | 372 (56.3) | 289 (43.7) | 62 (9.4) | 1.16 (0.94-1.42) | | 1.13 (0.80-1.62) | |
| **Extreme maternal BMI** | | | | | | | |
| No | 43,469 (59.7) | 29,302 (40.3) | 6,361 (8.7) | 1.00 | 0.03 | 1.00 | 0.25 |
| Underweight | 1,063 (62.9) | 627 (37.1) | 151 (8.9) | 0.88 (0.77-1.00) | | 0.97 (0.77-1.22) | |
| Obese | 3,129 (59.6) | 2,124 (40.4) | 497 (9.5) | 1.01 (0.93-1.09) | | 1.09 (0.95-1.24) | |
| **Maternal chronic hypertension (non-pregnancy related)** | | | | | | | |
| No | 47,058 (59.8) | 31,586 (40.2) | 6,896 (8.8) | 1.00 | 0.02 | 1.00 | 0.02 |
| Yes | 603 (56.4) | 467 (43.6) | 113 (10.6) | 1.15 (0.98-1.35) | | 1.28 (0.98-1.67) | |
| **Maternal exposure to teratogenic medication(s) or live vaccines** | | | | | | | |
| No | 44,876 (60.0) | 29,980 (40.1) | 6,514 (8.7) | 1.00 | 0.0003 | 1.00 | 0.0001 |
| Yes | 2,785 (57.3) | 2,073 (42.7) | 495 (10.2) | 1.11 (1.03-1.20) | | 1.22 (1.07-1.39) | |
| **Earliest influenza season a pregnancy overlapped with** | | | | | | | |
| 2009/10 | 5,292 (98.8) | 63 (1.2) | 0 (0.0) | 0.02 (0.01-0.03) | <0.0001 | 1.00 (empty) | <0.0001 |
| 2010/11 | 10,358 (77.8) | 2,954 (22.2) | 439 (3.3) | 0.45 (0.42-0.48) | | 0.30 (0.26-0.34) | |
| 2011/12 | 11,473 (61.0) | 7,332 (39.0) | 1,639 (8.7) | 1.00 | | 1.00 | |
| 2012/13 | 7,977 (49.4) | 8,185 (50.6) | 2,100 (13.0) | 1.61 (1.52-1.70) | | 1.84 (1.68-2.02) | |
| 2013/14 | 7,030 (51.6) | 6,596 (48.4) | 1,527 (11.2) | 1.47 (1.38-1.56) | | 1.52 (1.38-1.68) | |
| 2014/15 | 4,846 (47.3) | 5,409 (52.8) | 1,283 (12.5) | 1.75 (1.64-1.86) | | 1.85 (1.67-2.06) | |
| 2015/16 | 685 (31.2) | 1,514 (68.9) | 21 (1.0) | 3.46 (3.05-3.92) | | 0.21 (0.12-0.38) | |

| | No. pregnancies unvaccinated (%) n=47,661 | No. pregnancies vaccinated anytime in pregnancy (%) n=32,053 | No. pregnancies vaccinated in 1st trimester (%) n=7,009 | Odds ratio for vaccination anytime (99% CI) | *P* value | Odds ratio for vaccination in the 1st trimester (99% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| **No. of weeks the first trimester overlapped with influenza activity above baseline levels** | | | | | | | |
| None | 36,207 (56.3) | 28,161 (43.8) | 4,901 (7.6) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| 0-2 | 4,737 (70.9) | 1,943 (29.1) | 1,113 (16.7) | 0.53 (0.49-0.57) | | 1.74 (1.58-1.91) | |
| 2-4 | 1,236 (72.1) | 479 (27.9) | 157 (9.2) | 0.50 (0.43-0.57) | | 0.94 (0.75-1.17) | |
| 4-6 | 1,554 (73.7) | 554 (26.3) | 269 (12.8) | 0.46 (0.40-0.52) | | 1.28 (1.07-1.52) | |
| 6-8 | 2,433 (80.5) | 588 (19.5) | 354 (11.7) | 0.31 (0.28-0.35) | | 1.07 (0.92-1.25) | |
| 8-10 | 561 (76.9) | 169 (23.2) | 91 (12.5) | 0.39 (0.31-0.49) | | 1.20 (0.89-1.61) | |
| 10-12 | 933 (85.4) | 159 (14.6) | 124 (11.4) | 0.22 (0.18-0.27) | | 0.98 (0.77-1.26) | |
| **No. of children in maternal household** | | | | | | | |
| None | 15,629 (54.7) | 12,934 (45.3) | 2,900 (10.3) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| 1-2 | 26,891 (61.6) | 16,751 (38.4) | 3,629 (8.3) | 0.75 (0.72-0.78) | | 0.73 (0.68-0.78) | |
| ≥3 | 5,141 (68.5) | 2,368 (31.5) | 480 (6.4) | 0.56 (0.52-0.60) | | 0.50 (0.44-0.58) | |

Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index; CI, confidence interval.

**Supplementary Table 3 - Follow-up time among eligible infants.**

| Follow-up time | Proportion of infants (No.) N=78,150 |
|---|---|
| ≥3 months | 94.7 (74,031) |
| ≥6 months | 87.8 (68,589) |
| ≥1 year | 73.5 (57,442) |
| ≥2 years | 48.9 (38,184) |
| ≥3 years | 28.7 (22,446) |
| ≥4 years | 13.3 (10,369) |
| ≥5 years | 3.8 (2,995) |

Follow-up time was calculated as the length of time between delivery and the earliest of the following dates: the date the infant left the practice, the date the practice stopped collecting data, the date of death of the infant or the end of the study period (March 31, 2016).

**Supplementary Table 4 - Logistic and Cox regression models examining the relative odds and hazards of major malformations diagnosed in the year after delivery for those pregnancies vaccinated in the first trimester.**

| Model | First trimester vaccination + *a priori* confounders added | Other potential confounders added | ORs for major malformations using logistic regression (99% CI) | *P* values | HRs for major malformations using Cox regression (99% CI) | *P* values | Rho and *P* values for clustering |
|---|---|---|---|---|---|---|---|
| 1 | Vaccination | - | 1.18 (1.05-1.34) | <0.001 | 1.17 (1.04-1.32) | <0.001 | |
| 2a | Vaccination + Age | - | 1.18 (1.04-1.33) | | 1.17 (1.04-1.32) | | |
| 2b | Vaccination + Ethnicity | - | 1.18 (1.05-1.34) | | 1.18 (1.04-1.32) | | |
| 2c | Vaccination + Region | - | 1.13 (1.00-1.28) | | 1.13 (1.00-1.27) | | |
| 2d | Vaccination + Year | - | 1.14 (1.01-1.29) | | 1.13 (1.00-1.28) | | |
| 2e | Vaccination + Region + Year | | 1.08 (0.95-1.23) | | 1.08 (0.96-1.22) | | |
| 2f | Vaccination + Region + Year + Age | | 1.08 (0.95-1.22) | | 1.08 (0.95-1.21) | | |
| 2g | Vaccination + Region + Year + Ethnicity | | 1.09 (0.96-1.23) | | 1.08 (0.96-1.22) | | |
| 2h | Vaccination + Age, Ethnicity, Region, Year | - | 1.08 (0.95-1.23) | 0.10 | 1.08 (0.96-1.22) | 0.11 | |
| 3 | Vaccination + Age, Ethnicity, Region, Year | IMD | 1.08 (0.95-1.22) | | 1.07 (0.95-1.21) | | |
| 4 | Vaccination + Age, Ethnicity, Region, Year | No. children in home | 1.07 (0.94-1.21) | | 1.06 (0.94-1.20) | | |
| 5 | Vaccination + Age, Ethnicity, Region, Year | IMD, No. children in home | 1.06 (0.94-1.21) | | 1.06 (0.94-1.19) | | |
| 6a | Vaccination + Age, Ethnicity, Region, Year | Smoking | 1.08 (0.95-1.22) | | 1.08 (0.95-1.21) | | |
| 6b | Vaccination + Age, Ethnicity, Region, Year | Drinking | 1.08 (0.95-1.23) | | 1.08 (0.96-1.22) | | |
| 6c | Vaccination + Age, Ethnicity, Region, Year | Smoking, Drinking | 1.08 (0.95-1.23) | | 1.08 (0.95-1.21) | | |
| 7a | Vaccination + Age, Ethnicity, Region, Year | BMI | 1.08 (0.95-1.23) | | 1.08 (0.96-1.22) | | |
| 7b | Vaccination + Age, Ethnicity, Region, Year | Clinical risk group | 1.08 (0.95-1.22) | | 1.08 (0.95-1.21) | | |
| 7c | Vaccination + Age, Ethnicity, Region, Year | Hypertension | 1.08 (0.95-1.23) | | 1.08 (0.96-1.22) | | |
| 7d | Vaccination + Age, Ethnicity, Region, Year | Exposure to teratogenic medication/live vaccines | 1.08 (0.96-1.23) | | 1.08 (0.96-1.22) | | |
| 7e | Vaccination + Age, Ethnicity, Region, Year | BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines | 1.08 (0.95-1.23) | | 1.08 (0.95-1.21) | | |
| 8 | Vaccination + Age, Ethnicity, Region, Year | Influenza activity above baseline levels | 1.09 (0.96-1.23) | | 1.08 (0.96-1.22) | | |

| Model | First trimester vaccination + *a priori* confounders added | Other potential confounders added | ORs for major malformations using logistic regression (99% CI) | *P* values | HRs for major malformations using Cox regression (99% CI) | *P* values | Rho and *P* values for clustering |
|---|---|---|---|---|---|---|---|
| 9 | Vaccination + Age, Ethnicity, Region, Year | Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza activity above baseline levels | 1.06 (0.94-1.21) | 0.22 | 1.06 (0.94-1.19) | 0.23 | |
| 10 | Vaccination + Age, Ethnicity, Region, Year | cluster(mother) | 1.09 (0.95-1.24) | | - | | rho=0.18, p<0.001 |
| 11 | Vaccination + Age, Ethnicity, Region, Year | cluster(practice) | 1.09 (0.96-1.24) | | - | | rho=0.04, p<0.001 |
| 12 | Vaccination + Age, Ethnicity, Region, Year | Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza Activity + cluster(mother) | 1.07 (0.93-1.22) | | - | | rho=0.18, p<0.001 |
| 13 | Vaccination + Age, Ethnicity, Region, Year | Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza Activity + cluster(practice) | 1.07 (0.94-1.22) | | - | | rho=0.04, p<0.001 |

These models were complete case analyses and included all 78,150 eligible pregnancies. The univariable model (1), model adjusted for all *a priori* confounders (2h) and fully-adjusted model (9) are highlighted. Results were strikingly similar regardless of whether logistic or Cox regression were used. Abbreviations: Year, earliest influenza season the pregnancy overlapped with; IMD, Index of Multiple Deprivation; BMI, body mass index; OR, odds ratios; HR, hazard ratios; CI, confidence interval.

**Supplementary Table 5 - Logistic and Cox regression models examining the relative odds and hazards of major malformations diagnosed in the year after delivery for those pregnancies vaccinated anytime.**

| Model | Vaccination anytime in pregnancy + *a priori* confounders added | Other potential confounders added | ORs for major malformations using logistic regression (99% CI) | *P* values | HRs for major malformations using Cox regression (99% CI) | *P* values | Rho and *P* values for clustering |
|---|---|---|---|---|---|---|---|
| 1 | Vaccination | - | 1.10 (1.02-1.18) | 0.001 | 1.10 (1.03-1.18) | <0.001 | |
| 2a | Vaccination + Age | - | 1.10 (1.02-1.18) | | 1.10 (1.02-1.18) | | |
| 2b | Vaccination + Ethnicity | - | 1.10 (1.02-1.18) | | 1.10 (1.03-1.18) | | |
| 2c | Vaccination + Region | - | 1.07 (0.99-1.15) | | 1.07 (1.00-1.15) | | |
| 2d | Vaccination + Year | - | 1.07 (0.99-1.15) | | 1.06 (0.99-1.14) | | |
| 2e | Vaccination + Region + Year | | 1.03 (0.96-1.11) | | 1.03 (0.95-1.10) | | |
| 2f | Vaccination + Region + Year + Age | | 1.03 (0.95-1.11) | | 1.02 (0.95-1.10) | | |
| 2g | Vaccination + Region + Year + Ethnicity | | 1.03 (0.96-1.12) | | 1.03 (0.96-1.11) | | |
| 2h | Vaccination + Age, Ethnicity, Region, Year | - | 1.03 (0.96-1.11) | 0.29 | 1.03 (0.96-1.11) | 0.33 | |
| 3 | Vaccination + Age, Ethnicity, Region, Year | IMD | 1.02 (0.95-1.11) | | 1.02 (0.95-1.10) | | |
| 4 | Vaccination + Age, Ethnicity, Region, Year | No. children in home | 1.02 (0.94-1.10) | | 1.02 (0.94-1.09) | | |
| 5 | Vaccination + Age, Ethnicity, Region, Year | IMD, No. children in home | 1.01 (0.94-1.09) | | 1.01 (0.94-1.09) | | |
| 6a | Vaccination + Age, Ethnicity, Region, Year | Smoking | 1.03 (0.95-1.11) | | 1.03 (0.95-1.10) | | |
| 6b | Vaccination + Age, Ethnicity, Region, Year | Drinking | 1.03 (0.96-1.11) | | 1.03 (0.96-1.11) | | |
| 6c | Vaccination + Age, Ethnicity, Region, Year | Smoking, Drinking | 1.03 (0.95-1.11) | | 1.03 (0.95-1.10) | | |
| 7a | Vaccination + Age, Ethnicity, Region, Year | BMI | 1.03 (0.96-1.11) | | 1.03 (0.96-1.11) | | |
| 7b | Vaccination + Age, Ethnicity, Region, Year | Clinical risk group | 1.03 (0.95-1.11) | | 1.03 (0.95-1.10) | | |
| 7c | Vaccination + Age, Ethnicity, Region, Year | Hypertension | 1.03 (0.96-1.11) | | 1.03 (0.96-1.11) | | |
| 7d | Vaccination + Age, Ethnicity, Region, Year | Exposure to teratogenic medication/live vaccines | 1.03 (0.96-1.11) | | 1.03 (0.96-1.11) | | |
| 7e | Vaccination + Age, Ethnicity, Region, Year | BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines | 1.03 (0.96-1.11) | | 1.03 (0.96-1.11) | | |
| 8 | Vaccination + Age, Ethnicity, Region, Year | Influenza activity above baseline levels | 1.04 (0.96-1.12) | | 1.04 (0.96-1.12) | | |
| 9 | Vaccination + Age, Ethnicity, Region, Year | Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic | 1.02 (0.94-1.10) | 0.51 | 1.02 (0.94-1.10) | 0.54 | |

| Model | Vaccination anytime in pregnancy + *a priori* confounders added | Other potential confounders added | ORs for major malformations using logistic regression (99% CI) | *P* values | HRs for major malformations using Cox regression (99% CI) | *P* values | Rho and *P* values for clustering |
|---|---|---|---|---|---|---|---|
| | | medications/live vaccines, Influenza Activity above baseline levels | | | | | |
| 10 | Vaccination + Age, Ethnicity, Region, Year | cluster(mother) | 1.03 (0.95-1.12) | | - | | rho=0.18, p<0.001 |
| 11 | Vaccination + Age, Ethnicity, Region, Year | cluster(practice) | 1.03 (0.96-1.12) | | - | | rho=0.04, p<0.001 |
| 12 | Vaccination + Age, Ethnicity, Region, Year | Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza Activity + cluster(mother) | 1.02 (0.94-1.11) | | - | | rho=0.18, p<0.001 |
| 13 | Vaccination + Age, Ethnicity, Region, Year | Age, Ethnicity, Region, Year, IMD, No. children in home, Smoking, Drinking, BMI, Clinical risk group, Hypertension, Exposure to teratogenic medications/live vaccines, Influenza Activity + cluster(practice) | 1.02 (0.95-1.11) | | - | | rho=0.04, p<0.001 |

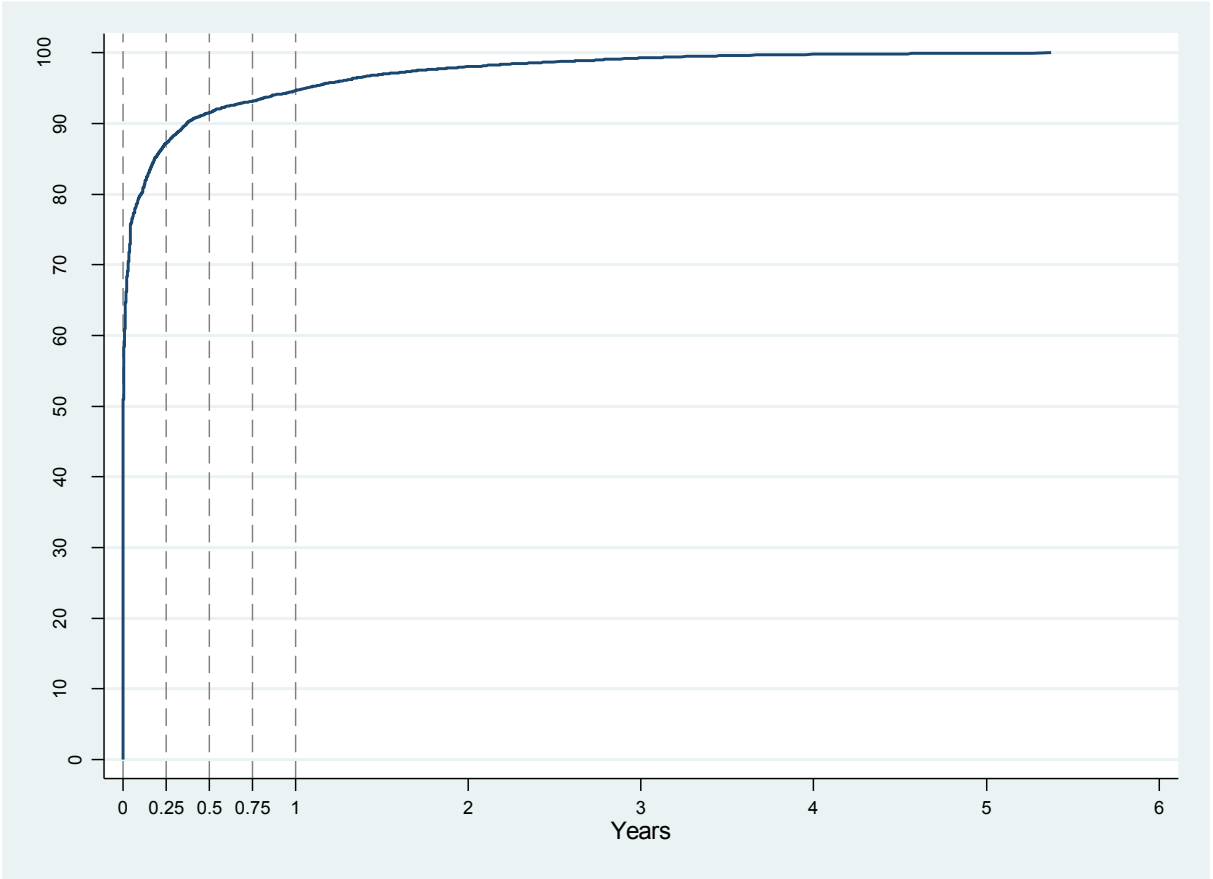
These models were complete case analyses and included all 78,150 eligible pregnancies. The univariable model (1), model adjusted for all a priori confounders (2h) and fully-adjusted model (9) are highlighted. Results were strikingly similar regardless of whether logistic or Cox regression were used. Abbreviations: Year, earliest influenza season the pregnancy overlapped with; IMD, Index of Multiple Deprivation; BMI, body mass index; OR, odds ratios; HR, hazard ratios; CI, confidence interval.

**Supplementary Table 6 - Examination of the association between all potential confounders and major malformations recorded in the first year of life.**

| | No. pregnancies resulting in no major malformation (%) n=73,898 | No. pregnancies resulting in a major malformation (%) n=5,816 | Odds ratios for major malformation (99% CI) | *P* value |
|---|---|---|---|---|
| **Maternal age (years)** | | | | |
| <18 | 753 (93.2) | 55 (6.8) | 0.93 (0.65-1.34) | 0.09 |
| 18-24 | 12,628 (93.1) | 943 (7.0) | 0.95 (0.86-1.05) | |
| 25-34 | 43,417 (92.7) | 3,398 (7.3) | 1.00 | |
| ≥35 | 17,100 (92.3) | 1,420 (7.7) | 1.06 (0.97-1.15) | |
| **Maternal ethnicity** | | | | |
| White | 62,755 (92.8) | 4,844 (7.2) | 1.00 | 0.001 |
| South Asian | 5,075 (91.5) | 474 (8.5) | 1.21 (1.06-1.38) | |
| Black | 2,665 (91.9) | 236 (8.1) | 1.15 (0.96-1.37) | |
| Other | 1,721 (92.2) | 145 (7.8) | 1.09 (0.87-1.37) | |
| Mixed | 1,007 (93.3) | 72 (6.7) | 0.93 (0.67-1.27) | |
| Unknown | 675 (93.8) | 45 (6.3) | - | |
| **Maternal IMD status** | | | | |
| 1=least deprived | 14,954 (92.2) | 1,262 (7.8) | 1.00 | 0.0009 |
| 2 | 14,048 (92.4) | 1,154 (7.6) | 0.97 (0.87-1.09) | |
| 3 | 14,388 (92.9) | 1,094 (7.1) | 0.90 (0.81-1.01) | |
| 4 | 15,251 (93.3) | 1,090 (6.7) | 0.85 (0.76-0.95) | |
| 5=most deprived | 15,257 (92.6) | 1,216 (7.4) | 0.94 (0.85-1.05) | |
| **Region** | | | | |
| London | 12,343 (94.1) | 769 (5.9) | 1.00 | <0.0001 |
| North East | 1,694 (91.9) | 150 (8.1) | 1.42 (1.12-1.81) | |
| North West | 10,852 (91.9) | 959 (8.1) | 1.42 (1.25-1.61) | |
| Yorkshire & The Humber | 1,364 (92.9) | 105 (7.2) | 1.24 (0.94-1.63) | |
| East Midlands | 776 (96.6) | 27 (3.4) | 0.56 (0.33-0.93) | |
| West Midlands | 7,799 (89.4) | 929 (10.6) | 1.91 (1.68-2.18) | |
| East of England | 7,397 (91.9) | 650 (8.1) | 1.41 (1.22-1.63) | |
| South West | 9,509 (93.9) | 616 (6.1) | 1.04 (0.90-1.20) | |
| South Central | 11,061 (92.8) | 863 (7.2) | 1.25 (1.10-1.43) | |
| South East Coast | 11,103 (93.7) | 748 (6.3) | 1.08 (0.94-1.24) | |
| **Mother was part of a clinical risk group** | | | | |
| No | 69,458 (92.7) | 5,441 (7.3) | 1.00 | 0.16 |
| Yes | 4,024 (92.2) | 342 (7.8) | 1.08 (0.93-1.26) | |
| Unknown | 416 (92.7) | 33 (7.4) | - | |
| **Maternal smoking status** | | | | |
| Non | 38,574 (92.5) | 3,139 (7.5) | 1.00 | 0.02 |
| Current | 16,680 (93.1) | 1,240 (6.9) | 0.91 (0.84-1.00) | |
| Ex | 18,273 (92.9) | 1,405 (7.1) | 0.94 (0.87-1.03) | |
| Unknown | 371 (92.1) | 32 (7.9) | - | |
| **Maternal hazardous drinking** | | | | |
| No | 73,274 (92.7) | 5,779 (7.3) | 1.00 | 0.08 |
| Yes | 624 (94.4) | 37 (5.6) | 0.75 (0.49-1.16) | |
| **Extreme maternal BMI** | | | | |
| No | 67,514 (92.8) | 5,257 (7.2) | 1.00 | 0.04 |
| Underweight | 1,552 (91.8) | 138 (8.2) | 1.14 (0.91-1.44) | |
| Obese | 4,832 (92.0) | 421 (8.0) | 1.12 (0.98-1.28) | |
| **Maternal chronic hypertension (non-pregnancy related)** | | | | |
| No | 72,907 (92.7) | 5,737 (7.3) | 1.00 | 0.91 |
| Yes | 991 (92.6) | 79 (7.4) | 1.01 (0.75-1.37) | |
| **Maternal exposure to teratogenic medication(s) or live vaccines** | | | | |
| No | 69,382 (92.7) | 5,474 (7.3) | 1.00 | 0.48 |
| Yes | 4,516 (93.0) | 342 (7.0) | 0.96 (0.83-1.11) | |

| | No. pregnancies resulting in no major malformation (%) n=73,898 | No. pregnancies resulting in a major malformation (%) n=5,816 | Odds ratios for major malformation (99% CI) | *P* value |
|---|---|---|---|---|
| **Earliest influenza season a pregnancy overlapped with** | | | | |
| 2009/10 | 4,997 (93.3) | 358 (6.7) | 0.96 (0.82-1.13) | <0.0001 |
| 2010/11 | 12,422 (93.3) | 890 (6.7) | 0.96 (0.86-1.08) | |
| 2011/12 | 17,503 (93.1) | 1,302 (6.9) | 1.00 | |
| 2012/13 | 14,926 (92.4) | 1,236 (7.7) | 1.11 (1.00-1.24) | |
| 2013/14 | 12,549 (92.1) | 1,077 (7.9) | 1.15 (1.03-1.29) | |
| 2014/15 | 9,452 (92.2) | 803 (7.8) | 1.14 (1.01-1.29) | |
| 2015/16 | 2,049 (93.2) | 150 (6.8) | 0.98 (0.78-1.24) | |
| **No. of weeks the first trimester overlapped with influenza activity above baseline levels** | | | | |
| None | 59,688 (92.7) | 4,680 (7.3) | 1.00 | 0.13 |
| 0-2 | 6,182 (92.5) | 498 (7.5) | 1.03 (0.91-1.17) | |
| 2-4 | 1,588 (92.6) | 127 (7.4) | 1.02 (0.80-1.30) | |
| 4-6 | 1,976 (93.7) | 132 (6.3) | 0.85 (0.67-1.08) | |
| 6-8 | 2,800 (92.7) | 221 (7.3) | 1.01 (0.84-1.21) | |
| 8-10 | 673 (92.2) | 57 (7.8) | 1.08 (0.76-1.54) | |
| 10-12 | 991 (90.8) | 101 (9.3) | 1.30 (0.99-1.71) | |
| **No. of children in maternal household** | | | | |
| 0 | 26,356 (92.3) | 2,207 (7.7) | 1.00 | 0.002 |
| 1-2 | 40,561 (92.9) | 3,081 (7.1) | 0.91 (0.84-0.98) | |
| ≥3 | 6,981 (93.0) | 528 (7.0) | 0.90 (0.79-1.03) | |

Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index; CI, confidence interval.




**Supplementary Figure 1 - Distribution of the timing of major malformation recordings in the study period.**

## 8.4 The prevalence of system-specific major congenital malformations by vaccination status

Ideally, safety studies examining MCMs as an outcome should examine the risk of individual conditions. This is because the types of malformation that occur following exposure to a teratogen depend on the timing and duration of the exposure in relation to the developmental stage of the foetus, as well as the molecular mechanism by which the teratogen disrupts development.[81] For example, thalidomide is known to cause severe limb reduction defects whereas anticonvulsants have been associated with neural tube defects (among other malformations).[81]

However, studies seldom examine specific MCMs due to their individual rarity which reduces statistical power and increases the risk of a type II error, particularly if analyses are also stratified by trimester of vaccination (or other exposure). Despite the large cohort identified for the analyses presented in this chapter, and follow-up beyond the first year of life, there were still low numbers of MCMs when these were divided into system-specific EUROCAT subgroups. The largest subgroups were limb (n=2,425) and congenital heart defects (n=789). The number of infants whose mother had received a seasonal influenza vaccine in the first trimester of pregnancy was low for most system-specific MCMs – with the highest numbers again seen among limb malformations (n=235), and congenital heart defects (n=67).

Numbers were even lower for particular subsets of conditions within the system-specific subgroups defined by EUROCAT. For example, an examination of ICD-10 coded diagnoses in HES (which could be mapped directly onto diagnoses defined by EUROCAT, unlike Read-coded diagnoses in CPRD) indicated that just 28 infants in the study population had evidence of a limb reduction defect (**Table 8.1**) and ≤5 of these infants were born to mothers who were vaccinated in the first trimester (**Table 8.1;** exact number not given to prevent deductive disclosure). The power to detect a doubling of the rate of limb reduction defects in the 6,872 infants whose mothers were vaccinated in the first trimester compared to the 46,669 infants

of mothers unvaccinated during pregnancy was approximately 30%. To achieve 80% power, both the number of women vaccinated in the first trimester and the number never vaccinated would need to be quadrupled.

Low statistical power and data sparsity leads many safety studies, including this one, to examine MCMs as an aggregate outcome. The caveat of this approach is that positive associations between vaccination and specific MCMs may be diluted. As an example, the prevalence rates of specific MCMs reported in **Table 8.1** suggest that limb defects occurred more frequently in infants of first-trimester vaccinated mothers than in infants whose mothers were never vaccinated (297 vs 244 per 10,000 live-births) (though it should be noted that this crude comparison of prevalence does not account for confounding). In an analysis examining MCMs as an aggregate outcome, a positive association between first-trimester vaccination and limb defects could be diluted by a lack of association (or associations in the opposite direction) for other MCMs.

One approach is to examine MCMs as an aggregate outcome and then examine those anatomical subgroups that are relatively homogeneous where there is sufficient power. In this work, limb and heart defects were separately examined as secondary outcomes (in addition to including them aggregated together with other MCMs in the main analysis) and no association with vaccination was found. However, even among these subgroups, the possibility of an association between first-trimester vaccination and particular limb or heart conditions cannot be discounted. For example, a positive association between first-trimester vaccination and limb reduction defects could be diluted by a null association between first-trimester vaccination and polydactyly, or by a negative association (if, for example, influenza itself increases the risk of this MCM, and influenza vaccination prevents infection) (**Table 8.1**).

The prevalence of system-specific MCMs among infants born to mothers vaccinated in the first trimester can be compared to the prevalence among infants whose mothers were unvaccinated throughout pregnancy to identify conditions for future exploration as numbers

become available. **Table 8.1** demonstrates that compared to infants born to unvaccinated mothers, infants whose mothers were vaccinated in the first trimester had an increased prevalence of:

- Atrial septal defects,
- Digestive malformations (driven by a small increase in the prevalence of congenital diaphragmatic hernias),
- Malformations of the ear, face and neck,
- Genital malformations (driven by an increase in the prevalence of hypospadias),
- Limb malformations (driven by an increase in the prevalence of talipes equinovarus and use of non-specific codes such as '*other congenital deformities of feet*'),
- Cleft lip with or without cleft palate, and
- Urinary malformations

These results should, however, be interpreted with caution due to very small numbers of infants born to mothers vaccinated in the first trimester (some numbers are suppressed in **Table 8.1** to prevent deductive disclosure of patient identities). Where entire subgroups (e.g. urinary malformations) demonstrated increased prevalence in infants born to mothers vaccinated in the first trimester, it was not always possible to pin-point what specific diagnoses were driving these increases (for example, examination of individual diagnoses such as congenital hydronephrosis did not explain the increase in prevalence of urinary malformations among infants born to mothers vaccinated in the first trimester). These MCMs could be usefully explored in future studies as numbers accumulate.

**Table 8.1 – Prevalence of system-specific major congenital malformations in the first year of life per 10,000 live-births, by vaccination status.**

| System-specific major congenital malformations | Total prevalence in EUROCAT (95% CI) (N=816,423) | Total prevalence in the study population (no.) (N=78,150) | Prevalence (no.), by vaccination status | |
|---|---|---|---|---|
| | | | Trimester 1[a] (N=6,872) | Never[a] (N=46,669) |
| **Abdominal** | 5.2 (4.8 - 5.8) | 4.4 (34) | - | 4.9 (23) |
| Gastroschisis | 4.0 (3.6 - 4.5) | 3.1 (24) | - | 4.1 (19) |
| Omphalocele | 1.0 (0.9 - 1.3) | 0.9 (7) | - | - |
| **Congenital heart defects** | 44.9 (43.5 - 46.4) | 72.0 (566) | 73.0 (50) | 72.0 (337) |
| Severe congenital heart disease | 17.2 (16.3 - 18.1) | 15.0 (118) | 12.0 (8) | 15.0 (69) |
| *Common arterial truncus* | 0.4 (0.3 - 0.6) | - | - | - |
| *Double outlet right ventricle* | 1.3 (1.1 - 1.6) | 1.7 (13) | - | 1.7 (8) |
| *Transposition of great vessels* | 3.6 (3.2 - 4.1) | 2.3 (18) | - | 2.1 (10) |
| *Single ventricle* | 0.4 (0.3 - 0.5) | - | - | - |
| *Atrioventricular septal defect* | 1.9 (1.6 - 2.2) | 2.0 (16) | - | 2.8 (13) |
| *Tetralogy of Fallot* | 3.1 (2.8 - 3.5) | 3.2 (25) | - | 3.0 (14) |
| *Tricuspid atresia and stenosis* | 0.6 (0.5 - 0.8) | - | - | - |
| *Ebstein's anomaly* | 0.3 (0.2 - 0.5) | - | - | - |
| *Pulmonary valve atresia* | 0.9 (0.7 - 1.1) | - | - | - |
| *Aortic valve atresia/stenosis* | 1.1 (0.9 - 1.3) | 1.2 (9) | - | 1.3 (6) |
| *Mitral valve anomalies* | 1.0 (0.8 - 1.3) | 2.2 (17) | - | 1.9 (9) |
| *Hypoplastic left heart* | 1.7 (1.5 - 2.1) | - | - | - |
| *Hypoplastic right heart* | 0.4 (0.2 - 0.5) | - | - | - |
| *Coarctation of aorta* | 3.6 (3.2 - 4.0) | 3.7 (29) | - | 3.4 (16) |
| *Aortic atresia/interrupted aortic arch* | 0.5 (0.4 - 0.7) | - | - | - |
| *Total anomalous pulmonary venous return* | 0.7 (0.5 - 0.9) | 0.9 (7) | - | - |
| Ventricular septal defect | 21.7 (20.7 - 22.7) | 22.1 (173) | 20.4 (14) | 23.8 (111) |
| Atrial septal defect | 7.5 (6.9 - 8.1) | 33.7 (263) | 39.3 (27) | 32.6 (152) |
| Pulmonary valve stenosis | 3.3 (3.0 - 3.8) | 2.7 (21) | - | 2.4 (11) |
| Patent ductus arteriosus[b] | 1.1 (0.9 - 1.4) | 25.0 (195) | 23.3 (16) | 24.9 (116) |
| **Digestive** | 14.0 (13.2 - 14.8) | 19.0 (151) | 28.0 (19) | 18.0 (82) |
| Oesophageal atresia ± trachea-oesophageal fistula | 2.1 (1.8 - 2.5) | 2.2 (17) | - | 2.4 (11) |
| Duodenal atresia or stenosis | 1.2 (0.9 - 1.4) | 0.8 (6) | - | - |
| Atresia or stenosis of other parts of the small intestine | 0.9 (0.7 - 1.1) | 1.0 (8) | - | - |
| Anorectal atresia and stenosis | 2.1 (1.8 - 2.5) | 1.8 (14) | - | 1.9 (9) |
| Hirschprung's disease | 1.3 (1.1 - 1.6) | 1.3 (10) | - | 1.5 (7) |
| Atresia of bile ducts | 0.2 (0.1 - 0.4) | - | - | - |
| Annular pancreas | 0.02 (0.0 - 0.2) | - | - | - |
| Diaphragmatic hernia | 2.1 (1.8 - 2.4) | 1.9 (15) | - | 1.9 (9) |
| **Ear, Face & Neck** | 0.9 (0.7 - 1.2) | 5.0 (39) | 8.7 (6) | 4.7 (22) |
| Anotia | 0.1 (0.03 - 0.2) | - | - | - |

| | | | | |
|---|---|---|---|---|
| **Eye** | 1.8 (1.5 - 2.1) | 3.7 (29) | - | 2.8 (13) |
| Anopthalmos/microphtalmos | 0.4 (0.3 - 0.5) | - | - | - |
| Congenital cataract | 0.5 (0.4 - 0.7) | 1.7 (13) | - | 1.5 (7) |
| Congenital glaucoma | 0.1 (0.04 - 0.2) | - | - | - |
| **Genital** | 18.4 (17.4 - 19.3) | 43.0 (335) | 52.0 (36) | 42.0 (197) |
| Hypospadias | 14.6 (13.8 - 15.4) | 31.0 (240) | 39.0 (27) | 31.0 (146) |
| Indeterminate sex | 0.5 (0.4 - 0.7) | - | - | - |
| **Limb** | 26.6 (25.5 - 27.7) | 260.0 (2029) | 297.0 (204) | 244.0 (1137) |
| Hip dislocation or dysplasia[c] | 4.9 (4.4 - 5.4) | 8.6 (67) | 8.7 (6) | 9.2 (43) |
| Club foot/Talipes equinovarus | 7.1 (6.6 - 7.7) | 11.8 (92) | 18.9 (13) | 11.1 (52) |
| Polydactyly | 6.3 (5.8 - 6.9) | 17.0 (133) | 12.0 (8) | 17.0 (78) |
| Syndactyly | 3.7 (3.3 - 4.1) | 9.3 (73) | - | 10.0 (48) |
| Limb reduction defects | 2.8 (2.4 - 3.2) | 3.6 (28) | - | 4.1 (19) |
| **Nervous system** | 9.0 (8.4 - 9.7) | 15.0 (117) | 17.0 (12) | 16.0 (75) |
| Neural tube defects | 2.1 (1.8 - 2.4) | 2.4 (19) | - | 3.0 (14) |
| *Anencephalus* | 0.2 (0.1 - 0.3) | - | - | - |
| *Encephalocele* | 0.3 (0.3 - 0.4) | - | - | - |
| *Spina bifida* | 1.6 (1.3 - 1.9) | 2.0 (16) | - | 2.4 (11) |
| Microcephaly | 0.8 (0.6 – 1.0) | 1.5 (12) | - | 1.3 (6) |
| Hydrocephalus | 3.1 (2.8 - 3.5) | 3.6 (28) | - | 3.9 (18) |
| Arhinencephaly/Holoprosencephaly | 0.1 (0.1 - 0.2) | - | - | - |
| **Orofacial** | 12.7 (12.0 - 13.5) | 12.0 (94) | 15.0 (10) | 12.0 (57) |
| Cleft palate | 4.9 (4.4 - 5.4) | 5.2 (41) | - | 5.4 (25) |
| Cleft lip ± Cleft palate | 7.8 (7.2 - 8.5) | 7.8 (61) | 12.0 (8) | 7.7 (36) |
| **Respiratory** | 3.7 (3.3 - 4.2) | 7.3 (57) | - | 7.9 (37) |
| Choanal atresia | 0.7 (0.5 - 0.9) | 0.8 (6) | - | - |
| Cystic adenomatous malformation of lung[d] | 1.9 (1.6 - 2.2) | 1.4 (11) | - | - |
| **Urinary** | 20.8 (19.8 - 21.8) | 36.0 (283) | 41.0 (28) | 34.0 (158) |
| Bilateral renal agenesis including Potter syndrome | 0.2 (0.1 - 0.3) | - | - | - |
| Multicystic renal dysplasia[e] | 3.2 (2.8 - 3.6) | 2.3 (18) | - | 1.7 (8) |
| Congenital hydronephrosis | 8.3 (7.7 – 9.0) | 16.0 (125) | 13.1 (9) | 14.6 (68) |
| Bladder exstrophy ± epispadia | 0.5 (0.4 - 0.7) | 1.4 (11) | - | 1.7 (8) |
| Posterior urethral valve and/or prune belly[f] | 0.4 (0.3 - 0.5) | 1.2 (9) | - | 1.3 (6) |

Major malformations were defined according to EUROCAT guidelines and identified in the first year of life from hospital admissions data. Prevalence rates in UK EUROCAT registries between 2010 and 2013 (prior to changes in the management of registries) are also included for reference. Some cells suppressed to prevent deductive disclosure. [a]Numbers in these columns do not sum to total number of infants; [b]Infants born ≥37 weeks; [c]EUROCAT included Q6580-6581 but only Q658 was available in HES; [d]EUROCAT included Q3380 but only Q338 was available in HES; [e]EUROCAT included Q6140-6141 but only Q614 was available in HES; [f]EUROCAT included Q6420 but only Q642 was available in HES.

## 8.5 Why did the analysis examine the safety of vaccination in the second and third trimesters as well as the first trimester?

The majority of organogenesis occurs in the first trimester of pregnancy and this is therefore the trimester of greatest interest when carrying out safety studies for which the outcome of interest is MCMs. Vaccination in the second trimester was examined for two reasons. First, although the risk of MCMs is highest for all organ systems in the first trimester, development continues beyond this period and some organ systems (e.g. the central nervous system) continue to be susceptible to teratogens.[304] Analyses of vaccinations occurring in the second trimester were therefore intended to account for this. Second, although gestational age at the time of vaccination was thought to have high accuracy (the Pregnancy Register uses all available information from primary care records and has demonstrated close agreement with gestational age data from HES), the possibility of misclassifying the trimester of exposure could not be discounted.[255] Analyses of the second trimester would capture any vaccinations that occurred in the first trimester but which were misclassified as occurring later (e.g. if the vaccination was recorded late). The sensitivity of the foetus to teratogens in the third trimester is very low and vaccination in this trimester should not demonstrate an association with MCMs. Including this trimester in analyses was therefore a pragmatic and feasible way of including a negative control. It was reassuring that there was no evidence of an association between vaccination in any trimester and MCMs.

## 8.6 Why were analyses restricted to live-births?

Vaccine safety analyses were originally planned to identify MCMs among live-births, miscarriages, terminations and stillbirths. For live-birth pregnancies with linked infant records, evidence of an MCM would be identified postnatally (in the infant record) or antenatally (in the maternal record). For remaining pregnancies, evidence of MCMs would be searched for antenatally in maternal records due to the absence of linked infant records.

MCMs in the antenatal period were likely to be under-ascertained, though the extent of this under-ascertainment was not initially known. Potential reasons for under-ascertainment included the moderate sensitivity of the 20-week ultrasound scan to detect MCMs and that many miscarriages and terminations would end before the scan took place.[305] However, under-ascertainment of MCMs would only bias effect measures if it occurred differentially among vaccinated or unvaccinated pregnancies. The shorter duration of miscarriages and terminations, as well as other factors such as maternal/foetal health concerns, meant that vaccination was thought to be less likely among such pregnancies. If most of these types of pregnancies were unvaccinated and MCMs were also under-ascertained, this could bias the effect measure upwards if these types of pregnancies were included in analyses. The potential for bias was therefore considered in detail for different pregnancy outcomes (**Table 8.2**). Following this, the antenatal ascertainment of MCMs and the vaccine uptake among different pregnancy outcomes were examined using the wider study population of 116,661 pregnancies **(Figure 8.2)**. Results are described in **Sections 8.6.1-8.6.3**

**Table 8.2 - Potential bias in the hazard ratios for MCMs, by pregnancy outcome**

| Pregnancy outcome | Is vaccination* more or less likely among these pregnancies? | Are malformations likely to be under-ascertained among these pregnancies? | Effect on the hazard ratio for MCMs |
|---|---|---|---|
| **Termination; pregnancy unwanted from the outset.** | Less likely because the woman does not intend to continue with the pregnancy. | Yes because these women may be less likely to attend scans and terminations are also likely to occur before the 20-week anomaly scan. | If the majority of these pregnancies are unvaccinated and there is also under-ascertainment of MCMs, the hazard ratio for MCMs may be **inflated.** |
| **Termination; pregnancy wanted but complicated by maternal or foetal health.** | Less likely because the pregnancy is shorter in duration (therefore less opportunity). Maternal/foetal health concerns could also result in lower vaccine uptake. | Yes because most terminations are likely to occur before the 20-week anomaly scan. | If the majority of these pregnancies are unvaccinated and there is also under-ascertainment of MCMs, the hazard ratio for MCMs may be **inflated.** |
| **Termination; pregnancy wanted but complicated by foetal MCM.** | Less likely because the pregnancy is shorter in duration (therefore less opportunity). Maternal/foetal health concerns could also result in lower vaccine uptake. | No. | If the majority of these pregnancies are unvaccinated and there is no under-ascertainment of malformations then the hazard ratio may be biased to the **null**. |
| **Miscarriage** | Less likely because the pregnancy is shorter in duration (therefore less opportunity). | Yes because most miscarriages are likely to occur before the 20-week anomaly scan. | If the majority of these pregnancies are unvaccinated and there is also under-ascertainment of MCMs, the hazard ratio for MCMs may be **inflated**. |
| **Early stillbirth** | Less likely because the pregnancy is shorter in duration (therefore less opportunity). | Yes because although the 20-week anomaly scan is likely to have taken place, its sensitivity is known to be low. | If the majority of these pregnancies are unvaccinated and there is also under-ascertainment of MCMs, the hazard ratio for MCMs may be **inflated.** |
| **Late stillbirth** | Not necessarily more or less likely to be vaccinated as the pregnancy length is normal. | Yes because although the 20-week anomaly scan is likely to have taken place, its sensitivity is known to be low. | Assuming the likelihood of vaccination is not biased and that the outcome is under-ascertained, the hazard ratio may be **unaffected**. |
| **Deliveries based on late pregnancy records** | Not necessarily more or less likely to be vaccinated as the pregnancy length is normal. | Yes because although the 20-week anomaly scan is likely to have taken place, its sensitivity is known to be low. | Assuming the likelihood of vaccination is not biased and that the outcome is under-ascertained, the hazard ratio may be **unaffected**. |
| **Live-births without a linked baby** | Not necessarily more or less likely to be vaccinated as the pregnancy length is normal. | Yes because although the 20-week anomaly scan is likely to have taken place, its sensitivity is known to be low. | Assuming the likelihood of vaccination is not biased and that the outcome is under-ascertained, the hazard ratio may be **unaffected**. |

*Vaccination anytime in pregnancy.

### 8.6.1 MCMs are under-recorded in the antenatal period

The proportion of pregnancies with an antenatal record of an MCM was much lower than the proportion of live-birth pregnancies linked to infant records that had postnatal evidence of an MCM. This suggested that MCMs were likely to be considerably under-ascertained in the antenatal period. Among the 78,150 pregnancies that resulted in a live-birth with linked infant records, the proportion with evidence of an MCM after delivery and anytime during the study period was 7.7% (n=6,029). Conversely, among the 116,661 pregnancies in the wider study population, just 0.3% (n=298) had antenatal evidence in the maternal record that could potentially relate to an MCM (**Table 8.3**). The proportion of pregnancies with antenatal evidence of an MCM varied by pregnancy outcome but was generally very low. The only exception was for stillbirths, of which 3.3% had evidence of an MCM recorded antenatally, although the absolute number of such cases was small (n=9) (**Table 8.3**).

**Table 8.3 - Number and proportion of pregnancies with an antenatal MCM record, by pregnancy outcome.**

| Pregnancy outcome (number of pregnancies) | No. of pregnancies with an antenatal MCM record in the maternal file (% of total pregnancies of the same outcome). |
|---|---|
| All pregnancy outcomes (n=116,661) | 298 (0.3) |
| Live-birth with linked infant records (n=78,150) | 149* (0.2) |
| Live-birth with no linked infant records (n=10,645) | 32 (0.3) |
| Stillbirth (n=276) | 9 (3.3) |
| Miscarriage (n=13,439) | 15 (0.1) |
| Termination/Probable termination (n=12,471) | 91 (0.7) |
| Unspecified loss (n=746) | 2 (0.3) |
| Deliveries based on late pregnancy records (n=934) | 0 (0.0) |

*Of the live-births with a linked infant, only 38 of the 149 (25.5%) with an antenatal malformation record went on to have a postnatal MCM record.

### 8.6.2 MCMs recorded antenatally have poor validity

Evidence of antenatal MCMs are based on the limited records available during pregnancy and may be less accurate and less reliable than postnatal diagnoses. As described in **Section 5.6**, antenatal codes used to identify MCMs were often non-specific and could represent eligible MCMs but also: ineligible anomalies (such as Down syndrome), suspected but unconfirmed anomalies, or problems noted on the ultrasound scan relating to the mother or the placenta rather than the foetus. Antenatal codes were therefore categorized from most (level 1 codes) to least (level 3 codes) specific.

Of the 298 pregnancies with antenatal evidence of an MCM, the majority (77.5%) had level 2 codes that related to suspected but unconfirmed anomalies as their most specific evidence (**Table 8.4**). The most frequently used codes among all 298 pregnancies were '*maternal care for suspected central nervous system malformation in fetus*' and '*maternal care for suspected fetal abnormality and damage, unspecified*' (**Table 8.5**). Only 19.1% (n=57) of pregnancies with antenatal evidence had level 1 codes (**Table 8.4**). The only types of pregnancy with level 1 codes were live-births (n=54) and terminations (n=3). Level 1 codes were not observed among stillbirths, miscarriages or unspecified losses.

**Table 8.4 - Most specific available antenatal evidence of MCM, by pregnancy outcome.**

| Pregnancy outcome | No. of pregnancies with antenatal evidence | No. of pregnancies with level 1 code as most specific evidence (%) | No. of pregnancies with level 2 code as most specific evidence (%) | No. of pregnancies with level 3 code as most specific evidence (%) |
|---|---|---|---|---|
| All pregnancy outcomes | 298 | 57 (19.1) | 231 (77.5) | 10 (3.4) |
| Live-birth with linked infant | 149 | 47 (31.5)* | 95 (63.8)** | 7 (4.7)*** |
| Live-birth with no linked infant | 32 | 7 (21.9) | 25 (78.1) | 0 |
| Stillbirth | 9 | 0 | 9 (100.0) | 0 |
| Miscarriage | 15 | 0 | 14 (93.3) | 1 (6.7) |
| Termination/Probable termination | 91 | 3 (3.3) | 86 (94.5) | 2 (2.2) |
| Unspecified loss | 2 | 0 | 2 (100.0) | 0 |
| Deliveries based on late pregnancy records | 0 | 0 | 0 | 0 |

*14.9% of these (n=7) went on to have a postnatal malformation recording; **31.6% of these (n=30) went on to have a postnatal malformation recording; ***14.3% of these (n=1) went on to have a postnatal malformation recording.

**Table 8.5 - Antenatal codes used among all pregnancy outcomes.**

| Antenatal Code Description | Specificity Level | No. of pregnancies code used in (%) |
|---|---|---|
| Maternal care for (suspected) central nervous system malformation in fetus | 2 | 111 (37.2) |
| Maternal care for (suspected) fetal abnormality and damage, unspecified | 2 | 108 (36.2) |
| U-S scan - fetal abnormality | 1 | 50 (16.8) |
| Known or suspected fetal abnormality | 2 | 14 (4.7) |
| A/N U/S scan for ? abnormality | 3 | 4 (1.3) |
| Suspect fetal anencephaly | 2 | 4 (1.3) |
| Abnormal findings on antenatal screening of mother | 3 | 3 (1.0) |
| Obstructed labour due to other abnormalities of fetus | 1 | 3 (1.0) |
| Maternal care for disproportion due to hydrocephalic fetus | 1 | 2 (0.7) |
| Suspect fetal spina bifida | 2 | 1 (0.3) |
| Abnormal ultrasonic finding on antenatal screening of mother | 3 | 1 (0.3) |
| Other fetal abnormality causing disproportion | 1 | 1 (0.3) |
| Fetus with cardiovascular abnormality | 1 | 1 (0.3) |
| A/N U/S scan abnormal | 3 | 1 (0.3) |
| [X]Maternal care/oth spcf known or suspected fetal problems | 2 | 1 (0.3) |
| U-S obstetric scan abnormal | 3 | 1 (0.3) |

Percentages do not add to 100 as some pregnancies could have more than one code.

Antenatal codes were also found to be poorly predictive of a postnatal diagnosis, which further suggested that their validity was likely to be low. Among the live-births with a linked infant, 149 had a code for an MCM detected antenatally but just 38 (25.5%) of these also had postnatal evidence in the infant record. This was not higher among those that had a level 1 code; of the 47 such live-birth pregnancies with a linked infant just 14.9% (n=7) had a postnatal malformation record.

The positive predictive value of antenatal codes could be estimated by calculating the proportion of live-births with a linked infant that had a particular antenatal code and went on to have postnatal evidence (assuming the latter was the 'gold standard') (**Table 8.6**). The positive predictive value of codes was highly variable but appeared to be lowest for most level 3 codes, as expected. Neither level 1 or 2 codes had consistently high positive predictive values. Based on all the above, the value of antenatal MCM codes appeared limited.

**Table 8.6 - Positive predictive values of antenatal codes used among live-birth pregnancies with a linked infant**.

| Antenatal Code Description | Specificity Level | No. of live-birth pregnancies code used in | No. of live-birth pregnancies with postnatal MCM evidence | Positive Predictive Value of code (95% CI) |
|---|---|---|---|---|
| Fetus with cardiovascular abnormality | 1 | 1 | 0 | 0 (0-97.5) |
| Obstructed labour due to other abnormalities of fetus | 1 | 1 | 0 | 0 (0-97.5) |
| U-S scan - fetal abnormality | 1 | 44 | 6 | 13.6 (5.2-27.4) |
| Maternal care for disproportion due to hydrocephalic fetus | 1 | 1 | 1 | 100.0 (2.5-100.0) |
| Known or suspected fetal abnormality | 2 | 6 | 4 | 66.7 (22.3-95.7) |
| Maternal care for (suspected) fetal abnormality and damage, unspecified | 2 | 68 | 10 | 14.7 (7.3-25.4) |
| [X]Maternal care/oth spcf known or suspected fetal problems | 2 | 1 | 0 | 0 (0-97.5) |
| Maternal care for (suspected) central nervous system malformation in fetus | 2 | 22 | 17 | 77.3 (54.6-92.2) |
| A/N U/S scan for ? abnormality | 3 | 2 | 0 | 0 (0-84.2) |
| Abnormal ultrasonic finding on antenatal screening of mother | 3 | 1 | 1 | 100.0 (2.5-100.0) |
| A/N U/S scan abnormal | 3 | 1 | 0 | 0 (0-97.5) |
| Abnormal findings on antenatal screening of mother | 3 | 2 | 0 | 0 (0-84.2) |
| U-S obstetric scan abnormal | 3 | 1 | 0 | 0 (0-97.5) |

Postnatal diagnoses were used as a gold standard.

### 8.6.3 Vaccine uptake is low among miscarriages and terminations

As expected, vaccine uptake was higher among live-births, stillbirths and deliveries based on late pregnancy records. The average uptake for these pregnancy outcomes was 39.5% which was similar to the average of published estimates of vaccine uptake for England over the same years.[76, 284, 306-309] Vaccine uptake was, however, very low among miscarriages (5.6%), terminations (1.2%) and unspecified losses (4.8%) – as expected due to their shorter duration and the likelihood of lower uptake of antenatal screening among pregnancies which were terminated (**Table 8.7**).

**Table 8.7 - Vaccine uptake by pregnancy outcome**

| Pregnancy outcome (number of pregnancies) | No. of pregnancies vaccinated (%) |
|---|---|
| All pregnancy outcomes (n=116,661) | 36,461 (31.3) |
| Live-birth with linked infant (n=78,150) | 31,481 (40.3) |
| Live-birth with no linked infant (n=10,645) | 3,650 (34.3) |
| Stillbirth (n=276) | 85 (30.8) |
| Miscarriage (n=13,439) | 756 (5.6) |
| Termination/Probable termination (n=12,471) | 149 (1.2) |
| Unspecified loss (n=746) | 36 (4.8) |
| Deliveries based on late pregnancy records (n=934) | 304 (32.5) |

### 8.6.4 Summary of exploration of antenatally-recorded MCMs

In summary, results indicated that under-ascertainment of MCMs was considerable during the antenatal period and there was also evidence to suggest that antenatal codes had low validity. Furthermore, vaccine uptake among miscarriages and terminations was particularly low. Therefore, including all pregnancy outcomes would result in under-ascertainment of the outcome and would occur differentially among the unvaccinated which would bias effect measures away from the null. Based on these results, it was decided that all vaccine safety analyses would be restricted to live-birth pregnancies with linked infants and all MCMs would be ascertained using only postnatal evidence from infant records (for which validity was thought to be good).[187, 192, 194, 216, 219]

## 8.7 Could the exclusion of terminations due to foetal anomalies have biased results?

Pregnant women are offered an ultrasound scan between 18 and 21 gestational weeks (referred to as the 20-week anomaly scan).[310] The main purpose of the scan is to screen for the presence of 11 different conditions, which include: anencephaly, spina bifida, cleft lip, congenital diaphragmatic hernia, gastroschisis, exomphalos, severe congenital heart defects, bilateral renal agenesis, lethal skeletal dysplasia and Edwards' or Patau's syndrome.[310] Over time, as technology has improved, scans have also been able to detect other conditions, including some that are minor and whose clinical significance is uncertain.[305] The 20-week scan provides prospective parents the opportunity to consider termination in the presence of a serious condition.

Between 2010 and 2013 (which coincided with the study period), 14.3% of MCMs identified by UK EUROCAT registries were identified among terminations due to foetal anomalies (TOPFAs).[294] The organ system with the highest proportion of malformations identified from TOPFAs was the nervous system (56.7% of nervous system malformations were identified among TOPFAs).[294] The conditions most commonly identified from TOPFAs in UK registry data

are presented in **Table 8.8** and include neural tube defects and other specific nervous system malformations, severe congenital heart defects, urinary and abdominal malformations. These conditions are therefore likely to have been considerably underrepresented in the study population used in this work, which relied exclusively on live-births.

**Table 8.8 – Most common non-chromosomal major congenital malformations among terminations due to foetal anomalies in UK EUROCAT registries between 2010 and 2013.**[294]

| Major congenital malformation | Total no. of cases | Percentage of cases by pregnancy outcome (95% CI) | | |
|---|---|---|---|---|
| | | Live-births | Stillbirths | Termination due to foetal anomaly |
| Anencephalus and similar | 426 | 3.8 (2.3-6.0) | 4.7 (3.2-7.1) | 91.6 (88.5-93.8) |
| Arhinencephaly/holoprosencephaly | 68 | 13.2 (7.1-23.3) | 5.9 (2.3-14.2) | 80.9 (70.0-88.5) |
| Bilateral renal agenesis* | 109 | 12.8 (7.8-20.4) | 7.3 (3.8-13.8) | 79.8 (71.3-86.3) |
| Spina Bifida | 466 | 28.1 (24.2-32.4) | 2.4 (1.3-4.2) | 69.5 (65.2-73.5) |
| Encephalocele | 83 | 27.7 (19.2-38.2) | 3.6 (1.2-10.1) | 68.7 (58.1-77.6) |
| Omphalocele | 205 | 42.4 (35.9-49.3) | 4.9 (2.7-8.8) | 52.7 (45.9-59.4) |
| Hypoplastic left heart | 244 | 58.2 (51.9-64.2) | 3.3 (1.7-6.3) | 38.5 (32.6-44.8) |
| Single ventricle | 50 | 62.0 (48.2-74.1) | 0.0 (0.0-7.1) | 38.0 (25.9-51.9) |
| Hydrocephalus | 415 | 61.5 (56.7-66.0) | 3.6 (2.2-5.9) | 34.9 (30.5-39.7) |
| Hypoplastic right heart | 46 | 63.0 (48.6-75.5) | 2.2 (0.4-11.3) | 34.8 (22.7-49.2) |
| Congenital diaphragmatic hernia | 222 | 76.6 (70.6-81.7) | 2.3 (1.0-5.2) | 21.2 (16.3-27.0) |

*Including Potter syndrome.

Not including pregnancies resulting in terminations due to foetal anomaly in vaccine safety analyses could bias results under certain circumstances. For example, women who register late for antenatal care are less likely to receive vaccination in the first trimester and may also be less likely to have the 20-week anomaly scan and an antenatal diagnosis of an MCM. These women would not have the opportunity to undergo a TOPFA and, if they went on to deliver a live-born infant, would be included in the study population. In contrast, women carrying a foetus with the same MCM who registered earlier for antenatal care would have a greater opportunity for both first trimester vaccination and antenatal diagnosis of the MCM; if these women chose to terminate after their 20-week scan, they would not be included in the study population. The differential inclusion of infants with MCMs born to unvaccinated vs vaccinated mothers would lead to an underestimate of the association between vaccination and these MCMs.

In England, data from Public Health England show high uptake of the antenatal 20-week scan; the national average was 96.6% in 2016/17, rising to 99.1% in 2018/19.[311] However, these

figures refer to women who had booked into antenatal care by 24 weeks gestation. A 2015/16 audit of the timeliness of antenatal bookings in London found that among 122,275 pregnant women, 9.9% had their booking after 21 weeks of gestation and would therefore not have been offered first-trimester vaccination and may not have received a scan.[70]

In the data used for the studies described in this thesis, 13,217 terminations and unspecified losses were identified and excluded. Of these, more than 98% occurred before the 16th week, before the 20-week anomaly scan, and therefore could not reasonably be TOPFAs. This is consistent with reports suggesting that TOPFAs account for approximately 1% of all terminations.[321] Although the Pregnancy Register may not capture all terminations (e.g. those performed by independent providers) there is no obvious reason to suggest that late terminations are less likely to be ascertained.

Further investigation of the conditions most likely to result in TOPFAs **(Table 8.8**), showed no evidence of higher prevalence of these MCMs among infants born to unvaccinated mothers included in this study compared to infants born to mothers who were vaccinated in the first trimester (**Table 8.1**). For eight of the 11 conditions, there were less than five infants in each group. Even after combining all 11 conditions, prevalence was not higher in infants born to unvaccinated women (10.1 per 10,000 live-births, n=47) compared to infants born to women vaccinated in the first trimester (14.6 per 10,000 live-births, n=10).

## 8.8 Could the exclusion of live-births without linked infant records have biased results?

A limitation of the SIIV safety analysis was the exclusion of approximately 11% of live-birth pregnancies, due to the lack of linked infant records. In the context of this study, selection bias could occur if live-birth pregnancies with linked infant records were more or less likely to have received the vaccine and more or less likely to result in an MCM than live-birth pregnancies without linked infant records.

Reasons for absence of a linked infant record were outlined in **Section 4.3.8 (Table 4.1)**, most of which were unlikely to be associated with vaccination or MCMs. Of the live-birth pregnancies without a linked infant, 7% could potentially have their lack of linkage explained by follow-up ending at the latest collection of practice data and 25% could have their lack of linkage explained by the mother leaving the practice before the infant had an opportunity to register. The end of data collection at practices was not associated with vaccination or MCMs and would therefore not result in selection bias. Mothers might leave the practice for a number of reasons after giving birth, many of which would be independent of vaccine uptake and MCMs (such as moving home to adjust to the new family size). However, two scenarios which could potentially be associated with vaccine uptake and MCMs were considered:

1. Mothers whose infants have an MCM leave the practice in order to move closer to a specialist hospital. If these women also tend to be more engaged with healthcare and are more likely to accept a vaccine then their exclusion may result in an underestimation of the hazard ratio.
2. Mothers may leave the practice as a result of unstable accommodation. These women may have fragmented healthcare and so may be more likely to be unvaccinated. They might be less likely to benefit from preventive healthcare and screening (so may have higher incidence of MCMs), but may also be less likely to have an MCM in their infant ascertained. Their exclusion could therefore result in under- or overestimation of the hazard ratio.

Both these scenarios are likely to be rare and only apply to a small percentage of mothers leaving the practice before the infant is registered. It was considered unlikely that either of these scenarios would result in considerable selection bias.

Linkage to infant records might not occur or may be delayed if delivery is followed by neonatal death or prolonged hospitalisation which would prevent registration at the mother's practice. Such a scenario could occur among infants with a severe MCM and was also considered. Less than 1% of live-births without linked infant records were found to have evidence of a

bereavement or neonatal hospitalisation in the maternal record around the time of delivery. Whilst it was somewhat reassuring that this proportion was not high (as it could suggest the death or hospitalisation of infants due to MCMs), it was difficult to draw any concrete conclusions given that these events are unlikely to be fully recorded in the maternal record.

## 8.9 Chapter summary and conclusions

The large, historical cohort study described in this chapter found no evidence to suggest an association between SIIV receipt in any trimester and major congenital malformations overall, congenital heart defects or limb defects. This was the largest such safety study examining first-trimester vaccination in Europe and provides further evidence to support the safety profile of SIIV among pregnancies that result in a live-birth.

# 9. Examining the association between pandemic influenza vaccination during pregnancy and major congenital malformations.

## 9.1 Introduction

This is the final results chapter of the thesis and addresses **Objective 6** which was to examine the association between maternal vaccination with PIIV and major congenital malformations in live-born infants. The steps involved in deriving the final study population for the analyses described here are provided in **Section 9.2**. In **Section 9.3**, the characteristics of the study population are described. In **Section 9.4**, results from the primary and secondary analyses on PIIV safety during pregnancy are outlined; these analyses examined major malformations in the year after delivery and from delivery until the end of the study period (March 31, 2016), respectively. The methods used were the same as those described in **Chapter 8**. **Section 9.5** describes the sensitivity analyses carried out; the first of these included vaccinations in the four weeks before pregnancy start, the second included major malformation diagnoses made after follow-up in CPRD had ended and the third excluded pregnant women with unknown BMI (the rationale for these is described in **Chapter 8**). Finally, **Section 9.6** provides a brief summary of the conclusions.

## 9.2 Deriving the final study population for analyses on PIIV safety

In **Chapter 4**, the criteria used to identify potentially eligible pregnancies for analyses in this thesis were outlined. These criteria identified 199,017 potentially eligible pregnancies. Further study-specific exclusion were then applied (**Figure 9.1**). A total of 21,693 live-births linked to an infant were identified for the analysis.

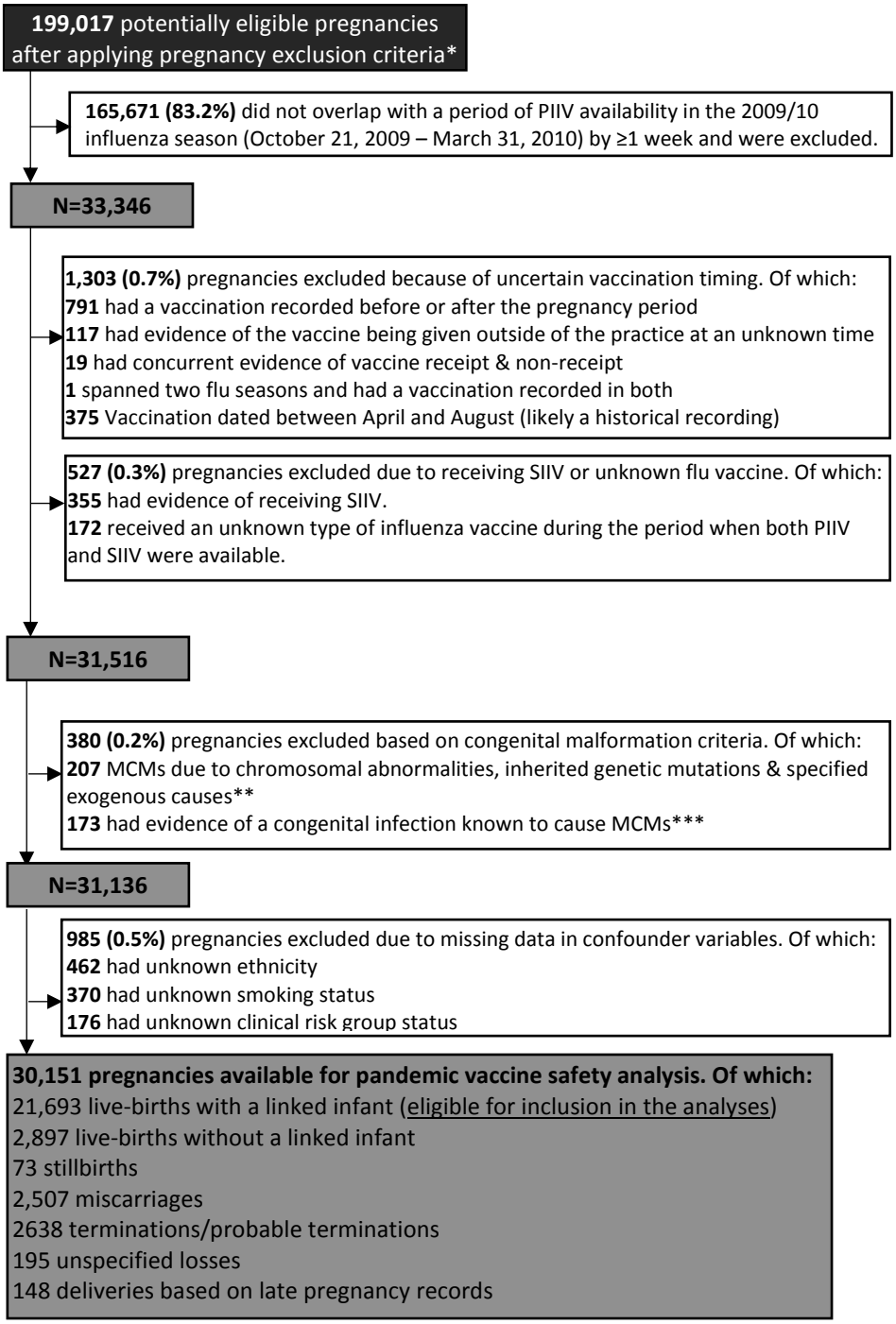



**Figure 9.1 – Deriving the study population for pandemic vaccine safety analyses.** *The initial population of 199,017 pregnancies included those ending between January 1, 2009 and March 31, 2016. All live-born infants were eligible for linkage to HES and ONS. The identification of the 199,017 potentially eligible pregnancies is described in Sections 4.2-4.3. **See Section 4.4.1; ***See Section 4.4.2.

## 9.3 Characteristics of the eligible study cohort

The PIIV safety analysis included 21,693 live-birth pregnancies (**Figure 9.1**). Vaccine uptake in this population was lower than that observed in the population eligible for the SIIV safety analysis. Just 19.4% (n=4,204) of pregnancies eligible to be included in this analysis received a vaccine; 3.8% (n=825) in the first trimester, 8.7% (n=1,893) in the second and 6.9% (n=1,486) in the third. Overall vaccine uptake in this population was consistent with an estimated uptake of 19.3% by another study using CPRD for the same period.[312]

Of the 21,693 infants born to eligible pregnancies, 90.2% (n=19,573) had at least one full year of follow-up and 44.1% (n=9,556) had at least five years (**Table 9.1**). In the year after delivery, 6.7% (n=1,444) of infants had evidence of an MCM. This increased to 7.6% (n=1,644) when follow-up was extended to the end of the study period (March 31, 2016).

**Table 9.1 - Follow-up time among infants included in the PIIV safety analysis**

| Follow-up time | Number of infants (%) N=21,693 |
|---|---|
| ≥3 months | 21,345 (98.4) |
| ≥6 months | 20,810 (95.9) |
| ≥1 year | 19,573 (90.2) |
| ≥2 years | 17,487 (80.6) |
| ≥3 years | 15,166 (69.9) |
| ≥4 years | 12,303 (56.7) |
| ≥5 years | 9,556 (44.1) |
| ≥6 years | 2,654 (12.2) |

Similarly to the uptake of SIIV during pregnancy, the likelihood of vaccination anytime in pregnancy with PIIV varied by region and was lower among women that were young, of black ethnicity, living in more deprived areas, current smokers or not part of a clinical risk group for which vaccination was recommended (**Table 9.2**). This was consistent with the sociodemographic, health and lifestyle factors known to be associated lower vaccine uptake and described in **Section 1.4**.

There were, however, some differences in the uptake of PIIV during pregnancy compared to SIIV. Receipt of SIIV during pregnancy was more likely among women exposed to other

potentially teratogenic drugs and/or live vaccines whereas this was not associated with PIIV receipt in pregnancy (**Supplementary Table 2** of Paper 2; **Table 9.2**). SIIV receipt was more likely among women whose first trimester did not overlap with a period of influenza activity above baseline levels whereas the converse was true for PIIV (**Supplementary Table 2** of Paper 2; **Table 9.2**). Differences in the timing of vaccine availability and motivation to offer and accept the vaccine in the pandemic and normal influenza seasons could explain these findings. Receipt of SIIV during pregnancy was less likely in multiparous women, which was consistent with observations about parity and vaccine uptake in the literature.[17] Conversely, PIIV receipt was more likely in households with 1-2 children.

In the study population used for the SIIV safety analysis, there was strong evidence to suggest that MCMs were associated with ethnicity, with increased odds among those born to South Asian mothers which was consistent with the previous literature (**Section 1.7.2**).[139] There was strong evidence for an association with region, with those in the West Midlands having the highest odds. There was also an association with maternal deprivation, flu season and the number of children in the household.

In this population, which was used for the PIIV safety analysis, the only baseline characteristic that exhibited strong evidence for an association with MCMs recorded in the first year of life was region (**Table 9.3**). Infants in the West Midlands and South East Coast had higher odds of an MCM than for any other region. Infants born to South Asian mothers also displayed increased odds of having an MCM recorded in the first year of life. However, ethnicity overall did not display strong evidence of an association with MCMs. It is possible that some of the associations seen in the study population for SIIV safety analyses were not observed in the population for this analysis on PIIV due to lower numbers in individual categories.

**Table 9.2- Receipt of PIIV in pregnancy, by characteristics.**

| | No. pregnancies unvaccinated (row %) n=17,894 | No. pregnancies vaccinated at anytime (row %) n=4,285 | No. pregnancies vaccinated in trimester 1 (row %) n=837 | Odds ratio for vaccination anytime (99% CI) | *P* value | Odds ratio for vaccination in the first trimester (99% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| Maternal age (years) | | | | | | | |
| <18 | 240 (87.9) | 33 (12.1) | 10 (3.7) | 0.57 (0.35-0.93) | <0.0001 | 0.87 (0.38-2.02) | 0.0008 |
| 18-24 | 3,453 (83.6) | 678 (16.4) | 120 (2.9) | 0.82 (0.72-0.92) | | 0.73 (0.56-0.95) | |
| 25-34 | 10,173 (80.6) | 2,444 (19.4) | 486 (3.9) | 1.00 | | 1.00 | |
| ≥35 | 4,028 (78.1) | 1,130 (21.9) | 221 (4.3) | 1.17 (1.05-1.30) | | 1.15 (0.93-1.42) | |
| Maternal ethnicity | | | | | | | |
| White | 15,595 (80.8) | 3,708 (19.2) | 711 (3.7) | 1.00 | <0.0001 | 1.00 | 0.0006 |
| S. Asian | 1,032 (75.6) | 334 (24.5) | 73 (5.3) | 1.36 (1.15-1.61) | | 1.55 (1.12-2.15) | |
| Black | 568 (86.5) | 89 (13.6) | 23 (3.5) | 0.66 (0.49-0.89) | | 0.89 (0.51-1.55) | |
| Other | 331 (79.6) | 85 (20.4) | 22 (5.3) | 1.08 (0.79-1.48) | | 1.46 (0.82-2.59) | |
| Mixed | 207 (86.3) | 33 (13.8) | <5 | 0.67 (0.41-1.09) | | 0.32 (0.07-1.43) | |
| Unknown | 161 (81.7) | 36 (18.3) | <5 | - | | - | |
| Maternal IMD status | | | | | | | |
| 1=Least Deprived | 3,790 (77.5) | 1,102 (22.5) | 196 (4.0) | 1.00 | <0.0001 | 1.00 | 0.1497 |
| 2 | 3,475 (78.8) | 933 (21.2) | 175 (4.0) | 0.92 (0.81-1.05) | | 0.97 (0.74-1.28) | |
| 3 | 3,448 (82.2) | 754 (17.9) | 166 (4.0) | 0.75 (0.66-0.86) | | 0.93 (0.70-1.23) | |
| 4 | 3,715 (82.2) | 807 (17.9) | 158 (3.5) | 0.75 (0.65-0.85) | | 0.82 (0.62-1.09) | |
| 5 = Most Deprived | 3,466 (83.4) | 689 (16.6) | 142 (3.4) | 0.68 (0.59-0.79) | | 0.79 (0.59-1.06) | |
| Region | | | | | | | |
| London | 2,686 (83.3) | 540 (16.7) | 130 (4.0) | 1.00 | <0.0001 | 1.00 | 0.0056 |
| North East | 473 (79.0) | 126 (21.0) | 28 (4.7) | 1.33 (1.00-1.76) | | 1.22 (0.70-2.12) | |
| North West | 2,704 (82.0) | 592 (18.0) | 115 (3.5) | 1.09 (0.92-1.29) | | 0.88 (0.63-1.23) | |
| Yorkshire & Humber | 536 (81.2) | 125 (18.9) | 38 (5.8) | 1.16 (0.87-1.54) | | 1.46 (0.90-2.39) | |
| East Midlands | 471 (81.9) | 104 (18.1) | 16 (2.8) | 1.10 (0.81-1.49) | | 0.70 (0.35-1.41) | |
| West Midlands | 1,918 (80.4) | 469 (19.7) | 93 (3.9) | 1.22 (1.02-1.46) | | 1.00 (0.70-1.43) | |
| East of England | 2,010 (77.8) | 573 (22.2) | 114 (4.4) | 1.42 (1.19-1.68) | | 1.17 (0.83-1.64) | |
| South West | 2,122 (78.0) | 598 (22.0) | 105 (3.9) | 1.40 (1.18-1.66) | | 1.02 (0.72-1.45) | |
| South Central | 2,626 (80.5) | 636 (19.5) | 90 (2.8) | 1.20 (1.02-1.42) | | 0.71 (0.49-1.02) | |
| South East Coast | 2,348 (81.8) | 522 (18.2) | 108 (3.8) | 1.11 (0.93-1.32) | | 0.95 (0.67-1.34) | |
| Mother was part of clinical risk group | | | | | | | |
| None | 16,974 (81.3) | 3,909 (18.7) | 740 (3.5) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| Yes | 810 (69.3) | 359 (30.7) | 92 (7.9) | 1.92 (1.62-2.28) | | 2.61 (1.93-3.51) | |
| Unknown | 110 (86.6) | 17 (13.4) | <5 | - | | - | |
| Maternal smoking status | | | | | | | |
| Non | 9,140 (80.0) | 2,287 (20.0) | 421 (3.7) | 1.00 | <0.0001 | 1.00 | 0.0009 |
| Current | 4,488 (83.5) | 885 (16.5) | 177 (3.3) | 0.79 (0.70-0.88) | | 0.86 (0.68-1.08) | |
| Ex | 4,129 (79.2) | 1,085 (20.8) | 237 (4.6) | 1.05 (0.94-1.17) | | 1.25 (1.01-1.54) | |
| Unknown | 137 (83.0) | 28 (17.0) | <5 | - | | - | |
| Maternal hazardous drinking | | | | | | | |
| No | 17,809 (80.7) | 4,268 (19.3) | 832 (3.8) | 1.00 | 0.4883 | 1.00 | 0.6292 |
| Yes | 85 (83.3) | 17 (16.7) | <5 | 0.83 (0.42-1.66) | | 1.26 (0.38-4.13) | |
| Extreme maternal BMI | | | | | | | |
| No | 16,439 (80.7) | 3,939 (19.3) | 768 (3.8) | 1.00 | 0.6850 | 1.00 | 0.8579 |
| Underweight | 338 (79.3) | 88 (20.7) | 18 (4.2) | 1.09 (0.80-1.48) | | 1.14 (0.61-2.14) | |
| Obese | 1,117 (81.2) | 258 (18.8) | 51 (3.7) | 0.96 (0.80-1.16) | | 0.98 (0.67-1.43) | |
| Maternal chronic hypertension (non-pregnancy related) | | | | | | | |
| None | 17,646 (80.7) | 4,222 (19.3) | 828 (3.8) | 1.00 | 0.6752 | 1.00 | 0.4334 |
| Yes | 248 (79.7) | 63 (20.3) | 9 (2.9) | 1.06 (0.74-1.53) | | 0.77 (0.32-1.86) | |
| Maternal exposure to teratogenic medication(s) or live vaccines | | | | | | | |
| No | 16,805 (80.8) | 4,001 (19.2) | 774 (3.7) | 1.00 | 0.1897 | 1.00 | 0.1001 |
| Yes | 1,089 (79.3) | 284 (20.7) | 63 (4.6) | 1.10 (0.92-1.31) | | 1.26 (0.89-1.78) | |
| No. of weeks the first trimester overlapped with influenza activity above baseline levels | | | | | | | |
| None | 11,685 (83.1) | 2,373 (16.9) | 82 (0.6) | 1.00 | <0.0001 | 1.00 | <0.0001 |
| 0-2 | 1,115 (79.0) | 296 (21.0) | 36 (2.6) | 1.31 (1.09-1.56) | | 4.60 (2.73-7.75) | |
| 2-4 | 1,159 (76.6) | 354 (23.4) | 68 (4.5) | 1.50 (1.27-1.78) | | 8.36 (5.44-12.85) | |
| 4-6 | 1,206 (77.5) | 351 (22.5) | 108 (6.9) | 1.43 (1.21-1.69) | | 12.76 (8.68-18.76) | |
| 6-8 | 2,729 (75.0) | 911 (25.0) | 543 (14.9) | 1.64 (1.47-1.84) | | 28.35 (20.79-38.66) | |
| No. of children in maternal household | | | | | | | |
| 0 | 7,095 (82.6) | 1,495 (17.4) | 311 (3.6) | 1.00 | <0.0001 | 1.00 | 0.0091 |
| 1-2 | 9,349 (79.0) | 2,480 (21.0) | 476 (4.0) | 1.26 (1.15-1.38) | | 1.16 (0.96-1.41) | |
| ≥3 | 1,450 (82.4) | 310 (17.6) | 50 (2.8) | 1.01 (0.85-1.21) | | 0.79 (0.53-1.17) | |

Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index; CI, confidence interval.

**Table 9.3 - Major malformations among those eligible for the PIIV safety analysis, by characteristics.**

| | No major malformation (row %) N=20,699 | Major malformation (row %) N=1,480 | Odds ratios for major malformations in the year after delivery (99% CI) | *P* value |
|---|---|---|---|---|
| Maternal age (years) | | | | |
| <18 | 258 (94.5) | 15 (5.5) | 0.80 (0.40-1.61) | 0.7039 |
| 18-24 | 3,867 (93.6) | 264 (6.4) | 0.95 (0.78-1.14) | |
| 25-34 | 11,767 (93.3) | 850 (6.7) | 1.00 | |
| ≥35 | 4,807 (93.2) | 351 (6.8) | 1.01 (0.85-1.20) | |
| Maternal ethnicity | | | | |
| White | 18,047 (93.5) | 1,256 (6.5) | 1.00 | 0.0807 |
| S. Asian | 1,252 (91.7) | 114 (8.4) | 1.31 (1.01-1.70) | |
| Black | 615 (93.6) | 42 (6.4) | 0.98 (0.65-1.49) | |
| Other | 382 (91.8) | 34 (8.2) | 1.28 (0.80-2.04) | |
| Mixed | 222 (92.5) | 18 (7.5) | 1.17 (0.62-2.20) | |
| Unknown | 181 (91.9) | 16 (8.1) | - | |
| Region | | | | |
| North East | 560 (93.5) | 39 (6.5) | 1.21 (0.76-1.95) | <0.0001 |
| North West | 3,072 (93.2) | 224 (6.8) | 1.27 (0.97-1.66) | |
| Yorkshire & Humber | 619 (93.7) | 42 (6.4) | 1.18 (0.75-1.87) | |
| East Midlands | 547 (95.1) | 28 (4.9) | 0.89 (0.52-1.53) | |
| West Midlands | 2,151 (90.1) | 236 (9.9) | 1.91 (1.46-2.50) | |
| East of England | 2,424 (93.8) | 159 (6.3) | 1.14 (0.86-1.53) | |
| South West | 2,553 (93.9) | 167 (6.1) | 1.14 (0.86-1.52) | |
| South Central | 3,069 (94.1) | 193 (5.9) | 1.10 (0.83-1.45) | |
| London | 3,051 (94.6) | 175 (5.4) | 1.00 | |
| South East Coast | 2,653 (92.4) | 217 (7.6) | 1.43 (1.09-1.87) | |
| Maternal IMD status | | | | |
| 1=Least Deprived | 4,556 (93.1) | 336 (6.9) | 1.00 | 0.0664 |
| 2 | 4,079 (92.5) | 329 (7.5) | 1.09 (0.89-1.35) | |
| 3 | 3,944 (93.9) | 258 (6.1) | 0.89 (0.71-1.11) | |
| 4 | 4,245 (93.9) | 277 (6.1) | 0.88 (0.71-1.10) | |
| 5 = Most Deprived | 3,875 (93.3) | 280 (6.8) | 0.98 (0.79-1.22) | |
| No. of children in maternal household | | | | |
| 0 | 7,999 (93.1) | 591 (6.9) | 1.00 | 0.5635 |
| 1-2 | 11,051 (93.4) | 778 (6.6) | 0.95 (0.82-1.10) | |
| ≥3 | 1,649 (93.7) | 111 (6.3) | 0.91 (0.69-1.20) | |
| Maternal smoking status | | | | |
| Non | 10,637 (93.1) | 790 (6.9) | 1.00 | 0.3445 |
| Current | 5,029 (93.6) | 344 (6.4) | 0.92 (0.78-1.09) | |
| Ex | 4,878 (93.6) | 336 (6.4) | 0.93 (0.78-1.10) | |
| Unknown | 155 (93.9) | 10 (6.1) | - | |
| Maternal hazardous drinking | | | | |
| No | 20,601 (93.3) | 1,476 (6.7) | 1.00 | 0.2289 |
| Yes | 98 (96.1) | <5 | 0.57 (0.15-2.12) | |
| Extreme maternal BMI | | | | |
| No | 19,006 (93.3) | 1,372 (6.7) | 1.00 | 0.4500 |
| Underweight | 399 (93.7) | 27 (6.3) | 0.94 (0.56-1.57) | |
| Obese | 1,294 (94.1) | 81 (5.9) | 0.87 (0.64-1.17) | |
| Mother was part of clinical risk group | | | | |
| No | 19,475 (93.3) | 1,408 (6.7) | 1.00 | 0.0353 |
| Yes | 1,108 (94.8) | 61 (5.2) | 0.76 (0.54-1.08) | |
| Unknown | 116 (91.3) | 11 (8.7) | - | |
| Maternal chronic hypertension (non-pregnancy related) | | | | |
| No | 20,410 (93.3) | 1,458 (6.7) | 1.00 | 0.7773 |
| Yes | 289 (92.9) | 22 (7.1) | 1.07 (0.60-1.89) | |
| Maternal exposure to teratogenic medication(s) or live vaccines | | | | |
| No | 19,406 (93.3) | 1,400 (6.7) | 1.00 | 0.1860 |
| Yes | 1,293 (94.2) | 80 (5.8) | 0.86 (0.63-1.16) | |
| No. of weeks the first trimester overlapped with influenza activity above baseline levels | | | | |
| None | 13,141 (93.5) | 917 (6.5) | 1.00 | 0.0371 |
| 0-2 | 1,338 (94.8) | 73 (5.2) | 0.78 (0.57-1.08) | |
| 2-4 | 1,401 (92.6) | 112 (7.4) | 1.15 (0.88-1.50) | |
| 4-6 | 1,445 (92.8) | 112 (7.2) | 1.11 (0.85-1.45) | |
| 6-8 | 3,374 (92.7) | 266 (7.3) | 1.13 (0.94-1.36) | |

Abbreviations: IMD, Index of Multiple Deprivation; BMI, body mass index; CI, confidence interval.

## 9.4 Primary and secondary analyses

There was no evidence to suggest an association between receipt of PIIV anytime in pregnancy and MCMs recorded in the year after delivery in univariable or fully-adjusted Cox regression models ($HR_{adjusted}$, 0.97; 99% CI, 0.81-1.15; p=0.62), with point estimates being highly similar in both (**Table 9.4**). The lack of association persisted when stratifying by trimester of vaccination, with the first trimester having a HR of 1.02 (99% CI, 0.72-1.46; p=0.86) in the fully-adjusted model (**Table 9.4**). Results were similar in models that included MCMs ascertained anytime from delivery until the end of the study period (**Table 9.4**).

## 9.5 Sensitivity analyses

Results were robust in sensitivity analyses examining first-trimester vaccination and MCMs ascertained in the year after delivery or anytime in the study period. Whilst point estimates increased slightly in sensitivity analyses that excluded 2,030 pregnancies with unknown BMI and those that included 39 additional pregnancies that received PIIV in the 4 weeks prior to the pregnancy start, there was no evidence of an association (**Table 9.5**). Allowing follow-up time in HES and ONS to continue after follow-up in CPRD had ended resulted in the identification of just 4 additional infants with MCMs in the year after delivery and just 52 by the end of the study period. Neither of these analyses revealed an association between first-trimester vaccination and MCMs (**Table 9.5**).

**Table 9.4 - Examining the association between pandemic influenza vaccination in pregnancy and MCMs.**

| Timing of vaccination (No. pregnancies) | No. MCMs/person-years (rate per 100 person-years) | HR, unadjusted (99% CI) | *P* value | HR, adjusted for *a priori* confounders (99% CI) | *P* value | HR, adjusted for all potential confounders (99% CI) | *P* value |
|---|---|---|---|---|---|---|---|
| **Models including MCMs ascertained in the year after delivery (N=1,444 MCMs)** | | | | | | | |
| **Never** (N=17,489) | 1,168/15,699 (7.4) | 1.00 | | 1.00 | | 1.00 | |
| **Any trimester** (N=4,204) | 276/3,784 (7.3) | 0.98 (0.83-1.17) | 0.79 | 0.97 (0.82-1.15) | 0.65 | 0.97 (0.81-1.15) | 0.62 |
| **Trimester 1** (N=825) | 60/731 (8.2) | 1.09 (0.78-1.53) | 0.52 | 1.07 (0.76-1.51) | 0.60 | 1.02 (0.72-1.46) | 0.86 |
| **Trimester 2** (N=1,893) | 124/1,697 (7.3) | 0.98 (0.77-1.25) | 0.84 | 0.98 (0.77-1.25) | 0.81 | 0.98 (0.76-1.25) | 0.82 |
| **Trimester 3** (N=1,486) | 92/1,356 (6.8) | 0.92 (0.70-1.22) | 0.46 | 0.91 (0.69-1.20) | 0.36 | 0.92 (0.69-1.23) | 0.47 |
| **Models including MCMs ascertained after delivery and anytime in the study period (N=1,644 MCMs)** | | | | | | | |
| **Never** (N=17,489) | 1,335/65,144 (2.0) | 1.00 | | 1.00 | | 1.00 | |
| **Any trimester** (N=4,204) | 309/15,989 (1.9) | 0.96 (0.81-1.13) | 0.50 | 0.95 (0.81-1.12) | 0.41 | 0.95 (0.81-1.12) | 0.45 |
| **Trimester 1** (N=825) | 68/2,922 (2.3) | 1.09 (0.79-1.50) | 0.49 | 1.07 (0.78-1.48) | 0.56 | 1.06 (0.76-1.48) | 0.66 |
| **Trimester 2** (N=1,893) | 135/7,121 (1.9) | 0.93 (0.74-1.18) | 0.43 | 0.93 (0.74-1.17) | 0.41 | 0.94 (0.75-1.20) | 0.53 |
| **Trimester 3** (N=1,486) | 106/5,946 (1.8) | 0.92 (0.71-1.19) | 0.42 | 0.91 (0.70-1.18) | 0.33 | 0.91 (0.70-1.18) | 0.35 |

*A priori* confounders were maternal age, maternal ethnicity and region. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. Abbreviations: MCM, major congenital malformations; IMD, Index of Multiple Deprivation; BMI, body mass index; HR, Hazard Ratio; CI, Confidence Interval.

**Table 9.5 - Examining the association between first trimester vaccination with pandemic influenza vaccine and MCMs in sensitivity analyses.**

| Models | HR, unadjusted (99% CI) | *P* value | HR, adjusted for *a priori* confounders (99% CI) | *P* value | HR, adjusted for all potential confounders (99% CI) | *P* value |
|---|---|---|---|---|---|---|
| **Models including MCMs diagnosed in the year after delivery** | | | | | | |
| **Main model** | 1.09 (0.78-1.53) | 0.52 | 1.07 (0.76-1.51) | 0.60 | 1.02 (0.72-1.46) | 0.86 |
| Including pregnancies vaccinated in the 4 weeks prior to the start[a] | 1.13 (0.81-1.57) | 0.34 | 1.11 (0.80-1.54) | 0.41 | 1.07 (0.76-1.51) | 0.60 |
| Including diagnoses made beyond truncation of follow-up in CPRD[b] | 1.09 (0.77-1.53) | 0.53 | 1.07 (0.76-1.50) | 0.62 | 1.02 (0.71-1.46) | 0.89 |
| Excluding pregnancies with unknown BMI[c] | 1.12 (0.78-1.59) | 0.43 | 1.10 (0.77-1.57) | 0.48 | 1.07 (0.74-1.55) | 0.65 |
| **Models including MCMs diagnosed after delivery and anytime in the study period** | | | | | | |
| **Main model** | 1.09 (0.79-1.50) | 0.49 | 1.07 (0.78-1.48) | 0.56 | 1.06 (0.76-1.48) | 0.66 |
| Including pregnancies vaccinated in the 4 weeks prior to the start[a] | 1.13 (0.83-1.54) | 0.29 | 1.12 (0.82-1.53) | 0.34 | 1.12 (0.81-1.54) | 0.38 |
| Including diagnoses made beyond truncation of follow-up in CPRD[d] | 1.05 (0.76-1.45) | 0.70 | 1.04 (0.75-1.43) | 0.76 | 1.03 (0.74-1.44) | 0.83 |
| Excluding pregnancies with unknown BMI[c] | 1.12 (0.80-1.55) | 0.39 | 1.10 (0.79-1.54) | 0.44 | 1.10 (0.78-1.56) | 0.47 |

*A priori* confounders were maternal age, maternal ethnicity and region. Other potential confounders included the number of weeks the first trimester overlapped with a period of influenza activity above baseline levels as well as the following maternal factors: IMD, number of children in the household, smoking status, hazardous drinking, extreme BMI, clinical risk group, chronic hypertension and exposure to teratogenic drugs and/or live vaccines. Abbreviations: MCM, major congenital malformations; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics death certificate data; BMI, body mass index; IMD, Index of Multiple Deprivation; HR, Hazard Ratio; CI, Confidence Interval

## 9.6 Chapter summary and conclusions

This historical cohort study examined PIIV receipt during pregnancy, stratified by trimester, and MCMs in live-born infants. No evidence was found to suggest an association between vaccination anytime in pregnancy (HR, 0.97; 95% CI, 0.81-1.15; p=0.62) or first-trimester vaccination (HR, 1.02; 99% CI, 0.72-1.46; p=0.86) and MCMs in the year after delivery. Results were almost identical to those of a pooled analysis of six studies examining first-trimester PIIV and MCMs (Odds Ratio, 1.02; 95% CI, 0.89-1.17).[23] The lack of evidence for an association with MCMs persisted with longer follow-up and across all sensitivity analyses.

The strengths and limitations of these analyses have already been described in the previous chapter, which explored the safety of SIIV. Whilst the safety of PIIV with respect to MCMs has been explored by a number of studies, replicating these analyses here provided confidence in the methods used in this thesis (and consequently, the methods used to assess SIIV safety). The results of the analysis carried out here were not only almost identical to pooled estimates from other studies, but the characteristics of the vaccinated and unvaccinated populations as well as the characteristics of those with and without major malformations were in line with what was expected based on published literature.

# Discussion

This section brings together the findings from **Chapter 2** and **Chapters 7-9**, and their interpretation. In **Chapter 10**, the aims and objectives of the thesis are summarized, the key results are described, and an overview of the main strengths of the work is provided. In **Chapter 11**, the challenges of using electronic health records to examine the safety of drugs and vaccines given in pregnancy with respect to MCMs are discussed. Interpretation of the findings, recommendations for further research and conclusions are provided in **Chapter 12.**

# 10. Discussion I: Key results and strengths of the research

## 10.1 Recapitulation of the aims and objectives of the thesis

The aim of this thesis was to use routinely-collected, multiply-linked UK electronic health records to assess the safety of SIIV and PIIV administration during pregnancy with respect to major congenital malformations. A systematic review of the methods used to identify recorded diagnoses of congenital malformations and the validity of these diagnoses in UK electronic health records was first carried out (**Objective 1**). This informed the development of an algorithm to identify major malformations in linked CPRD, HES and ONS data (**Objective 2**). Using this novel algorithm, major malformations were identified in linked data. The agreement between data sources in ascertaining major malformations and the unique contribution of each was quantified (**Objective 3**). The rates of major malformations in stand-alone CPRD were compared with rates in previously published stand-alone THIN data whilst rates in stand-alone CPRD, stand-alone HES and linked CPRD-HES-ONS were compared with those from EUROCAT (**Objective 4**). The association between maternal SIIV and major malformations, stratified by the trimester of pregnancy, was then examined (**Objective 5**). Finally, the association between maternal PIIV and major malformations was explored (**Objective 6**).

## 10.2 Summary of main results

### 10.2.1 The identification and validity of congenital malformation diagnoses in UK EHR

**What was known?**

Data available in UK electronic health records are collected for clinical purposes, not for research. Therefore, although there are chapters dedicated to congenital malformations in both the Read code system ('P' chapter) and ICD-10 ('Q' chapter), diagnoses may be recorded using different codes within each chapter as well as codes outside of these chapters. Standardized code lists to define and identify diagnoses of interest in UK EHR are not typically available and researchers develop their own code lists for their own studies.[126] This can lead to differences between code lists for the same condition(s) depending on the inclusion criteria used. The implications of this were demonstrated in a recent study in which the prevalence of congenital malformations among live born infants ranged from 1.8% to 4.1% depending on the ICD-10 code list used to interrogate hospital data linked to birth and death records.[245]

The validity of diagnoses recorded in UK electronic health records is generally considered to be good. In 2010, a systematic review of validation studies of 183 different clinical diagnoses in the CPRD reported a high median PPV of 89% (range, 24-100), with most validations carried out by requesting additional information from GPs (e.g. questionnaires or complete paper records).[180] In 2011, another systematic review examined diagnostic and procedure coding accuracy in hospital data for a range of diagnoses, with most validations relying on case notes as the reference standard.[181] The median diagnostic PPV was also high (80%; IQR, 63-94) although most studies examined ICD-9 codes rather than the currently used ICD-10 codes. The PPV of primary diagnoses was particularly high (96%; IQR 89-96) and was thought to have improved as a result of annual audits of data quality and the requirement to record definitive diagnoses for reimbursement purposes.[181]

To date, no study has examined the methods used to identify congenital malformations in UK electronic health records despite their importance in post-marketing safety studies and the

challenges involved in capturing this wide array of conditions. Previous systematic reviews of validation studies in CPRD and HES are almost a decade old and have not specifically examined congenital malformations.[180,181]

**What does this thesis add?**

As part of this thesis, 54 studies were reviewed systematically to summarize the methods used to identify congenital malformations in UK EHR. The validity of malformation diagnoses recorded in these data sources was also explored.

The 36 studies using primary care data to identify congenital malformations used diagnostic codes from several areas of the Read coding system, including the 'P' chapter dedicated to such diagnoses, and frequently used EUROCAT guidelines to develop case definitions. The types of codes used varied across studies. Most striking was the use of diagnostic codes from non-'P' chapters in 53% of primary care studies as these could potentially be used to record either congenital or non-congenital conditions. Codes relating to procedures were used in 56% of studies, codes for a history of congenital malformations in 39% and codes for relevant administrative tasks in 33%. Conversely, the 18 studies using secondary care data (of which almost half also used birth and death records) relied on codes from the ICD-10 'Q' chapter – half also used OPCS-4 procedure codes.

Eight studies validated congenital malformations identified in primary care data,[187, 192, 194, 208, 209, 216, 219, 222] of which only one was included in the previous systematic review of validations in CPRD.[219] The PPV (the only measure of validity assessed) was high for congenital malformations overall, major malformations and heart defects (80-100%), moderate for neural tube defects (71%) and lowest for developmental hip dysplasia (56%).[187, 192, 194, 208, 209, 216, 219, 222] There was heterogeneity across studies in the reference standard used, and the PPV was shown to vary according to the reference standard that was chosen.[194] None of the studies identifying congenital malformations in secondary care data performed validations. Just one study examined the validity of diagnoses recorded in death records and, using hospital

admissions as a reference standard, demonstrated that death records under-ascertained life-limiting congenital malformations by 11-20%.[237]

The review here has not only highlighted the need for fuller reporting of the methods and code lists used in EHR studies of congenital malformations, but also the need for further validation studies. Ideally, these should assess a wide range of malformation subgroups and other measures of validity in addition to PPV.

### 10.2.2 The value of primary care, hospital admissions and mortality data in identifying major congenital malformations in anonymised UK EHR

**What was known?**

Studies using UK EHR to identify congenital malformations have not used linked primary and secondary care data to increase ascertainment. Instead, as described in the systematic review presented in this thesis, they typically used stand-alone primary care data or stand-alone secondary care data (with some also using linked or unlinked birth or death records). Studies carrying out post-marketing safety assessments of drugs and vaccines given in pregnancy relied chiefly on primary care data. However, there is a growing body of evidence to suggest that agreement between electronic health record databases can be low and that using stand-alone data sources risks under-ascertaining conditions.[288-291] At the time of this work, this had not yet been explored for congenital malformations.

**What does this thesis add?**

Work presented in this thesis demonstrated the value of linked CPRD and HES in increasing ascertainment of congenital malformations. Code lists to identify major malformations in linked primary care, hospital admission and mortality data were developed in accordance with EUROCAT guidelines and with the input of a consultant neonatologist.[86, 283] Among 7,901 infants with a major malformation diagnosed in the year after delivery, agreement between CPRD and HES was low - just 20%. Almost 65% of infants had a diagnosis exclusively in HES and 15% exclusively in CPRD. Results were robust to increased follow-up beyond one year. Even

after excluding non-specific skin malformation diagnoses in ICD-10, some of which may have referred to minor conditions, the proportion with evidence exclusively in HES remained high (56%). Death certificates or procedures carried out during hospital admissions identified very few additional individuals that did not already have evidence of their diagnosis in CPRD or HES. For most malformation subgroups, agreement between CPRD and HES was also low and did not improve markedly with longer follow-up.

### 10.2.3 Prevalence comparisons of major malformations identified in UK EHR data sources and in registries

**What was known?**

In previous studies, the prevalence of major malformations was generally higher in primary care data than in registries, or was comparable.[201, 209, 218] However, prevalence comparisons were mainly limited to THIN data.[201] Between 1990 and 2009, the prevalence ratio for major malformations among live-births between THIN and UK EUROCAT data was 1.18 (95% CI, 1.16-1.20).[201] Heart, limb, genital, musculoskeletal and eye malformations all had higher prevalence in THIN. In CPRD, just two subgroups were examined; congenital heart malformations had a higher prevalence than in EUROCAT whilst the prevalence of nervous system malformations was comparable.[209, 218] For some subgroups or rare malformations the prevalence was lower in primary care data although prevalence increased with longer follow-up.[201, 218]

**What does this thesis add?**

Use of the code list developed for this thesis enabled good ascertainment of major malformations in the electronic health record datasets examined. The prevalence of major malformations in stand-alone CPRD data was 244 per 10,000 live-births (95% CI, 236-253), compared to 198 per 10,000 live-births (95% CI, 195-201) in published data from THIN.[201] Malformation subgroups had similar prevalence in CPRD and THIN with the exception of limb, urinary, digestive and eye malformations which had higher prevalence in CPRD, and nervous system malformations which a had higher prevalence in THIN.[201]

After comparing the code list developed here to identify major malformations in CPRD with that used for the THIN study, the higher prevalence of digestive, eye and urinary malformations in CPRD could be explained by the greater sensitivity of the Read code list developed for the studies described in this thesis. Differences in code lists did not appear to explain the higher prevalence of limb malformations or lower prevalence of nervous system malformations in CPRD.

The prevalence of major malformations overall was higher in stand-alone CPRD, stand-alone HES and linked CPRD-HES-ONS than in EUROCAT between 2009 and 2013 (the period before changes in the organization of contributing EUROCAT registries). Prevalence was higher in stand-alone CPRD than in EUROCAT for limb, heart, genital and eye malformations, consistent with published comparisons between THIN and EUROCAT.[201] In stand-alone HES and in linked CPRD-HES-ONS data, all subgroups had a higher prevalence than in EUROCAT except for abdominal and orofacial malformations, which had comparable prevalence. Finally, major limb malformations had a considerably higher prevalence in stand-alone HES compared to EUROCAT (Prevalence Ratio, 8.3; 95% CI, 7.7-8.9) and this was similar in linked CPRD-HES-ONS data. This was likely a result of the large number of non-specific limb codes in ICD-10; >90% of infants with a limb malformation in HES had such a code.

### 10.2.4 The safety of influenza vaccination during pregnancy and major congenital malformations

**What was known?**

A small number of observational studies, all based in North America, have examined the safety of maternal receipt of SIIV with respect to major malformations in live-born infants.[50, 90, 101, 103, 104] None of these have identified evidence of an association. However, with the exception of a study by Kharbanda *et al.*[103] which was published after the work in this thesis had started, available evidence was limited by short follow-up (restricted to the period around delivery) and low numbers of first-trimester vaccinations.[50, 90, 101, 104]

The study by Kharbanda *et al*. is the only study to have examined a large number of first-trimester vaccinated pregnancies (n>52,000) and followed infants up for a year after delivery.[103] The adjusted prevalence ratio for major malformations comparing pregnancies vaccinated in the first trimester to unvaccinated pregnancies was 1.02 (95% CI, 0.94-1.10; p=0.6). This was similar for subgroups such as cardiac defects (Prevalence Ratio, 0.98; 95% CI, 0.87-1.10; p=0.8) and muscular or limb defects (Prevalence Ratio, 0.93; 95% CI, 0.67-1.30; p=0.7). To date, no study in Europe or the UK has assessed the safety of maternal SIIV with respect to major malformations.

The majority of studies that have examined the safety of maternal influenza vaccination and major malformations have examined PIIV. Individually, none of the studies have identified evidence of an association with major malformations overall. One systematic review pooled ten analyses examining major malformations following PIIV receipt anytime in pregnancy and reported an odds ratio of 1.02 (95% CI, 0.91-1.14).[23] Restricting to six analyses in which PIIV was received in the first trimester gave an identical odds ratio of 1.02 (95% CI, 0.89-1.17).[23] A more recent systematic review pooled seven analyses and calculated an adjusted odds ratio of 1.03 (95% CI, 0.99-1.07) for major malformations following PIIV receipt in pregnancy.[22] The limitations of these studies are similar to those for SIIV. Most studies had low numbers of first-trimester vaccinations and short follow-up. However, unlike safety studies on SIIV, studies examining PIIV have assessed safety in relation to MCMs in a wider range of settings.

**What does this thesis add?**

This thesis presents the largest European safety study on maternal SIIV and major malformations using a large UK-based historical cohort to date. In addition to providing further evidence of safety in a different setting, it addresses several limitations highlighted by previous systematic reviews of the related literature, with an appreciably longer follow-up of infants (including beyond the first year of life) and a large numbers of pregnancies vaccinated in the first trimester.

Use of the CPRD/LSHTM Pregnancy Register enabled examination of vaccine uptake by UK pregnant women by trimester.[255] Among 78,150 pregnancies delivering a live-born singleton infant between September 2010 and March 2016, 8.8% had received a vaccine in the first trimester, 14.9% in the second and 16.5% in the third. In fully-adjusted models, the hazard ratio for major malformations recorded in the year after delivery among those vaccinated in the first trimester compared to those never vaccinated was 1.06 (99% CI, 0.94-1.19; p=0.23). There was no evidence for an association between first-trimester SIIV and major malformations. Results were very similar for those vaccinated anytime in pregnancy (HR, 1.02; 99% CI, 0.94-1.10; p=0.54) or in subsequent trimesters. Similar estimates were obtained after including diagnoses made after the first year of life. There was also no evidence of an association between first-trimester vaccination and limb malformations ($HR_{adj}$, 1.03; 99% CI, 0.86-1.25; p=0.66) or congenital heart defects ($HR_{adj}$, 0.91; 99% CI, 0.64-1.29; p=0.49). These results were consistent with those presented by Kharbanda *et al.*

This thesis also presents the largest examination of PIIV and major malformations in UK data. The analysis included 21,693 pregnancies delivering a live-born singleton between 2009 and 2010. Of these, 3.8% received a vaccine in the first trimester, 8.7% in the second and 6.9% in the third. The fully-adjusted model did not reveal any evidence for an association between first-trimester vaccination and major malformations in the first year of life, with a hazard ratio of 1.02 (99% CI, 0.72-1.46; p=0.86). Results were similar for vaccination anytime in pregnancy ($HR_{adj}$, 0.97; 99% CI, 0.81-1.15; p=0.62). These results were in line with pooled analyses of the safety of PIIV in systematic reviews.[22, 23]

## 10.3 Strengths

### 10.3.1 The use of large, multiply-linked EHR databases

This research was conducted using large, representative, routinely-collected primary care data linked to hospital admissions and mortality data. At the time this work began, CPRD comprised data on over 11 million patients and included almost 700 practices across the UK, making it

one of the largest electronic health record databases worldwide.[126] The large size of this database was key in allowing the examination of major congenital malformations, a rare outcome, and (as discussed further below) increasing study power to examine vaccination by the trimester of pregnancy.

The ascertainment of MCMs was maximised by the existing linkage of primary care records to hospitalisation and mortality data for 75% of English practices.[126] Many congenital malformations are likely to be diagnosed in hospital, at the time of delivery or in early childhood, and some may only be identified following death. Hospitalisations and deaths are required to be communicated to general practice but these may be delayed or incompletely encoded in the electronic primary care record (researchers, for example, do not have access to information entered by the general practitioner as free-text or scanning hospital letters).[287] Linkage of these databases enabled more complete capture of these rare conditions, as demonstrated by the finding that the majority of infants with a major congenital malformation had evidence of their condition exclusively in HES.

A further key strength of these data is their potential for long-term follow-up. A frequently cited limitation of previous safety studies examining maternal influenza vaccination was that these studies ascertained congenital malformations around the time of delivery and did not capture later diagnoses.[20-24] In an attempt to address this, more recent studies have attempted follow-up of one year. However, there is evidence that some congenital malformations may be diagnosed or recorded after the first year of life.[218, 244, 313] Others have also emphasized the need for further evidence on long-term paediatric outcomes following maternal influenza vaccination.[314] In the maternal vaccine safety assessments described in this thesis, in addition to examining congenital malformations in the first year of life, a further analysis was carried out in which all available follow-up time in the study period was used. Almost 50% of infants had more than two years of follow-up and over 5% of all major malformations in the cohort were identified after the first year of life.

### 10.3.2 The use of the newly-developed CPRD/LSHTM Pregnancy Register

The use of the newly-developed and recently validated CPRD/LSHTM Pregnancy Register, which aims to identify all pregnancy episodes among women aged 11-49 years, was a key strength of the work described in this thesis.[255] Whilst the potential of EHR for post-marketing safety studies in pregnancy is widely recognized, identifying pregnancy episodes and their timing in these data is challenging as this information is not systematically recorded.[255] This complicates the ascertainment of gestational age at the time of exposure and the examination of exposures in different trimesters.

The Pregnancy Register algorithm is unique in that it uses all the available pregnancy data to identify pregnancy episodes and their onset, end and trimester dates.[255] The work conducted in this thesis benefitted from this comprehensive approach in three ways:

1. A large number of first-trimester vaccinated pregnancies were easily identified. This was crucial in the safety studies described here because congenital malformations were the outcome of interest and most organogenesis occurs in the first trimester. In the wider literature, available evidence on the safety of first-trimester vaccination with respect to congenital malformations has been limited by low numbers of pregnant women vaccinated in the first trimester.[20-24] The use of the Pregnancy Register meant that the safety assessment of SIIV in the first trimester presented here is the largest such assessment outside of the US.

2. The potential misclassification of vaccination timing was minimized. The accuracy of estimated gestational age at the time of vaccination is important when examining trimester-sensitive outcomes such as congenital malformations. In this work, gestational age at the time of vaccination was thought to have high accuracy due to the use of all available information on gestational age in primary care records by the Pregnancy Register algorithm. Gestational age in the Pregnancy Register has been

validated using linked HES data and close agreement was observed (median difference of 0 weeks' gestation, IQR 0-0 weeks).[255]

3. Transparency with regards to live-birth pregnancies that could not be linked to the records of a live-born infant. In **Section 4.3.8,** the possible reasons for incomplete linkage between the mother and infant in the Mother-Baby Link were outlined. Incomplete linkage is a complicating factor for safety studies of drugs and vaccines given in pregnancy. In the Pregnancy Register, live-birth pregnancies that are not linked to infant records are captured and can be easily identified.[255] This allowed the extent of incomplete linkage to be explored and reported, in contrast to other drug safety studies in pregnancy that have typically not provided this information.

### 10.3.3 Development and use of a novel algorithm for identifying congenital malformations

At the time this work was conducted there was no established algorithm for the identification of congenital malformations in UK electronic health records. Developing Read, ICD-10 and OPCS-4 code lists to identify the wide array of conditions in these data posed a challenge. A systematic review of the methods used to identify these conditions in UK electronic health records, and any validations, was first carried out and was invaluable in informing the development of a novel algorithm to identify congenital malformations in this thesis.

Guidelines published by EUROCAT, a well-established network of population-based registries for congenital malformations with over 40 years of surveillance experience across Europe, were used to define major malformations and subgroups.[86] Code lists developed using these guidelines were reviewed with a consultant neonatologist. Read codes outside of the 'P' chapter, which might not always be congenital in nature, were considered for inclusion in code lists to increase the ascertainment of major malformations in primary care data (an approach observed in several other studies included in the systematic review) but were only included if they were likely to relate to conditions with congenital causes in the majority of the study

population. The ascertainment of major malformations overall in stand-alone and linked data using these code lists was found to be higher than that in THIN or EUROCAT registries and similar results were seen for many subgroups.[201]

### 10.3.4 Careful approach in determining exposed and unexposed cohorts

Establishing the vaccination status and trimester of vaccination receipt was critical in the maternal vaccination safety studies carried out here. Each pregnant woman could have multiple records relating to influenza vaccination across a particular vaccination season, some of which could be conflicting. To establish the best possible consensus, all the available evidence for each woman across each pregnancy and season was considered.

The earliest record of vaccine receipt during a vaccination season was considered to be the most accurate information on vaccination timing. This assumed that vaccination evidence from different files in CPRD could be treated equally when, conventionally, evidence from the clinical file is thought to be the least reliable. To explore this assumption, the proportion of pregnant women whose earliest evidence of vaccination came from the clinical file was quantified and found to be <1% (outlined in **Section 6.3**), which indicated that the potential misclassification introduced by using the earliest record of vaccination was minimal. Pregnant women for whom there was uncertainty in vaccination timing or the type of influenza vaccine received were excluded from analyses using detailed criteria (outlined in **Sections 6.4-6.5**).

Seasonal influenza vaccine uptake in the study population, established using this approach, was found to be similar to national '*Immform'* data.[284, 307-309] Pandemic influenza vaccination uptake established here was also similar to the uptake observed by another study using CPRD over the same period.[312] This detailed and comprehensive approach is likely to have minimized the misclassification of the trimester of vaccination.

Despite the various strengths outlined in this chapter, there are also several challenges in using UK electronic health records to examine the safety of drugs and vaccines administered during pregnancy and the risk of MCMs. These challenges are highlighted in the subsequent chapter.

# 11. Discussion II : Challenges in using UK electronic health records for safety studies concerning major congenital malformations.

The large size, longitudinal nature, generalizability and richness of electronic health record databases makes them a useful resource for pharmacoepidemiological research. Nevertheless, there are a number of potential limitations that need to be considered.

This discussion chapter describes the challenges of using these data to ascertain MCMs and conduct safety studies. These are of course not the only challenges encountered when conducting safety studies with MCMs as the outcome of interest but, rather, the key issues which require particular attention when using electronic health records. **Section 11.1** summarizes the limitations of clinical coding systems and practices, how these affect validity and ascertainment of MCMs, and alternative approaches. **Section 11.2** describes other potential sources of misclassification. **Section 11.3** summarizes the limited ability of these data to examine terminations due to foetal anomaly and the implications of this. **Section 11.4** summarizes the implications of having limited ability to examine major malformation subgroups and individual conditions. In **Sections 11.5 to 11.7**, other potential limitations are considered, including other possible selection bias, residual confounding, and limitations to generalisability.

## 11.1 Validity of MCMs recorded in UK electronic health records: limitations of clinical coding systems and practices.

Misclassification occurs when the information on the outcome, exposure or covariates is incorrect. The systematic review carried out in **Chapter 2** found that validation studies in CPRD have demonstrated high PPVs for congenital malformations overall, major malformations and heart defects (80-100%) and moderate or low PPVs for neural tube defects (71%) and developmental hip dysplasia (56%), respectively.[187, 192, 194, 208, 209, 216, 219, 222]

No estimates of PPV for congenital malformations in HES data were identified but, internationally, studies have examined the validity of ICD codes for MCMs and demonstrated variation in PPV. For example, validation studies of congenital heart defects recorded using ICD-8 and ICD-10 codes in the Danish National Patient Registry have shown high PPV (86-100%) using medical records, echocardiography and/or autopsy reports as reference standards.[315] In the US, validation studies of congenital heart defects recorded using ICD-9 codes in Medicaid claims data, with medical records as the reference standard, have estimated lower PPVs than Danish studies (68-78%).[316, 317] Another US study that examined the validity of congenital heart defects from ICD-9 codes in the US Vaccine Safety Datalink by reviewing medical records found a high PPV (88%).[318] Coding practices across countries vary and so these PPVs are not reliable indicators of the PPV in HES data. However, these studies demonstrate a wide range of PPVs for a single MCM subgroup in secondary care data and therefore highlight the importance of considering the validity of code-lists used to identify MCMs and any resulting misclassification of the outcome of interest in the studies comprising this thesis.

The prevalence of all congenital malformations among live-births is estimated to be 2-3%.[80-82] However, in the work described here, the prevalence of just MCMs was considerably higher. Among the 78,150 infants in the seasonal influenza vaccine safety study, more than 7% had evidence of an MCM recorded in the first year of life. Compared to UK EUROCAT registries, CPRD-HES-ONS data displayed higher prevalence for almost all MCM subgroups, with HES data

accounting for the majority of the difference. Interestingly, MCM prevalence in the US Vaccine Safety Datalink (which includes diagnoses made in hospital) was similar to EUROCAT (1.7% VS 2%) although for some subgroups the prevalence of MCM subgroups was considerably higher than that seen in EUROCAT.[318] The high prevalence of MCMs in the data used in this thesis suggested that although the algorithm developed to identify MCMs for this work had high sensitivity, this may have been at the expense of PPV. Inherent limitations of clinical coding systems and practices could contribute to this elevated prevalence. These limitations and their potential to inflate prevalence estimates are summarized below.

### 11.1.1 Non-specific codes outside of the dedicated congenital malformation chapters

**Diagnostic Read codes from outside the Read 'P' chapter for congenital malformations**

In primary and secondary care records, MCM diagnoses can be encoded using codes from the Read 'P' and ICD-10 'Q' chapters for congenital malformation diagnoses, respectively. MCMs may, however, also be recorded using codes from other chapters that can be used to encode non-congenital conditions. When developing code-lists to identify MCMs from electronic health records, researchers may include codes from dedicated chapters as well as codes from other chapters that could relate to congenital or non-congenital conditions.

Including codes from other chapters may result in more complete ascertainment of individuals with MCMs but may also capture some individuals with non-congenital conditions, thus lowering PPV. The systematic review in **Chapter 2** demonstrated that researchers often considered including relevant diagnostic codes from outside the Read 'P' chapter in their code-lists but did not specify the criteria used to decide their inclusion. Codes beyond the 'Q' ICD-10 chapter were not considered, possibly because clinical coding in hospital data is directly tied to reimbursement and therefore it is less likely that MCMs will be recorded using codes outside of the dedicated chapter for congenital malformation diagnoses.[261]

In line with the above, the ICD-10 code-list developed here to identify individuals with MCMs only included diagnosis codes from the 'Q' ICD-10 chapter whereas the Read code-list included

relevant diagnosis codes regardless of whether they were part of the 'P' chapter for congenital malformations or not (**Chapter 5**). For example, the 'P' chapter code '*congenital mitral stenosis*' was considered alongside the 'G' chapter code '*mitral stenosis*'. Whilst the former code could only relate to a congenital condition, the latter could also be used to encode non-congenital conditions such as mitral stenosis following rheumatic fever.

Read codes outside the 'P' chapter dedicated to congenital malformations were only included if the consultant neonatologist agreed that they were most likely to indicate an MCM in the study population and in the study period. In this example, the 'G' chapter code '*mitral stenosis*' was included because rheumatic fever was not prevalent among children in the UK during the study period. If such a code was present in an individual under 5 years of age, the cause was overwhelmingly likely to be congenital.

The possibility that a small number of infants with diagnosis codes from outside the Read 'P' chapter did not have an MCM cannot be discounted but it is unlikely that the inclusion of such codes drove the large difference in prevalence between CPRD-HES-ONS data and EUROCAT. The requirement for non-'P' chapter Read diagnosis codes to have a congenital aetiology in the majority of the study population during the study period, and the clinical input of a consultant neonatologist, meant their inclusion was unlikely to have lowered the PPV of the algorithm. Furthermore, the difference in prevalence between CPRD-HES-ONS data and EUROCAT appeared to be driven primarily through increased ascertainment in HES data and diagnostic codes from outside the 'Q' chapter for congenital malformations were not used.

**Non-diagnostic codes outside of the 'P' and 'Q' chapters for congenital malformations**

Procedures to repair MCMs are recorded using Read codes in CPRD and OPCS-4 codes in HES but there are no chapters dedicated to procedures for congenital malformations in either coding system. The Read system also allows clinicians to encode other information such as administrative tasks relating to the management of chronic conditions, observations following

examination, and clinical history but again there is no dedicated chapter for those relating specifically to congenital malformations.

Relevant non-diagnostic Read codes from outside the congenital malformation 'P' chapter, and OPCS-4 procedure codes, were only included in code-lists if they were known to relate to a particular MCM. For example, the Read code for '*correction of pectus excavatum*' was included because pectus excavatum is an MCM. Conversely, the Read code for '*insertion of prosthesis into chest wall'* was not included because even though it could relate to a corrective procedure for an MCM, it could also relate to procedures for traumatic injury. Based on these criteria, the use of these codes was also unlikely to explain the elevated prevalence of MCMs observed in these studies.

### 11.1.2 Non-specific codes within chapters dedicated to congenital malformations

**Codes from the 'P' and 'Q' chapters that could relate to major or minor malformations**

Although both the 'P' chapter in the Read system and 'Q' chapter in ICD-10 are dedicated to diagnostic codes for congenital malformations, both contain non-specific codes that could relate to an array of congenital malformations, major and minor. Examples of such codes include '*other congenital deformities of feet*' and '*other congenital deformities of skull, face and jaw'.*

EUROCAT guidelines specify that some non-specific codes should not be used to record MCMs, including *'other congenital deformities of skull, face and jaw'* and '*other congenital deformities of feet*'.[282] However, clinical coders in primary and secondary care do not follow EUROCAT guidelines and may use these codes to record MCM diagnoses. Such codes were retained in code-lists to ensure the ascertainment of those infants who did have an MCM. However, some infants identified using these codes will have had minor malformations which would inflate the prevalence estimates.

The prevalence of limb malformations was 10 times higher in CPRD-HES-ONS compared to EUROCAT, with the majority of this increase attributed to high prevalence in HES (**Section 7.5.1**). This increased prevalence could be explained by the large number of potentially non-specific codes for these conditions in the ICD-10 'Q' chapter and, to a lesser extent, in the Read 'P' chapter. In the work described in this thesis, the proportion of infants with a limb malformation that had a non-specific code as the only recorded evidence of their condition was 52.7% in CPRD and 91.9% in HES (**Section 7.3**). The most common non-specific code among infants with a limb malformation was '*other congenital deformities of feet*' which could refer to any major or minor malformation. Other relatively common, non-specific codes included:

- '*Syndactyly*' and '*fused toes*' - EUROCAT specifies that syndactyly of the 2nd and 3rd toes is a minor malformation but Read and ICD-10 codes do not specify the affected toes.[283]
- Codes relating to hip anomalies such as '*other congenital deformities of hip*' - which could refer to hip dislocations defined as major by EUROCAT, or hip subluxations defined as minor by EUROCAT.[283]
- '*Talipes equinovarus'* - EUROCAT distinguishes between those that are malformations and those that are postural in origin but Read and ICD-10 codes do not. [283]

The ICD-10 coding system used in HES lacks the granularity of the BPA-modified ICD-10 system used by EUROCAT. The BPA-modification adds an extra digit to certain ICD-10 codes which can be used to define malformations not specified explicitly in ICD-10, demonstrate uncertainty in the diagnosis, specify laterality and/or help distinguish between major and minor conditions. For example, in EUROCAT, code Q825 '*congenital non-neoplastic naevus*' can be further specified as Q8250 '*naevus flammeus'*, Q8251 '*strawberry naevus'*, Q8252 '*mongolian blue spot'* and, Q8258 '*other specified congenital non-neoplastic naevus'*.[283] EUROCAT guidelines define Q8250-8252 as minor, but these more detailed codes are unavailable in ICD-10 and so

code Q825 was included.[283] Read codes tend to be more granular than ICD-10 codes as there are often multiple Read codes that relate to a single ICD-10 code. A lack of granularity, among ICD-10 codes in particular, means that minor conditions are likely to be captured and inflate prevalence estimates for MCMs.

Based on the above, non-specific ICD-10 codes from the 'Q' chapter dedicated to congenital malformation diagnoses appeared to be a main driver of the increased prevalence of MCMs seen in the studies described here. Including these non-specific codes in code-lists developed for this work is likely to have identified a number of children with minor malformations and explains the high prevalence of MCMs compared to EUROCAT. Indeed, among the study population for the seasonal vaccine safety analyses, hip conditions, talipes equinovarus and syndactyly were approximately two or more times as prevalent in HES than in EUROCAT, suggesting they played a large part in increasing the prevalence of limb malformations overall. (**Table 8.1**).[294]

The above demonstrates that some individuals who had only a minor malformation are likely to have been included in the study. It is possible that this could occur more frequently among vaccinated women. Women with higher levels of healthcare engagement might be more likely to accept the vaccine and more likely to present infants with minor conditions to healthcare professionals. If these are coded with non-specific codes, infants would be misclassified as having a major malformation and the measure of effect would be inflated. However, there was no evidence for an association between vaccination in pregnancy and any of the major malformations examined in adjusted models.

**Codes for which additional criteria were required to identify MCMs**

Some conditions are only considered by EUROCAT to be true MCMs if they meet additional criteria which may or may not be available to researchers using electronic health records. For example, '*congenital hydronephrosis*' is defined by EUROCAT as an MCM only if there is a pelvis dilatation of >10 mm.[283] Such details are not captured by Read or ICD-10 codes.

Additional details recorded in the free-text of primary care records are not available to researchers. It was therefore not possible to discern whether infants with these codes had an MCM or not. All infants with such codes were conservatively treated as having MCMs. The inclusion of congenital hydronephrosis Read codes were shown to account for an increased prevalence of urinary system malformations in CPRD (**Section 7.4.2**). This was also demonstrated in **Chapter 8**, where the prevalence of congenital hydronephrosis in the HES records of infants in the seasonal influenza vaccines safety study was 16 per 10,000 live-births (**Table 8.1**), twice as high as that reported by EUROCAT.[294]

Some codes are defined as MCMs by EUROCAT provided they are not related to a premature birth. An example of this is '*patent ductus arteriosus*' which is defined as an MCM if the gestational age at birth is at least 37 weeks.[283] In the vaccine safety analyses carried out for this thesis, gestational age at birth was obtained from the Pregnancy Register and was used to determine whether infants with patent ductus arteriosus had an MCM that was unrelated to prematurity. The prevalence of this condition among the study population for the seasonal vaccine safety analysis was considerably higher than the prevalence in UK EUROCAT registries (25 vs 1 per 10,000 births).[294] This could be due to inaccuracies in the recorded gestational age at birth although validation of the Pregnancy Register against matched delivery records in HES found the median weeks difference in gestational age to be 0 (IQR 0-0).[255] The difference in prevalence is more likely to be a result of differences in the thresholds for recording such conditions in electronic health records and EUROCAT (see **Section 11.1.3**).

These two examples demonstrate that non-specific codes for which additional details are required to determine whether they relate to MCMs are likely to have contributed considerably to the elevated prevalence of MCMs seen in this work. These codes were included to ensure that children with severe congenital hydronephrosis or patent ductus arteriosus were not missed.

### 11.1.3 Coding thresholds

The threshold for coding diagnoses in electronic health records is likely lower than that in EUROCAT due to the need for the former to capture the entirety of the patient's medical history. Some MCMs, such as atrial septal defects and patent ductus arteriosus, vary in their severity and may sometimes resolve on their own with time. Less severe MCMs which resolve on their own or do not cause symptoms are less likely to be captured by EUROCAT but may still be encoded in the patient's routine clinical records. As Read and ICD-10 codes do not contain information about the severity of the condition, it is not possible for researchers to distinguish between those conditions which are MCMs and those which resolve on their own or those with no clinical significance. There was evidence to suggest different coding thresholds were another key driver of the increased prevalence seen in CPRD-HES-ONS, with both atrial septal defects and patent ductus arteriosus displaying considerably higher prevalence compared to EUROCAT (**Table 8.1**).[294]

### 11.1.4 Tentative diagnoses

Codes in the patient's record may sometimes reflect tentative diagnoses made by clinicians that require further investigation and have not yet been confirmed. Some may later be found to be unrelated conditions but this will not be known to researchers. Tentative coding is more likely to occur in primary care records due to the role of GPs in referring patients to other areas of the health service for further care and investigation. It may also be less likely in secondary care records due to the close ties between clinical coding and reimbursement.[261] Nevertheless, this could have contributed to an increased prevalence in electronic health records compared to EUROCAT.

### 11.1.5 Temporal changes in coding practices

The quality of coding in electronic health records can vary over time due to changes in coding practices. In primary care, financial incentives are used to drive improvements in the recording of specific data items as part of the Quality and Outcomes Framework.[126] This is unlikely to

have affected the prevalence of MCMs in CPRD as the recording of these conditions is not incentivised. In HES, a 2010 audit report highlighted the need to improve recording of diagnoses and procedures across specialist NHS Trusts as well as the recording of co-morbidities nationally.[319] While this could have resulted in an increase of non-specific coding of co-morbidities, a 2014 audit showed that co-morbidities continued to be under-recorded.[320] The impact of these changes on MCMs recorded in HES is therefore uncertain.

### 11.1.6 Summary of the key factors that may have increased the prevalence of MCMs

The key limitation when identifying MCMs from electronic health records is the uncertainty in the PPV of non-specific codes that are part of the dedicated 'P' and 'Q' chapters for congenital malformations in Read and ICD-10. These non-specific codes can refer to major or minor malformations. Alternatively, they may relate to conditions for which additional details are required to make a judgement on the clinical significance of the condition. Lower coding thresholds in routinely collected electronic health records (compared to EUROCAT) and the potential for tentative diagnoses to be recorded in primary care also have the potential to lower the PPV of code-lists. Finally, whilst diagnostic, procedure and other codes outside of the dedicated congenital malformation chapters were unlikely to have had a considerable effect on the PPV of the code-lists used in this work due to the stringent inclusion criteria employed, they should be recognized as a potential source of non-specificity when planning new studies.

### 11.1.7 Alternative approaches

To increase the PPV of algorithms for the identification of MCMs, some researchers using other electronic data sources incorporated additional rules requiring multiple records of the same diagnosis on different dates or the presence of diagnostic codes in multiple data sources. Studies which have required congenital heart defect codes to be present on at least two dates or present in both in-patient and out-patient records have demonstrated increased PPV compared to algorithms that do not include such rules.[316-318]

Studies using electronic health records should consider developing bespoke algorithms reflecting the expected clinical trajectory of particular MCMs. For example, most congenital diaphragmatic hernias are diagnosed shortly after delivery and undergo a procedure for repair by their first birthday. The identification rule for this condition could be the presence of a diagnosis and procedure in the first year of life. The caveat is that, in this case, the identification rule would not pick up those infants who are diagnosed but not clinically stable enough to undergo a procedure in their first year of life. Further refinement to the algorithm would be needed; for example to consider evidence from death certificates in the absence of other evidence or to consider evidence reflecting sequelae that occur commonly in infants with severe congenital diaphragmatic hernia that are clinically unstable.

This approach would necessitate considerable expert input from a range of clinicians including neonatologists and paediatric surgeons. Furthermore, the usefulness of this approach when using UK hospitalisation data may be limited for those conditions which may be diagnosed around the time of delivery but which are managed in out-patient facilities, as the completeness of recording of diagnoses and procedures in HES out-patient data is currently very low.[261] The low agreement seen between HES admissions data and CPRD in this work (**Chapter 7**) also raises questions about potentially defining MCMs based on the presence of codes in both these data sources. Validation studies examining the PPV of different algorithms for the same condition would be useful when considering combinations of codes and data sources used to identify MCMs.

## 11.2 Other misclassification

### 11.2.1 Misclassification of influenza vaccination status and its timing within pregnancy

As discussed previously, the overall estimates of vaccine uptake were highly comparable to those from the national '*Immform*' data.[284, 307-309] The immunisation and therapy files in CPRD, from which the vast majority of evidence of influenza vaccination receipt was identified, are also considered highly reliable. GPs are also required to document vaccinations that are given

by other healthcare providers, although at the time of the safety study that was carried out for this thesis, vaccination was almost entirely carried out in primary care.[73] Any under-ascertainment of vaccination is likely to be non-differential with respect to major malformations in the infant and would therefore bias the hazard ratio to the null.

A key strength of the work described in this thesis was the use of the Pregnancy Register algorithm, which considers all the available pregnancy data recorded in CPRD to estimate the timing and duration of pregnancy, an approach thought to increase accuracy.[255] However, imprecision in timings could still occur and result in misclassification of the timing of vaccination if, for example, pregnancies were assigned a fixed pregnancy duration due to the absence of records used to estimate the onset of pregnancy.

Pregnancies in the Pregnancy Register were examined carefully to identify any potential for misclassification of the trimester of vaccination. Pregnancies were excluded if the estimated delivery date preceded the infant's month/year of birth or if the duration of the pregnancy was incompatible with a live-birth (**Sections 4.3.2 & 4.3.4**). When determining the trimester in which a woman was vaccinated, all vaccination records across a season were considered and the earliest record was used only after the potential for misclassification introduced by the clinical file was assessed and judged to be very low (**Section 6.3**). Pregnancies were also excluded from analyses if the timing of vaccination was uncertain such as if the woman had evidence of receiving the vaccine somewhere other than her practice. Finally, it was reassuring that a sensitivity analysis exploring first-trimester vaccination and including those vaccinations occurring in the 4 weeks prior to pregnancy also did not find evidence of an association with MCMs.

### 11.2.2 Misclassification of potential confounders

The severe nature of major malformations and the contractual requirement of GPs to document vaccinations means that these are likely to be well-recorded overall. This was not the case for all potential confounders, although the use of multiply-linked data was used to

increase their ascertainment where possible (e.g. for ethnicity) and women had to be registered at a practice for at least six months before the start of pregnancy for the same reason. For smoking, hazardous drinking, and BMI, there was often no record to indicate maternal status at the start of pregnancy and the best possible estimate was obtained by examining all the woman's available records using a series of hierarchical decisions (**Section 4.6**). For smoking and drinking, which are widely discouraged during pregnancy, it was possible that some pregnant women who did participate in these activities did not report doing so and consequently their status was misclassified. Accurate and timely recording of these data is more likely to occur among women who accept vaccination. Misclassification of confounders could have resulted in residual confounding, discussed in **Section 11.6**, below.

### 11.2.3 Further approaches to explore the impact of misclassification.

As discussed above, misclassification of MCMs, maternal influenza vaccination and its timing, and confounders could result, under certain scenarios, in biasing the hazard ratio towards the null. One approach to examine this and to test the dataset's capability to detect associations with MCMs is to use known teratogens as positive controls.

In their 2011 publication, Charlton *et al.* demonstrated that CPRD data could be used to identify the known associations between first trimester sodium valproate monotherapy and risk of spina bifida, and first trimester anti-epileptic drug polytherapy and risk of any MCM, when compared to women with no anti-epileptic drug exposure.[193] However, the effect estimate for spina bifida had very wide 95% confidence intervals due to the small numbers, and evidence for an association between first trimester sodium valproate monotherapy and risk of any MCM was weak (RR, 2.00; 95% CI, 0.99-4.07). When compared to data from the UK Epilepsy and Pregnancy Register, CPRD identified fewer first-trimester exposures to valproate and a lower prevalence of MCMs among such pregnancies; the latter is likely to be due to the use of stand-alone primary care CPRD data, with no linked HES data to maximise ascertainment of MCMs.[193]

In the studies carried out for this thesis, pregnant women in the study population with evidence of exposure to several known teratogenic medications were identified. However, the medications were not used as positive controls. Of the 78,150 pregnancies in the seasonal vaccine safety analysis, 6.1% were found to have an exposure to a teratogenic medication in the period spanning six months before the start of pregnancy and the end of the first trimester. However, only 0.6% of these had a prescription which occurred in the first trimester and the number of MCMs among these was low (n=39). Given these small numbers, it was considered unlikely that these medications would be able to usefully act as positive controls. However, the possibility that an association between influenza vaccination and MCMs was not detected cannot be discounted and future studies should consider the potential use of positive controls to test the ability of such databases to identify the effects of drugs and vaccinations.

## 11.3 Limited ability to examine terminations due to foetal anomaly

UK electronic health records have limited ability to examine MCMs among pregnancies that do not end in a live-birth. MCMs are poorly recorded in the mother's record during the antenatal period and those that are recorded were found to have poor validity (**Section 8.6.1-8.6.2**).

Terminations due to foetal anomaly are of particular interest because over 14% of MCMs reported in UK EUROCAT data between 2010 and 2013 occurred among this particular pregnancy outcome.[294] Terminations due to foetal anomaly can occur if an MCM is detected during the 20-week anomaly scan. TOPFAs account for 1-2% of all terminations and approximately half of these are a result of an MCM, with the most common conditions being malformations of the nervous system and congenital heart defects (the other 50% of TOPFAs are a result of chromosomal anomalies or conditions in which the foetus is affected by maternal factors such as inherited disorders) (**Section 8.7**).[321] UK electronic health records are currently not well placed to examine these outcomes, not only because MCMs detected antenatally are poorly recorded but also because terminations may be carried out by

independent providers and may never be recorded in the pregnant woman's primary care record.

A concern in relation to the safety analyses carried out for this thesis was that restricting the study population to live-born infants could have biased the study findings. This could have occurred if there was differential inclusion of infants with MCMs born to unvaccinated mothers, if these mothers were less likely to attend the 20-week anomaly scan and have the opportunity for a TOPFA. However, almost all the recorded terminations occurred before the 16$^{th}$ week of pregnancy, before the 20-week anomaly scan could take place. In addition, among infants born to unvaccinated women there was no evidence of higher prevalence of the 11 MCMs most likely to result in a TOPFA (**Section 8.7**).

Nevertheless, MCMs that occur frequently among terminated pregnancies are underrepresented in analyses examining live-births and this means that associations between vaccination and these conditions could not be determined. UK EUROCAT registries that collect information on terminations due to foetal anomaly could usefully complement safety studies carried out using electronic health records.

## 11.4 Limited ability to examine major malformation subgroups

Electronic health record databases offer a number of advantages for post-marketing safety studies of drugs and vaccines given in pregnancy including large cohorts, the potential for long-term follow-up and routine data collection. However, even these data may be limited in their ability to detect associations between particular drugs or vaccines and adverse outcomes – particularly if both the exposure to the drug/vaccine and the adverse outcome occur with low frequency in the population.

In the safety analyses, it was not possible to examine the risk of individual MCMs or most MCM subgroups due to their rarity, especially after stratifying by trimester of vaccination. For some MCMs, it was estimated that both the number of women receiving first trimester

vaccination and the number of women never vaccinated would need to be quadrupled to achieve sufficient study power (**Section 8.4**). The decision was therefore taken to examine MCMs as an aggregate outcome, which allowed sufficient power. However, using this aggregate outcome raises the issue that a positive association between first-trimester vaccination and specific MCMs could be masked by a lack of association for other MCMs. As UK electronic health data continue to accumulate, there may be sufficient numbers for future studies to explore the safety of maternal vaccination with respect to specific malformation subgroups or conditions.

## 11.5 Other selection bias

In cohort studies, selection bias can occur when exposed and unexposed groups differ in their follow-up or outcome ascertainment. In **Section 8.7 and 11.3**, the potential for bias due to vaccinated women being more likely to undergo anomaly screening and subsequent termination is discussed. Other possible selection bias also needs consideration.

Over 10% of eligible live-birth pregnancies were excluded from analyses because linkage to infant records was unavailable and the outcome could not be ascertained. The many possible reasons for lack of linkage were discussed in **Section 4.3.8**, the vast majority of which are unlikely to be associated with vaccination. There was a possibility that a small number of infants were not linked because they never registered at the same practice as the mother and these infants may have been more likely to have MCMs (e.g. they never registered because they were hospitalized for prolonged periods, because they died or because the mother moved away). As these scenarios were considered rare and were not necessarily associated with vaccine uptake, the likelihood of selection bias was judged to be low (**Section 8.8**).

## 11.6 Residual confounding

Residual confounding occurs when there are unmeasured differences between exposed and unexposed cohorts that are not adjusted for. Systematic reviews of studies examining

congenital malformations following maternal influenza vaccination highlighted the lack of adjustment for confounders as a key limitation of the available evidence.[20-24] In this work, a large number of potential confounders were identified with the use of a conceptual framework and adjusted for individually and in groups.

The potential for the misclassification of confounders is described in **Section 11.2.2.** There were also some potential confounders that could not be directly measured. One such example was healthcare engagement. Women with higher levels of healthcare engagement are likely to have higher vaccine uptake and may also be more likely to seek care earlier when they become aware that their infant may have a medical condition. This can bias the association of the hazard ratio upwards if infants of women with lower levels of healthcare engagement were less likely to have a major malformation ascertained during follow-up. To some extent, this may have been addressed through analyses that allowed for longer follow-up and by adjusting for factors such as deprivation, ethnicity and geographic region, which could influence healthcare engagement by affecting health beliefs and/or healthcare access. Assessing health beliefs, access and engagement and their contributions as risk factors for congenital malformations has been an area of difficulty in the wider literature and studies have similarly relied on characteristics that are more straightforward to measure. The possibility of residual confounding cannot be discounted, although it was reassuring that fully-adjusted models did not suggest any evidence for an association between maternal influenza vaccination and all major malformations, or limb or heart defects.

## 11.7 Generalisability

The studies described here are only generalizable to pregnancies resulting in a live-born singleton with linked infant records. Results cannot be extrapolated to multiple births or foetal malformations among other pregnancy outcomes such as terminations and pregnancy losses. Although the devolved administrations in the UK are very similar, it is important to note that linked data only include patients from English practices and so may not be generalizable to the

whole of the UK. However, given the biological nature of any associations and the fact that the population of patients with linked data is not considered to be appreciably different to those in the whole of CPRD (which includes patients across the UK), this is unlikely to be the case.[254]

### 11.8 Chapter summary

This chapter highlights the challenges involved when using UK electronic health records to examine MCMs as an outcome of interest in post-marketing safety studies. Previous studies have relied exclusively on primary care data to carry out such analyses. As many MCMs will be diagnosed in a hospital setting, relying on primary care data may result in incomplete capture of MCMs (for example, because encoding these diagnoses may be delayed or because the GP may record diagnoses using free-text or by scanning hospital letters which are unavailable to researchers). Linked primary care, secondary care and mortality data were used to maximize ascertainment of MCMs in this work but limitations of the coding systems, particularly in ICD-10 which contains a large number of non-specific codes, meant that conditions which were minor or non-congenital may have been captured. It was also not possible to examine terminations due to foetal anomalies or specific MCM subgroups and individual conditions in these data. The conclusions that could be drawn from the analyses conducted were therefore limited to live-birth pregnancies and all MCMs, congenital heart defects and limb defects. The final chapter provides a full interpretation of the work as well as recommendations for future research.

# 12. Interpretation, recommendations for future work and conclusions

This chapter begins with a summary of the findings from the studies in this thesis. Recommendations for future research are provided and the chapter ends with the overall conclusions from this work.

## 12.1 Interpretation

Routinely-collected, linked UK electronic health records have a number of strengths that make them well-suited for studies examining the post-marketing safety of drugs and vaccines in pregnancy. However, identifying congenital malformations in these data is not without its challenges and limitations and researchers must consider these for each individual data source.

In primary care data, researchers have to contend with: the use of codes from many different chapters to encode diagnoses; potential delays in recording diagnoses; the possibility that diagnoses have been recorded tentatively and the possibility that diagnoses have been recorded using free-text or by scanning hospital letters which are not available to researchers. However, there is evidence to suggest that congenital malformation diagnoses identified in primary care records are true diagnoses which might explain why post-marketing safety studies have relied on stand-alone primary care records.[187, 192, 194, 208, 209, 216, 219]

In hospital admissions data, there is a paucity of evidence with regards to the validity of congenital malformation diagnoses although the need to record definitive diagnoses for reimbursements suggests the majority of diagnoses are likely to be accurate.[181] This need to record definitive diagnoses is also likely to explain why studies utilizing these data have been able to rely exclusively on the comparatively small number of ICD-10 codes from the dedicated chapter on congenital malformations. A caveat, however, seems to be that ICD-10 codes are sometimes non-specific – making it difficult to distinguish in some instances whether individuals with such codes have major or minor conditions, and increasing prevalence

estimates of MCMs. This perhaps explains why no previous study using secondary care data has attempted to distinguish between major and minor malformations.

Linkage of primary care records and hospital admissions data has the potential to increase the ascertainment of congenital malformations and mitigate the issues around delayed recording and use of free-text or scanned hospital letters in primary care. Indeed, linkage in the work described here demonstrated that a sizeable proportion of these diagnoses are recorded exclusively in hospital admissions data. However, this needs to be carefully balanced against the potential loss of power that can come with linkage as well as the potential of decreased PPV if non-specific ICD-10 codes are included. Validation studies using hospitalization data are needed to inform the inclusion of these non-specific codes. Linked death records and procedure data from hospital admissions only identified a small number of additional individuals but may prove useful for future studies requiring evidence of MCMs from multiple codes or data sources.

Linked primary care, secondary care and mortality data were used to conduct the vaccine safety studies in this thesis. There is a fairly large body of evidence on the safety of PIIV and the results in this study were highly consistent with that.[20-24] No association with major malformations was found in any trimester, regardless of follow-up time, and measures of effect were similar to those pooled from several previous studies. This supports the methods used in this thesis and the analysis of the safety of SIIV which also found no evidence for an association with major malformations, limb malformations or heart defects among live-births.

This was the first such study in the UK and in Europe. Overall, it adds further weight to the good safety profile of this vaccine in pregnant women. Based on this evidence and the evidence that the vaccine is known to provide moderate/good protection against lab-confirmed influenza in pregnant women and their newborn infants, healthcare providers should continue to feel confident in offering the vaccine to pregnant women. This work did not, however, examine terminations due to foetal anomaly and therefore the interpretation of

results cannot be extrapolated to the MCMs that are typically detected antenatally and associated with induced terminations.

## 12.2 Recommendations for further research

The work in this thesis has consistently highlighted that further validation studies of congenital malformation diagnoses in UK electronic health records would be useful. Validation studies of MCM diagnoses recorded in HES have not been carried out and are needed to establish the PPV of codes from the 'Q' ICD-10 chapter, with a particular emphasis on the PPV of non-specific 'Q' chapter codes that could refer to major or minor conditions.

Although validation studies in primary care data are available and have indicated generally good PPV for congenital malformations overall, for MCMs and for congenital heart defects, validation studies of additional MCM subgroups are needed. Furthermore, validation studies have mainly examined the PPV of recorded diagnoses and little is known about other measures of validity (e.g. sensitivity, specificity and negative predictive value). Future studies should consider examining these other measures of validity. Further validation studies could also provide an opportunity to assess the validity of non-specific Read codes in the 'P' chapter that could encode major or minor malformations, and codes outside the 'P' chapter that could be used by clinicians to code both congenital and non-congenital conditions. Work will also be needed to assess the validity of the equivalent SNOMED codes to the Read codes currently used for MCMs as UK general practices switch from the Read coding system to use of SNOMED.[247]

One future potential and feasible approach to increase the PPV of algorithms used to identify MCMs, is to consider defining cases as those with multiple records of the same diagnosis (or a diagnosis and procedure) on different dates or as those with codes in multiple data sources. The validity of these algorithms could be tested and compared with those that require only a single code to be present. A current constraint to such an approach is that primary care physicians are not obliged to record diagnoses repeatedly, and in-patient HES data are

restricted to diagnoses made during a hospital admission. Children with MCMs may have multiple encounters with healthcare but many such encounters will be in hospital outpatient settings and, currently, diagnostic information in outpatient HES has very low levels of completeness. As diagnostic coding in these outpatient data improves with time, safety studies may be able to better identify children with MCMs who have multiple diagnostic codes recorded, as well as including individuals with MCMs who are managed predominantly in these settings. The work in this thesis also identified variation in the recording of congenital malformation diagnoses across data sources. Therefore, in parallel, future researchers should also attempt to examine whether there are any factors that increase the propensity of a diagnosis to be encoded in one data source but not another.

Although further validation studies are needed, this will not be feasible for many researchers due to constraints around time and funding. The validity of the dataset can, in these cases, be examined in part by testing its ability to detect a known teratogenic association such as the one between valproate and spina bifida – although this does depend on having sufficient numbers and statistical power to detect such an association.

Indeed, as data accrue, future research on maternal influenza vaccination safety should attempt to assess additional malformation subgroups and individual conditions. With the exception of limb and heart defects, there were not enough cases in the data used for this thesis to examine particular subgroups or conditions. As data continue to accumulate over time, and with the new availability of linked hospital and primary care data from CPRD Aurum practices and the planned extension of the Pregnancy Register to CPRD Aurum data, it may be possible to explore these when sufficient numbers become available. [322]

If possible, future work should also aim to complement available evidence which has focused primarily on MCMs among live-births with assessments of terminations due to foetal anomalies. In the short term, possible complementary studies could be explored using data from UK EUROCAT registries that collect information on terminations due to foetal anomaly,

with additional data collection on vaccination status. In the longer term, any future move to link CPRD data to the UK National Congenital Anomaly and Rare Disease Registration Service data would enable examination of associations between maternal influenza vaccination and malformations that are diagnosed antenatally and result in a termination.

Examining longer-term paediatric outcomes such as pervasive developmental disorders would also be useful as numbers become available. Ongoing efforts to link hospital data to educational databases is also likely to provide an opportunity to examine long-term educational outcomes. Although this thesis has focused on outcomes among infants, future research should also consider other pregnancy and maternal outcomes which continue to concern pregnant women.

## 12.3 Conclusions

Routinely-collected, multiply-linked UK electronic health records can be used to investigate congenital malformations in post-marketing safety studies of drugs and vaccines given in pregnancy. Linkage of these data maximizes ascertainment of these rare conditions but raises important questions about how to interpret and handle differential recording of diagnoses across data sources. Population-based historical cohort studies using linked primary care records, hospital admissions and mortality data were carried out to assess the safety of SIIV and PIIV in pregnancy, stratified by trimester. There was no evidence to suggest that receipt of either of these vaccines, in any individual trimester or at any time in pregnancy, was associated with major malformations recorded in the year after delivery. Results were similar when examining major malformations in early childhood. Future studies should consider examining terminations due to foetal anomalies, additional malformation subgroups and long-term paediatric outcomes such as pervasive developmental disorder.

# References


1. World Health Organization. Influenza (Seasonal) Fact Sheet. 2018. Available from: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal).
2. Cox NJ, Subbarao K. Global epidemiology of influenza: past and present. Annu Rev Med. 2000;51:407-21
3. World Health Organization. The immunological basis for immunization series: Influenza vaccines. 2017.
4. Smeaton L, Green D. Influenza vaccination in pregnancy: A review. British Journal of Midwifery. 2017;25(10):624-9
5. Public Health England. The Green Book Chapter 19: Influenza. 2019. Available from: https://www.gov.uk/government/publications/influenza-the-green-book.
6. World Health Organization. Pandemic Influenza. 2019. Available from: http://www.euro.who.int/en/health-topics/communicable-diseases/influenza/pandemic-influenza.
7. Public Health England. The Green Book Chapter 23a: Pandemic influenza. 2009. Available from:https://webarchive.nationalarchives.gov.uk/20101122195608/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_110403.pdf
8. World Health Organization. Influenza Vaccines: WHO Position Paper. Wkly Epid Rec. 2005;80(33):279
9. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB, Centers for Disease C, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2004 May 28;53(RR-6):1-40
10. European Centre for Disease Prevention and Control. Seasonal influenza vaccination in Europe. Vaccination recommendations and coverage rates in the EU Member States for eight influenza seasons: 2007–2008 to 2014–2015. 2017.
11. Ng S, Wu P, Nishiura H, Ip DKM, Lee EST, Cowling BJ. An analysis of national target groups for monovalent 2009 pandemic influenza vaccine and trivalent seasonal influenza vaccines in 2009-10 and 2010-11. BMC Infectious Diseases. 2011;11(1):230
12. Donaldson L, Beasley C, Ridge K. The H1N1 swine flu vaccination programme 2009-2010. 2009.
13. Davies S, Beasley C, Ridge K. The influenza immunisation programme 2010/11. 2010.
14. European Centre for Disease Prevention and Control. Seasonal influenza vaccination and antiviral use in EU/EEA Member States. 2018.
15. Campbell H, Van Hoek AJ, Bedford H, Craig L, Yeowell A-L, Green D, et al. Attitudes to immunisation in pregnancy among women in the UK targeted by such programmes. British Journal of Midwifery. 2015;23(8):566-73
16. Wilcox CR, Calvert A, Metz J, Kilich E, MacLeod R, Beadon K, et al. Determinants of Influenza and Pertussis Vaccination Uptake in Pregnancy: A Multicenter Questionnaire Study of Pregnant Women and Healthcare Professionals. Pediatr Infect Dis J. 2019;38(6):625-30
17. Yuen CY, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women - a systematic review. Vaccine. 2014;32(36):4602-13
18. Bratton KN, Wardle MT, Orenstein WA, Omer SB. Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis. Clinical infectious diseases. 2015;60(5):e11-9
19. Fell DB, Platt RW, Lanes A, Wilson K, Kaufman JS, Basso O, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. BJOG. 2015;122(1):17-26
20. McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine. 2015;33(18):2108-17

21. Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj C. Vaccines for preventing influenza in healthy adults. The Cochrane database of systematic reviews. 2018;2:CD001269

22. Giles ML, Krishnaswamy S, Macartney K, Cheng A. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. Hum Vaccin Immunother. 2019;15(3):687-99
23. Polyzos KA, Konstantelias AA, Pitsa CE, Falagas ME. Maternal Influenza Vaccination and Risk for Congenital Malformations: A Systematic Review and Meta-analysis. Obstetrics and gynecology. 2015;126(5):1075-84
24. Jeong S, Jang EJ, Jo J, Jang S. Effects of maternal influenza vaccination on adverse birth outcomes: A systematic review and Bayesian meta-analysis. PloS one. 2019;14(8):e0220910
25. Woolston W, Conley D. Epidemic pneumonia (spanish influenza) in pregnancy: Effect in one hundred and one cases. Journal of the American Medical Association. 1918;71(23):1898-9
26. Harris JW. Influenza occurring in pregnant women: A statistical study of thirteen hundred and fifty cases. Journal of the American Medical Association. 1919;72(14):978-80
27. Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. American journal of obstetrics and gynecology. 2011;205(1):10-8
28. Campbell A, Rodin R, Kropp R, Mao Y, Hong Z, Vachon J, et al. Risk of severe outcomes among patients admitted to hospital with pandemic (H1N1) influenza. CMAJ. 2010;182(4):349-55
29. Fuhrman C, Bonmarin I, Paty AC, Duport N, Chiron E, Lucas E, et al. Severe hospitalised 2009 pandemic influenza A(H1N1) cases in France, 1 July-15 November 2009. Eurosurveillance. 2010;14;15(2)
30. Gerardin P, El Amrani R, Cyrille B, Gabriele M, Guillermin P, Boukerrou M, et al. Low clinical burden of 2009 pandemic influenza A (H1N1) infection during pregnancy on the island of La Reunion. PloS one. 2010;5(5):e10896
31. Hanslik T, Boelle PY, Flahault A. Preliminary estimation of risk factors for admission to intensive care units and for death in patients infected with A(H1N1)2009 influenza virus, France, 2009-2010. PLoS currents. 2010;2:Rrn1150
32. Kelly H, Mercer G, Cheng A. Quantifying the risk of pandemic influenza in pregnancy and indigenous people in Australia in 2009. Eurosurveillance. 2009;14(50)
33. Koegelenberg CF, Irusen EM, Cooper R, Diacon AH, Taljaard JJ, Mowlana A, et al. High mortality from respiratory failure secondary to swine-origin influenza A (H1N1) in South Africa. QJM. 2010;103(5):319-25
34. Oliveira W, Carmo E, Penna G, Kuchenbecker R, Santos H, Araujo W, et al. Pandemic H1N1 influenza in Brazil: analysis of the first 34,506 notified cases of influenza-like illness with severe acute respiratory infection (SARI). Eurosurveillance. 2009;14(42)
35. Yang P, Deng Y, Pang X, Shi W, Li X, Tian L, et al. Severe, critical and fatal cases of 2009 H1N1 influenza in China. The Journal of infection. 2010 Oct;61(4):277-83
36. Zarychanski R, Stuart TL, Kumar A, Doucette S, Elliott L, Kettner J, et al. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. CMAJ. 2010 Feb 23;182(3):257-64
37. Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. The Lancet Infectious diseases. 2008 Jan;8(1):44-52
38. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. American journal of epidemiology. 1998 Dec 1;148(11):1094-102
39. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk J. Saving Lives, Improving Mothers' Care Lessons learned to inform future maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity, 2009-2012. 2014.

40. Fell DB, Savitz DA, Kramer MS, Gessner BD, Katz MA, Knight M, et al. Maternal influenza and birth outcomes: systematic review of comparative studies. BJOG. 2017 Jan;124(1):48-59
41. Skowronski DM, De Serres G. Is routine influenza immunization warranted in early pregnancy? Vaccine. 2009 Jul 30;27(35):4754-70
42. Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Jr., Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. The New England journal of medicine. 2000 Jan 27;342(4):225-31
43. Ampofo K, Gesteland PH, Bender J, Mills M, Daly J, Samore M, et al. Epidemiology, complications, and cost of hospitalization in children with laboratory-confirmed influenza infection. Pediatrics. 2006 Dec;118(6):2409-17
44. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report: Recommendations and Reports. 2005;54(8):1-41
45. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. The New England journal of medicine. 2014 Sep 4;371(10):918-31
46. Tapia MD, Sow SO, Tamboura B, Teguete I, Pasetti MF, Kodio M, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. The Lancet Infectious diseases. 2016 Sep;16(9):1026-35
47. Omer SB, Richards JL, Madhi SA, Tapia MD, Steinhoff MC, Aqil AR, et al. Three randomized trials of maternal influenza immunization in Mali, Nepal, and South Africa: Methods and expectations. Vaccine. 2015 Jul 31;33(32):3801-12
48. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. The New England journal of medicine. 2008 Oct 9;359(15):1555-64
49. Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. American journal of perinatology. 2004 Aug;21(6):333-9
50. Munoz FM, Greisinger AJ, Wehmanen OA, Mouzoon ME, Hoyle JC, Smith FA, et al. Safety of influenza vaccination during pregnancy. American journal of obstetrics and gynecology. 2005 Apr;192(4):1098-106
51. Munoz F, Mouzoon M, Smith F, editors. Safety and effectiveness of influenza vaccine in pregnant women and their infants. Pediatric Academic Societies' Annual Meeting; 2007.
52. France EK, Smith-Ray R, McClure D, Hambidge S, Xu S, Yamasaki K, et al. Impact of maternal influenza vaccination during pregnancy on the incidence of acute respiratory illness visits among infants. Archives of pediatrics & adolescent medicine. 2006 Dec;160(12):1277-83
53. Haberg SE, Trogstad L, Gunnes N, Wilcox AJ, Gjessing HK, Samuelsen SO, et al. Risk of fetal death after pandemic influenza virus infection or vaccination. The New England journal of medicine. 2013 Jan 24;368(4):333-40
54. Mølgaard-Nielsen D, Fischer T, Krause T, Hviid A. Effectiveness of maternal immunization with trivalent inactivated influenza vaccine in pregnant women and their infants. Journal of internal medicine. 2019;286(4):469-80
55. Richards JL, Hansen C, Bredfeldt C, Bednarczyk RA, Steinhoff MC, Adjaye-Gbewonyo D, et al. Neonatal outcomes after antenatal influenza immunization during the 2009 H1N1 influenza pandemic: impact on preterm birth, birth weight, and small for gestational age birth. Clinical infectious diseases. 2013 May;56(9):1216-22
56. Steinhoff MC, Katz J, Englund JA, Khatry SK, Shrestha L, Kuypers J, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. The Lancet infectious diseases. 2017;17(9):981-989.

57. Thompson MG, Kwong JC, Regan AK, Katz MA, Drews SJ, Azziz-Baumgartner E, et al. Influenza Vaccine Effectiveness in Preventing Influenza-associated Hospitalizations During Pregnancy: A Multi-country Retrospective Test Negative Design Study, 2010-2016. Clinical infectious diseases. 2019 Apr 24;68(9):1444-53
58. Thompson MG, Li DK, Shifflett P, Sokolow LZ, Ferber JR, Kurosky S, et al. Effectiveness of seasonal trivalent influenza vaccine for preventing influenza virus illness among pregnant women: a population-based case-control study during the 2010-2011 and 2011-2012 influenza seasons. Clinical infectious diseases. 2014 Feb;58(4):449-57
59. Centers for Disease Control and Prevention. Vaccine Effectiveness: How Well Do the Flu Vaccines Work? 2018. Available from: https://www.cdc.gov/flu/vaccines-work/vaccineeffect.htm.
60. Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vazquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clinical infectious diseases. 2010 Dec 15;51(12):1355-61
61. Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, et al. Maternal influenza vaccination and effect on influenza virus infection in young infants. Archives of pediatrics & adolescent medicine. 2011 Feb;165(2):104-11
62. Poehling KA, Szilagyi PG, Staat MA, Snively BM, Payne DC, Bridges CB, et al. Impact of maternal immunization on influenza hospitalizations in infants. American journal of obstetrics and gynecology. 2011 Jun;204(6 Suppl 1):S141-8
63. Dabrera G, Zhao H, Andrews N, Begum F, Green H, Ellis J, et al. Effectiveness of seasonal influenza vaccination during pregnancy in preventing influenza infection in infants, England, 2013/14. Eurosurveillance. 2014;19(45):20959
64. Shakib JH, Korgenski K, Presson AP, Sheng X, Varner MW, Pavia AT, et al. Influenza in Infants Born to Women Vaccinated During Pregnancy. Pediatrics. 2016 Jun;137(6)
65. Walker JL, Zhao H, Dabrera G, Andrews N, Thomas SL, Tsang C, et al. Assessment of Effectiveness of Seasonal Influenza Vaccination During Pregnancy in Preventing Influenza Infection in Infants in England, 2013-2014 and 2014-2015. J Infect Dis. 2020 Jan 1;221(1):16-20
66. Schmid P, Rauber D, Betsch C, Lidolt G, Denker ML. Barriers of Influenza Vaccination Intention and Behavior - A Systematic Review of Influenza Vaccine Hesitancy, 2005 - 2016. PloS one. 2017;12(1):e0170550
67. MacDougall DM, Halperin SA. Improving rates of maternal immunization: Challenges and opportunities. Hum Vaccin Immunother. 2016 Apr 2;12(4):857-65
68. Wilson RJ, Paterson P, Jarrett C, Larson HJ. Understanding factors influencing vaccination acceptance during pregnancy globally: A literature review. Vaccine. 2015 Nov 25;33(47):6420-9
69. Wilson R, Paterson P, Larson HJ. Strategies to improve maternal vaccination acceptance. BMC Public Health. 2019 Mar 25;19(1):342
70. McDonald H, Moren C, Scarlett J. Health inequalities in timely antenatal care: audit of pre- and post-referral delays in antenatal bookings in London 2015-16. J Public Health. 2020.
71. Baxter D. Approaches to the vaccination of pregnant women: experience from Stockport, UK, with prenatal influenza. Hum Vaccin Immunother. 2013 Jun;9(6):1360-3
72. Bisset KA, Paterson P. Strategies for increasing uptake of vaccination in pregnancy in high-income countries: A systematic review. Vaccine. 2018 May 11;36(20):2751-9
73. NHS England. Enhanced services specification: Seasonal influenza and pneumococcal immunisation enhanced service. 2014. Available from: https://www.england.nhs.uk/wp-content/uploads/2014/06/flu-pneumo-immu-spec.pdf
74. Department of Health and Social Care. The influenza immunisation programme 2013/14. 2013.
75. Health Protection Agency. Pandemic H1N1 (Swine) Influenza Vaccine Uptake amongst Patient Groups in Primary Care in England 2009/10. 2010.
76. Health Protection Agency. Surveillance of influenza and other respiratory viruses in the UK: 2011-2012 report. 2012.

77. Public Health England. Surveillance of influenza and other respiratory viruses in the UK: Winter 2018 to 2019. 2019.
78. Department of Health and Social Care. The national flu immunisation programme 2019/20. 2019.
79. World Health Organization. Congenital anomalies. 2016. Available from: https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies.
80. Centers for Disease Control and Prevention. Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. MMWR Morb Mortal Wkly Rep. 2008 Jan 11;57(1):1-5
81. Christianson A, Howson CP, Modell B. March of Dimes: global report on birth defects, the hidden toll of dying and disabled children. 2005.
82. Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. Adv Exp Med Biol. 2010;686:349-64
83. British Isles Network of Congenital Anomaly Registers. Congenital Anomaly Statistics 2012: England and Wales. 2014. Available from: http://www.binocar.org/content/Annual%20report%202012_FINAL_nologo.pdf
84. World Health Organization. Birth Defects: Report by the Secretariat. 2010. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_10-en.pdf
85. Centers for Disease Control and Prevention. Congenital anomalies – definitions. 2018. Available from: https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-1/chapter1-4.html
86. Boyd PA, Haeusler M, Barisic I, Loane M, Garne E, Dolk H. Paper 1: the EUROCAT network—organization and processes. Birth Defects Research Part A: Clinical and Molecular Teratology. 2011;91(S1):S2-S15
87. Rehman W, Arfons LM, Lazarus HM. The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development. Ther Adv Hematol. 2011 Oct;2(5):291-308
88. Lerner KL, Lerner BW. Medicine, health, and bioethics: essential primary sources. 2006.
89. Keller-Stanislawski B, Englund JA, Kang G, Mangtani P, Neuzil K, Nohynek H, et al. Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. Vaccine. 2014 Dec 12;32(52):7057-64
90. Sheffield JS, Greer LG, Rogers VL, Roberts SW, Lytle H, McIntire DD, et al. Effect of influenza vaccination in the first trimester of pregnancy. Obstetrics and gynecology. 2012 Sep;120(3):532-7
91. Louik C, Ahrens K, Kerr S, Pyo J, Chambers C, Jones KL, et al. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: exposure prevalence, preterm delivery, and specific birth defects. Vaccine. 2013 Oct 17;31(44):5033-40
92. Chambers CD, Johnson D, Xu R, Luo Y, Louik C, Mitchell AA, et al. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants. Vaccine. 2013 Oct 17;31(44):5026-32
93. Cleary BJ, Rice U, Eogan M, Metwally N, McAuliffe F. 2009 A/H1N1 influenza vaccination in pregnancy: uptake and pregnancy outcomes - a historical cohort study. Eur J Obstet Gynecol Reprod Biol. 2014 Jul;178:163-8
94. Kallen B, Olausson PO. Vaccination against H1N1 influenza with Pandemrix((R)) during pregnancy and delivery outcome: a Swedish register study. BJOG. 2012 Dec;119(13):1583-90
95. Oppermann M, Fritzsche J, Weber-Schoendorfer C, Keller-Stanislawski B, Allignol A, Meister R, et al. A(H1N1)v2009: a controlled observational prospective cohort study on vaccine safety in pregnancy. Vaccine. 2012 Jun 22;30(30):4445-52
96. Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. JAMA. 2012 Jul 11;308(2):165-74

97. Deinard AS, Ogburn P, Jr. A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome. American journal of obstetrics and gynecology. 1981;140(3):240-5
98. Launay O, Krivine A, Charlier C, Truster V, Tsatsaris V, Lepercq J, et al. Low rate of pandemic A/H1N1 2009 influenza infection and lack of severe complication of vaccination in pregnant women: a prospective cohort study. PloS one. 2012;7(12):e52303

99. Mackenzie IS, MacDonald TM, Shakir S, Dryburgh M, Mantay BJ, McDonnell P, et al. Influenza H1N1 (swine flu) vaccination: a safety surveillance feasibility study using self-reporting of serious adverse events and pregnancy outcomes. Br J Clin Pharmacol. 2012 May;73(5):801-11
100. Rubinstein F, Micone P, Bonotti A, Wainer V, Schwarcz A, Augustovski F, et al. Influenza A/H1N1 MF59 adjuvanted vaccine in pregnant women and adverse perinatal outcomes: multicentre study. BMJ. 2013 Feb 4;346:f393
101. Chambers CD, Johnson DL, Xu R, Luo YJ, Louik C, Mitchell AA, et al. Safety of the 2010–11, 2011–12, 2012–13, and 2013–14 seasonal influenza vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS. Vaccine. 2016;34(37):4443-9
102. Fabiani M, Bella A, Rota MC, Clagnan E, Gallo T, D'Amato M, et al. A/H1N1 pandemic influenza vaccination: A retrospective evaluation of adverse maternal, fetal and neonatal outcomes in a cohort of pregnant women in Italy. Vaccine. 2015 May 5;33(19):2240-7
103. Kharbanda EO, Vazquez-Benitez G, Romitti PA, Naleway AL, Cheetham TC, Lipkind HS, et al. First Trimester Influenza Vaccination and Risks for Major Structural Birth Defects in Offspring. J Pediatr. 2017;187:234-9 e4
104. Louik C, Kerr S, Van Bennekom CM, Chambers C, Jones KL, Schatz M, et al. Safety of the 2011-12, 2012-13, and 2013-14 seasonal influenza vaccines in pregnancy: Preterm delivery and specific malformations, a study from the case-control arm of VAMPSS. Vaccine. 2016;34(37):4450-9
105. Ludvigsson JF, Strom P, Lundholm C, Cnattingius S, Ekbom A, Ortqvist A, et al. Risk for Congenital Malformation With H1N1 Influenza Vaccine: A Cohort Study With Sibling Analysis. Ann Intern Med. 2016 Dec 20;165(12):848-55
106. McNeil MM, Gee J, Weintraub ES, Belongia EA, Lee GM, Glanz JM, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine. 2014;32(42):5390-8
107. Trotta F, Da Cas R, Spila Alegiani S, Gramegna M, Venegoni M, Zocchetti C, et al. Evaluation of safety of A/H1N1 pandemic vaccination during pregnancy: cohort study. BMJ. 2014;348:g3361
108. Lin TH, Lin SY, Lin CH, Lin RI, Lin HC, Chiu TH, et al. AdimFlu-S((R)) influenza A (H1N1) vaccine during pregnancy: the Taiwanese Pharmacovigilance Survey. Vaccine. 2012 Mar 30;30(16):2671-5
109. Heikkinen T, Young J, van Beek E, Franke H, Verstraeten T, Weil JG, et al. Safety of MF59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study. American journal of obstetrics and gynecology. 2012 Sep;207(3):177 e1-8
110. UK Teratology Information Service. Scientific Publications. 2013. Available from: http://www.uktis.org/html/scientific_publications.html.
111. UK Teratology Information Service. Reporting an exposure in pregnancy. 2018. Available from: http://www.uktis.org/html/reporting.html.
112. UK Epilepsy & Pregnancy Register. UK Epilepsy & Pregnancy Register. 2016. Available from: http://www.epilepsyandpregnancy.co.uk/home.htm.
113. UK Epilepsy & Pregnancy Register. Publications. 2016. Available from: http://www.epilepsyandpregnancy.co.uk/pages/publications.htm.

114. Richardson JL, Martin F, Dunstan H, Greenall A, Stephens S, Yates LM, et al. Pregnancy outcomes following maternal venlafaxine use: A prospective observational comparative cohort study Reprod Toxicol. 2019 Mar;84:108-113.
115. British and Irish Network of Congenital Anomaly Researchers. Papers. Available from: http://www.binocar.org/ourresearch/papers.
116. Public Health England. National Congenital Anomaly and Rare Disease Registration Service: Congenital anomaly statistics 2016. 2018. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/751553/Congenital_anomaly_statistics_2016.pdf
117. Greenlees R, Neville A, Addor MC, Amar E, Arriola L, Bakker M, et al. Paper 6: EUROCAT member registries: organization and activities. Birth Defects Research Part A: Clinical and Molecular Teratology. 2011;91(S1):S51-S100

118. Kinsner-Ovaskainen A, Lanzoni M, Garne E, Loane M, Morris J, Neville A, et al. A sustainable solution for the activities of the European network for surveillance of congenital anomalies: EUROCAT as part of the EU Platform on Rare Diseases Registration. Eur J Med Genet. 2018 Sep;61(9):513-7
119. Budd JLS. Regional congenital anomaly registers in the UK. Obstetrics, Gynaecology & Reproductive Medicine. 2007;17(11):333-4
120. EUROCAT. PHE Northern England. 2020. Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-members/registries/PHE-Northern%20England_en.
121. EUROCAT. PHE Wessex. 2020. Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-members/registries/PHE%20Wessex_en.
122. British and Irish Network of Congenital Anomaly Researchers. Wessex Antenatally Detected Anomalies Register (WANDA). 2011. Available from: http://www.binocar.org/wanda.
123. Public Health England. National congenital anomaly and rare disease registration service: Congenital anomaly statistics 2015. 2017. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/716574/Congenital_anomaly_statistics_2015_v2.pdf
124. EUROCAT. PHE Thames Valley. 2020. Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-members/registries/PHE%20Thames%20Valley_en.
125. The Cleft Registry and Audit Network. Annual Report on cleft lip and/or palate. 2012.
126. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015 Jun;44(3):827-36
127. Gnani S, Majeed A. A user's guide to data collected in primary care in England. 2006.
128. Wachter R. Making IT work: harnessing the power of health information technology to improve care in England. Report to the National Advisory Group on Health Information Technology in England. 2016. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/550866/Wachter_Review_Accessible.pdf
129. Hollier LM, Leveno KJ, Kelly MA, McIntire DD, Cunningham FG. Maternal age and malformations in singleton births. Obstetrics & Gynecology. 2000;96(5, Part 1):701-6
130. Loane M, Dolk H, Morris J. Maternal age-specific risk of non-chromosomal anomalies. BJOG. 2009;116(8):1111-9
131. Morris JK, Wald Nj Fau - Mutton DE, Mutton De Fau - Alberman E, Alberman E. Comparison of models of maternal age-specific risk for Down syndrome live births. Prenat Diagn. 2003;23(3):252-8.
132. Loane M, Dolk H Fau - Bradbury I, Bradbury I. Increasing prevalence of gastroschisis in Europe 1980-2002: a phenomenon restricted to younger mothers? Paediatr Perinat Epidemiol. 2007;21(4):363-9.

133. Reefhuis J, Honein MA. Maternal age and non-chromosomal birth defects, Atlanta--1968-2000: teenager or thirty-something, who is at risk? Birth Defects Res A Clin Mol Teratol. 2004;70(9):572-9.
134. Kazaura MR, Lie Rt Fau - Irgens LM, Irgens Lm Fau - Didriksen A, Didriksen A Fau - Kapstad M, Kapstad M Fau - Egenaes J, Egenaes J Fau - Bjerkedal T, et al. Increasing risk of gastroschisis in Norway: an age-period-cohort analysis. American Journal of Epidemiology. 2004;159(4):358-363.
135. Goetzinger KR, Shanks AL, Odibo AO, Macones GA, Cahill AG. Advanced maternal age and the risk of major congenital anomalies. Am J Perinatol. 2017;34(3):217-222.
136. Baird PA, Sadovnick AD, Yee IM. Maternal age and birth defects: a population study. The Lancet. 1991;337(8740):527-30
137. Pradat P. Epidemiology of major congenital heart defects in Sweden, 1981-1986. Journal of Epidemiology & Community Health. 1992;46(3):211-5

138. Frederiksen LE, Ernst A, Brix N, Lauridsen LLB, Roos L, Ramlau-Hansen CH, et al. Risk of adverse pregnancy outcomes at advanced maternal age. Obstetrics & Gynecology. 2018;131(3):457-63
139. Sheridan E, Wright J, Small N, Corry PC, Oddie S, Whibley C, et al. Risk factors for congenital anomaly in a multiethnic birth cohort: an analysis of the Born in Bradford study. The Lancet. 2013;382(9901):1350-9
140. Knowles RL, Ridout D, Crowe S, Bull C, Wray J, Tregay J, et al. Ethnic and socioeconomic variation in incidence of congenital heart defects. Archives of Disease in Childhood. 2017;102(6):496-502
141. Bittles AH. Consanguineous marriages and congenital anomalies. Lancet. 2013 Oct 19;382(9901):1316-7
142. Weightman AL, Morgan HE, Shepherd MA, Kitcher H, Roberts C, Dunstan FD. Social inequality and infant health in the UK: systematic review and meta-analyses. BMJ Open. 2012;2(3)
143. Matijasevich A, Victora CG, Lawlor DA, Golding J, Menezes AM, Araujo CL, et al. Association of socioeconomic position with maternal pregnancy and infant health outcomes in birth cohort studies from Brazil and the UK. J Epidemiol Community Health. 2012 Feb;66(2):127-35
144. Vrijheid M, Dolk H, Stone D, Abramsky L, Alberman E, Scott JE. Socioeconomic inequalities in risk of congenital anomaly. Arch Dis Child. 2000 May;82(5):349-52
145. Yang J, Carmichael SL, Canfield M, Song J, Shaw GM, National Birth Defects Prevention S. Socioeconomic status in relation to selected birth defects in a large multicentered US case-control study. American journal of epidemiology. 2008 Jan 15;167(2):145-54
146. Richardson SD, Josberger RE. Maternal Medicaid Recipient Status and Congenital Malformations among New York State Live Births in 2010. Birth Defects Res. 2017 Nov 1;109(18):1460-70
147. Yu D, Feng Y, Yang L, Da M, Fan C, Wang S, et al. Maternal socioeconomic status and the risk of congenital heart defects in offspring: a meta-analysis of 33 studies. PloS one. 2014;9(10):e111056
148. Rankin J, Pattenden S, Abramsky L, Boyd P, Jordan H, Stone D, et al. Prevalence of congenital anomalies in five British regions, 1991-99. Arch Dis Child Fetal Neonatal Ed. 2005 Sep;90(5):F374-9
149. Armstrong BG, Dolk H, Pattenden S, Vrijheid M, Loane M, Rankin J, et al. Geographic variation and localised clustering of congenital anomalies in Great Britain. Emerg Themes Epidemiol. 2007 Jul 6;4:14
150. Yang J, Qiu H, Qu P, Zhang R, Zeng L, Yan H. Prenatal Alcohol Exposure and Congenital Heart Defects: A Meta-Analysis. PloS one. 2015;10(6):e0130681

151. Grewal J, Carmichael SL, Ma C, Lammer EJ, Shaw GM. Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies. Birth Defects Res A Clin Mol Teratol. 2008 Jul;82(7):519-26
152. Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. BJOG. 2007 Mar;114(3):243-52
153. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. Hum Reprod Update. 2011;17(5):589-604
154. Leite M, Albieri V, Kjaer SK, Jensen A. Maternal smoking in pregnancy and risk for congenital malformations: results of a Danish register-based cohort study. Acta Obstet Gynecol Scand. 2014 Aug;93(8):825-34
155. Stegmann BJ, Carey JC. TORCH Infections. Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections. Curr Womens Health Rep. 2002 Aug;2(4):253-8
156. Luteijn JM, Brown MJ, Dolk H. Influenza and congenital anomalies: a systematic review and meta-analysis. Hum Reprod. 2014 Apr;29(4):809-23
157. Moretti ME, Bar-Oz B, Fried S, Koren G. Maternal hyperthermia and the risk for neural tube defects in offspring: systematic review and meta-analysis. Epidemiology. 2005 Mar;16(2):216-9
158. Ludvigsson JF, Neovius M, Soderling J, Gudbjornsdottir S, Svensson AM, Franzen S, et al. Periconception glycaemic control in women with type 1 diabetes and risk of major birth defects: population based cohort study in Sweden. BMJ. 2018 Jul 5;362:k2638
159. Garne E, Loane M, Dolk H, Barisic I, Addor MC, Arriola L, et al. Spectrum of congenital anomalies in pregnancies with pregestational diabetes. Birth Defects Res A Clin Mol Teratol. 2012 Mar;94(3):134-40
160. Tomson T, Xue H, Battino D. Major congenital malformations in children of women with epilepsy. Seizure. 2015 May;28:46-50
161. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. BJOG. 2013 Jun;120(7):812-22
162. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014 Apr 15;348:g2301
163. Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. The New England journal of medicine. 2006 Jun 8;354(23):2443-51
164. Seely EW, Ecker J. Chronic hypertension in pregnancy. Circulation. 2014 Mar 18;129(11):1254-61
165. Li DK, Yang C, Andrade S, Tavares V, Ferber JR. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: a retrospective cohort study. BMJ. 2011 Oct 18;343:d5931
166. Bateman BT, Huybrechts KF, Fischer MA, Seely EW, Ecker JL, Oberg AS, et al. Chronic hypertension in pregnancy and the risk of congenital malformations: a cohort study. American journal of obstetrics and gynecology. 2015 Mar;212(3):337 e1-14
167. Stothard KJ, Tennant PW, Bell R, Rankin J. Maternal overweight and obesity and the risk of congenital anomalies: a systematic review and meta-analysis. JAMA. 2009 Feb 11;301(6):636-50
168. Persson M, Cnattingius S, Villamor E, Soderling J, Pasternak B, Stephansson O, et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. BMJ. 2017 Jun 14;357:j2563
169. Rankin J, Tennant PW, Stothard KJ, Bythell M, Summerbell CD, Bell R. Maternal body mass index and congenital anomaly risk: a cohort study. Int J Obes. 2010 Sep;34(9):1371-80

170. Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. Pediatrics. 2003 May;111(5 Pt 2):1152-8
171. Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, et al. Prepregnancy obesity as a risk factor for structural birth defects. Archives of pediatrics & adolescent medicine. 2007 Aug;161(8):745-50
172. Feng Y, Yu D, Chen T, Liu J, Tong X, Yang L, et al. Maternal parity and the risk of congenital heart defects in offspring: a dose-response meta-analysis of epidemiological observational studies. PloS one. 2014;9(10):e108944
173. Glinianaia SV, Tennant PW, Rankin J. Risk estimates of recurrent congenital anomalies in the UK: a population-based register study. BMC Med. 2017 Jan 31;15(1):20
174. Duong HT, Hoyt AT, Carmichael SL, Gilboa SM, Canfield MA, Case A, et al. Is maternal parity an independent risk factor for birth defects? Birth Defects Res A Clin Mol Teratol. 2012 Apr;94(4):230-6
175. Charlton R, Snowball J, Sammon C, de Vries C. The Clinical Practice Research Datalink for drug safety in pregnancy research: an overview. Therapie. 2014;69(1):83-9
176. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ. 2014 Jul 11;349:g4219

177. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). International Journal of Epidemiology. 2017;46(4):1093-1093i
178. Office For National Statistics. User guide to mortality statistics. 2018. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017
179. Dave S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. Pharmacoepidemiol Drug Saf. 2009 Aug;18(8):704-7
180. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. British journal of clinical pharmacology. 2010;69(1):4-14
181. Burns EM, Rigby E, Mamidanna R, Bottle A, Aylin P, Ziprin P, et al. Systematic review of discharge coding accuracy. J Public Health. 2012 Mar;34(1):138-48
182. Clinical Practice Research Datalink. Bibliography. 2020. Available from: https://www.cprd.com/Bibliography/
183. QResearch. Research Papers. 2020. Available from: https://www.qresearch.org/publications/research-papers/.
184. Boston Collaborative Drug Surveillance Program. Publications. 2019. Available from: http://www.bu.edu/bcdsp/publications-2/
185. The Health Improvement Network. Publications. 2019. Available from: https://www.ucl.ac.uk/epidemiology-health-care/research/primary-care-and-population-health/research/thin-database/publications.
186. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36
187. Cea-Soriano L, Garcia-Rodriguez LA, Brodovicz KG, Masso Gonzalez E, Bartels DB, Hernandez-Diaz S. Safety of non-insulin glucose-lowering drugs in pregnant women with pre-gestational diabetes: A cohort study. Diabetes Obes Metab. 2018 Jul;20(7):1642-51
188. Baril L, Rosillon D, Willame C, Angelo MG, Zima J, van den Bosch JH, et al. Risk of spontaneous abortion and other pregnancy outcomes in 15-25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom. Vaccine. 2015 Nov 27;33(48):6884-91
189. Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C, Troncon MG, Agostinis L, Wallander MA, et al. Use of cimetidine, omeprazole, and ranitidine in pregnant women and pregnancy outcomes. American journal of epidemiology. 1999 Sep 1;150(5):476-81

190. Petersen I, Collings SL, McCrea RL, Nazareth I, Osborn DP, Cowen PJ, et al. Antiepileptic drugs prescribed in pregnancy and prevalence of major congenital malformations: comparative prevalence studies. Clin Epidemiol. 2017;9:95-103
191. Petersen I, Sammon CJ, McCrea RL, Osborn DPJ, Evans SJ, Cowen PJ, et al. Risks associated with antipsychotic treatment in pregnancy: Comparative cohort studies based on electronic health records. Schizophr Res. 2016 Oct;176(2-3):349-56
192. Charlton RA, Snowball JM, Nightingale AL, Davis KJ. Safety of Fluticasone Propionate Prescribed for Asthma During Pregnancy: A UK Population-Based Cohort Study. J Allergy Clin Immunol Pract. 2015 Sep-Oct;3(5):772-9 e3
193. Charlton RA, Weil JG, Cunnington MC, Ray S, de Vries CS. Comparing the General Practice Research Database and the UK Epilepsy and Pregnancy Register as tools for postmarketing teratogen surveillance: anticonvulsants and the risk of major congenital malformations. Drug Saf. 2011 Feb 1;34(2):157-71
194. Charlton RA, Weil JG, Cunnington MC, de Vries CS. Identifying major congenital malformations in the UK General Practice Research Database (GPRD): a study reporting on the sensitivity and added value of photocopied medical records and free text in the GPRD. Drug Saf. 2010 Sep 1;33(9):741-50
195. Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. Nicotine replacement therapy in pregnancy and major congenital anomalies in offspring. Pediatrics. 2015 May;135(5):859-67
196. Ban L, Gibson JE, West J, Fiaschi L, Sokal R, Smeeth L, et al. Maternal depression, antidepressant prescriptions, and congenital anomaly risk in offspring: a population-based cohort study. BJOG. 2014 Nov;121(12):1471-81
197. Ban L, Tata LJ, Fiaschi L, Card T. Limited risks of major congenital anomalies in children of mothers with IBD and effects of medications. Gastroenterology. 2014 Jan;146(1):76-84
198. Ban L, West J, Gibson JE, Fiaschi L, Sokal R, Doyle P, et al. First trimester exposure to anxiolytic and hypnotic drugs and the risks of major congenital anomalies: a United Kingdom population-based cohort study. PloS one. 2014;9(6):e100996
199. Ban L, Fleming KM, Doyle P, Smeeth L, Hubbard RB, Fiaschi L, et al. Congenital Anomalies in Children of Mothers Taking Antiepileptic Drugs with and without Periconceptional High Dose Folic Acid Use: A Population-Based Cohort Study. PloS one. 2015;10(7):e0131130
200. Ban L, West J, Abdul Sultan A, Dhalwani NN, Ludvigsson JF, Tata LJ. Limited risks of major congenital anomalies in children of mothers with coeliac disease: a population-based cohort study. BJOG. 2015 Dec;122(13):1833-41
201. Sokal R, Fleming KM, Tata LJ. Potential of general practice data for congenital anomaly research: Comparison with registry data in the United Kingdom. Birth Defects Res A Clin Mol Teratol. 2013 Aug;97(8):546-53
202. Sokal R, Tata LJ, Fleming KM. Sex prevalence of major congenital anomalies in the United Kingdom: a national population-based study and international comparison meta-analysis. Birth Defects Res A Clin Mol Teratol. 2014 Feb;100(2):79-91
203. Vasilakis-Scaramozza C, Aschengrau A, Cabral HJ, Jick SS. Asthma drugs and the risk of congenital anomalies. Pharmacotherapy. 2013 Apr;33(4):363-8
204. Vasilakis-Scaramozza C, Aschengrau A, Cabral H, Jick SS. Antidepressant use during early pregnancy and the risk of congenital anomalies. Pharmacotherapy. 2013 Jul;33(7):693-700
205. Vasilakis-Scaramozza C, Aschengrau A, Cabral HJ, Jick SS. Antihypertensive drugs and the risk of congenital anomalies. Pharmacotherapy. 2013 May;33(5):476-82
206. Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, et al. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population-based study. Thorax. 2008 Nov;63(11):981-7
207. Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. Pharmacotherapy. 1999 Feb;19(2):221-2

208. Jick SS, Terris BZ. Anticonvulsants and congenital malformations. Pharmacotherapy. 1997 May-Jun;17(3):561-4
209. Devine S, West SL, Andrews E, Tennis P, Eaton S, Thorp J, et al. Validation of neural tube defects in the full featured--general practice research database. Pharmacoepidemiol Drug Saf. 2008 May;17(5):434-44
210. Tata LJ, Card TR, Logan RF, Hubbard RB, Smith CJ, West J. Fertility and pregnancy-related events in women with celiac disease: a population-based cohort study. Gastroenterology. 2005 Apr;128(4):849-55
211. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. Renal failure in patients with neurogenic lower urinary tract dysfunction. Neuroepidemiology. 2001 May;20(2):138-43
212. Lawrenson R, Wyndaele JJ, Vlachonikolis I, Farmer C, Glickman S. A UK general practice database study of prevalence and mortality of people with neural tube defects. Clin Rehabil. 2000 Dec;14(6):627-30
213. Chi CC, Mayon-White RT, Wojnarowska FT. Safety of topical corticosteroids in pregnancy: a population-based cohort study. J Invest Dermatol. 2011 Apr;131(4):884-91
214. Petersen I, Evans SJ, Gilbert R, Marston L, Nazareth I. Selective serotonin reuptake inhibitors and congenital heart anomalies: comparative cohort studies of women treated before and during pregnancy and their children. J Clin Psychiatry. 2016 Jan;77(1):e36-42
215. Margulis AV, Abou-Ali A, Strazzeri MM, Ding Y, Kuyateh F, Frimpong EY, et al. Use of selective serotonin reuptake inhibitors in pregnancy and cardiac malformations: a propensity-score matched cohort in CPRD. Pharmacoepidemiol Drug Saf. 2013 Sep;22(9):942-51
216. Hammad TA, Margulis AV, Ding Y, Strazzeri MM, Epperly H. Determining the predictive value of Read codes to identify congenital cardiac malformations in the UK Clinical Practice Research Datalink. Pharmacoepidemiol Drug Saf. 2013 Nov;22(11):1233-8
217. Billett J, Cowie MR, Gatzoulis MA, Vonder Muhll IF, Majeed A. Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis. Heart. 2008 Sep;94(9):1194-9
218. Wurst KE, Ephross SA, Loehr J, Clark DW, Guess HA. Evaluation of the General Practice Research Database congenital heart defects prevalence: comparison to United Kingdom national systems. Birth Defects Res A Clin Mol Teratol. 2007 Apr;79(4):309-16
219. Wurst KE, Ephross SA, Loehr J, Clark DW, Guess HA. The utility of the general practice research database to examine selected congenital heart defects: a validation study. Pharmacoepidemiol Drug Saf. 2007 Aug;16(8):867-77
220. Bannister J, Szatkowski L, Sharkey D, Tan S, Fiaschi L, Ban L. Early Life Incidence of Gastrointestinal and Respiratory Infections in Children With Gastroschisis: A Cohort Study. J Pediatr Gastroenterol Nutr. 2018 Nov;67(5):580-5
221. Perry DC, Bruce CE, Pope D, Dangerfield P, Platt MJ, Hall AJ. Comorbidities in Perthes' disease: a case control study using the General Practice Research database. J Bone Joint Surg Br. 2012 Dec;94(12):1684-9
222. Broadhurst C, Rhodes AML, Harper P, Perry DC, Clarke NMP, Aarvold A. What is the incidence of late detection of developmental dysplasia of the hip in England?: a 26-year national study of children diagnosed after the age of one. Bone Joint J. 2019 Mar;101-B(3):281-7
223. Zylbersztejn A, Gilbert R, Hjern A, Hardelid P. Origins of disparities in preventable child mortality in England and Sweden: a birth cohort study. Arch Dis Child. 2020 Jan;105(1):53-61
224. Zylbersztejn A, Gilbert R, Hjern A, Wijlaars L, Hardelid P. Child mortality in England compared with Sweden: a birth cohort study. Lancet. 2018 May 19;391(10134):2008-18
225. Dimopoulos K, Muthiah K, Alonso-Gonzalez R, Banner NR, Wort SJ, Swan L, et al. Heart or heart-lung transplantation for patients with congenital heart disease in England. Heart. 2019 Apr;105(8):596-602

226. Kempny A, Dimopoulos K, Uebing A, Diller GP, Rosendahl U, Belitsis G, et al. Outcome of cardiac surgery in patients with congenital heart disease in England between 1997 and 2015. PloS one. 2017;12(6):e0178963
227. Singhal A, Ross J, Seminog O, Hawton K, Goldacre MJ. Risk of self-harm and suicide in people with specific psychiatric and physical disorders: comparisons between disorders using English national record linkage. J R Soc Med. 2014 May;107(5):194-204
228. Billett J, Majeed A, Gatzoulis M, Cowie M. Trends in hospital admissions, in-hospital case fatality and population mortality from congenital heart disease in England, 1994 to 2004. Heart. 2008 Mar;94(3):342-8
229. Fitzsimons KJ, Copley LP, van der Meulen JH, Panagamuwa C, Deacon SA. Grommet Surgery in Children With Orofacial Clefts in England. Cleft Palate Craniofac J. 2017 Jan;54(1):80-9
230. Fitzsimons KJ, Copley LP, Smallridge JA, Clark VJ, van der Meulen JH, Deacon SA. Hospital admissions for dental treatment among children with cleft lip and/or palate born between 1997 and 2003: an analysis of Hospital Episode Statistics in England. Int J Paediatr Dent. 2014 May;24(3):200-8
231. Fitzsimons KJ, Copley LP, Deacon SA, van der Meulen JH. Hospital care of children with a cleft in England. Arch Dis Child. 2013 Dec;98(12):970-4
232. Fitzsimons KJ, Mukarram S, Copley LP, Deacon SA, van der Meulen JH. Centralisation of services for children with cleft lip or palate in England: a study of hospital episode statistics. BMC Health Serv Res. 2012 Jun 10;12:148
233. McAllister DA, Morling JR, Fischbacher CM, Reidy M, Murray A, Wood R. Enhanced detection services for developmental dysplasia of the hip in Scottish children, 1997-2013. Arch Dis Child. 2018 Nov;103(11):1021-6
234. Dharmasena A, Keenan T, Goldacre R, Hall N, Goldacre MJ. Trends over time in the incidence of congenital anophthalmia, microphthalmia and orbital malformation in England: database study. Br J Ophthalmol. 2017 Jun;101(6):735-9
235. Lansdale N, Al-Khafaji N, Green P, Kenny SE. Population-level surgical outcomes for infantile hypertrophic pyloric stenosis. J Pediatr Surg. 2018 Mar;53(3):540-4
236. Wilkinson DJ, Green PA, Beglinger S, Myers J, Hudson R, Edgar D, et al. Hypospadias surgery in England: Higher volume centres have lower complication rates. J Pediatr Urol. 2017 Oct;13(5):481 e1- e6
237. Jarvis S, Fraser LK. Comparing routine inpatient data and death records as a means of identifying children and young people with life-limiting conditions. Palliat Med. 2018 Feb;32(2):543-53
238. Jarvis S, Parslow RC, Carragher P, Beresford B, Fraser LK. How many children and young people with life-limiting conditions are clinically unstable? A national data linkage study. Arch Dis Child. 2017 Feb;102(2):131-8
239. Fraser LK, Lidstone V, Miller M, Aldridge J, Norman P, McKinney PA, et al. Patterns of diagnoses among children and young adults with life-limiting conditions: A secondary analysis of a national dataset. Palliat Med. 2014 Jun;28(6):513-20
240. Fraser LK, Miller M, Hain R, Norman P, Aldridge J, McKinney PA, et al. Rising national prevalence of life-limiting conditions in children in England. Pediatrics. 2012 Apr;129(4):e923-9
241. Ferencz C, Loffredo C, Correa-Villasenor A, Wilson P. Genetic and environmental risk factors of major cardiovascular malformations: the Baltimore-Washington Infant Study: 1981–1989. Perspectives in pediatric cardiology. 1997;5:867-8
242. Wren C, Richmond S, Donaldson L. Temporal variability in birth prevalence of cardiovascular malformations. Heart. 2000 Apr;83(4):414-9
243. Lewis JD, Bilker Wb Fau - Weinstein RB, Weinstein Rb Fau - Strom BL, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiology and Drug Safety. 2005;14(7):443-451.

244. Bishop C, Small N, Mason D, Corry P, Wright J, Parslow RC, et al. Improving case ascertainment of congenital anomalies: findings from a prospective birth cohort with detailed primary care record linkage. BMJ Paediatr Open. 2017;1(1):e000171
245. Zylbersztejn A, Verfurden M, Hardelid P, Gilbert R, Wijlaars L. Phenotyping congenital anomalies in administrative hospital records. Paediatr Perinat Epidemiol. 2020 Jan;34(1):21-8
246. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS medicine. 2015 Oct;12(10):e1001885
247. NHS Digital. SNOMED CT Implementation in Primary Care. 2019. Available from: https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct/snomed-ct-implementation-in-primary-care.
248. Walley T, Mantgani A. The UK general practice research database. The Lancet. 1997;350(9084):1097-9
249. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Therapeutic advances in drug safety. 2012;3(2):89-99
250. Garcia Rodriguez LA, Perez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol. 1998;45(5):419-25
251. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, vanStaa T, Grundy E, et al. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. Journal of Public Health. 2013;36(4):684-92
252. Padmanabhan S, Carty L, Cameron E, Ghosh RE, Williams R, Strongman H. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. European Journal of Epidemiology. 2019;34(1):91-9
253. Setakis E, Puri S, Williams TJ, Vanstaa TP. 736. Representiveness of Subset of the General Practice Research Database (gprd) Linked to Other Data Sources. Pharmacoepidemiology and Drug Safety. 2010;19:S311
254. Gallagher AM, Puri S, van Staa TP. 528. Linkage of the General Practice Research Database
(gprd) with Other Data Sources. Pharmacoepidemiology and Drug Safety. 2011;20:230-1
255. Minassian C, Williams R, Meeraus WH, Smeeth L, Campbell OMR, Thomas SL. Methods to generate and validate a Pregnancy Register in the UK Clinical Practice Research Datalink primary care database. Pharmacoepidemiology and Drug Safety. 2019 Jun 13;28(7)
256. Charlton R. The General Practice Research Database as an alternative to registries for studying drug safety in pregnancy: anticonvulsants as a case study. University of Bath; 2012.
257. Andrade SE, Raebel MA, Morse AN, Davis RL, Chan KA, Finkelstein JA, et al. Use of prescription medications with a potential for fetal harm among pregnant women. Pharmacoepidemiology and drug safety. 2006;15(8):546-54
258. Devine S, West S, Andrews E, Tennis P, Hammad TA, Eaton S, et al. The identification of pregnancies within the general practice research database. Pharmacoepidemiology and drug safety. 2010;19(1):45-50
259. Hardy JR, Holford TR, Hall GC, Bracken MB. Strategies for identifying pregnancies in the automated medical records of the General Practice Research Database. Pharmacoepidemiology and drug safety. 2004;13(11):749-59
260. Sultan AA, West J, Tata LJ, Fleming KM, Nelson-Piercy C, Grainge MJ. Risk of first venous thromboembolism in pregnant women in hospital: population based cohort study from England. BMJ. 2013;347:f6099
261. Boyd A. Understanding Hospital Episode Statistics (HES). London, UK: CLOSER. 2017. Available from: https://www.closer.ac.uk/wp-content/uploads/CLOSER-resource-Understanding-HES.pdf
262. Medicines and Healthcare products Regulatory Agency. CPRD linked data. 2019. Available from: https://www.cprd.com/linked-data.

263. NHS Digital. The HES processing cycle and data quality. 2016.
264. Dattani N, Rowan S. Causes of neonatal deaths and stillbirths: a new hierarchical classification in ICD-10 Presents a hierarchical classification that will be used for deriving a single cause group for stillbirths and neonates in ICD-10 replacing the classifications used in ICD-9. Health Statistics Quarterly. 2002 (15):16-22
265. Office For National Statistics. User guide to child and infant mortality statistics. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetochildmortalitystatistics.
266. Gallagher AM, Dedman D, Padmanabhan S, Leufkens HGM, de Vries F. The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. Pharmacoepidemiol Drug Saf. 2019 May;28(5):563-9
267. Office For National Statistics. Impact of registration delays on morality statistics. 2016. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/impactofregistrationdelaysonmortalitystatistics2016.

268. Mathers CD, Ma Fat D, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. Bulletin of the world health organization. 2005;83:171-7c
269. Department for Communities and Local Government. The English indices of deprivation 2015: Technical Report. 2015. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/464485/English_Indices_of_Deprivation_2015_-_Technical-Report.pdf.
270. National Health Service. Stillbirth. 2018. Available from: https://www.nhs.uk/conditions/stillbirth/.
271. National Health Service. Miscarriage. 2018. Available from: https://www.nhs.uk/conditions/miscarriage/.
272. National Health Service. Abortion. 2018. Available from: https://www.nhs.uk/conditions/abortion/.
273. Stegmann BJ, Carey JC. TORCH Infections. Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections. Curr Womens Health Rep. 2002;2(4):253-8.
274. Evans C, Chasekwa B, Ntozini R, Humphrey JH, Prendergast AJ. Head circumferences of children born to HIV-infected and HIV-uninfected mothers in Zimbabwe during the preantiretroviral therapy era. AIDS. 2016;30(15):2323-8
275. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. The New England journal of medicine. 1998 Apr 16;338(16):1128-37
276. British National Formulary. Cytotoxic drugs. 2020. Available from: https://bnf.nice.org.uk/treatment-summary/cytotoxic-drugs.html.
277. British National Formulary. Thalidomide. 2020. Available from: https://bnf.nice.org.uk/drug/thalidomide.html#monitoringRequirements.
278. Royal College of General Practitioners Research and Surveillance Centre. Weekly Returns Service Annual Report 2014-15. 2015. Available from: https://www.rcgp.org.uk//media/Files/CIRC/Research-and-Surveillance-Centre/RSC-Annual-Report-1415/RCGP-RSC-Annual-Report-2014_15_Online.ashx?la=en
279. Charlton RA, Weil Jg Fau - Cunnington MC, Cunnington Mc Fau - de Vries CS, de Vries CS. Identifying major congenital malformations in the UK General Practice Research Database (GPRD): a study reporting on the sensitivity and added value of photocopied medical records and free text in the GPRD. Drug Saf. 2010;33(9):741-750.

280. Sokal R, Fleming K,Tata LJ. Potential of general practice data for congenital anomaly research: Comparison with registry data in the United Kingdom. Birth Defects Res A Clin Mol Teratol. 2013 Aug;97(8):546-53
281. Wurst KE, Ephross S, Loehr J, Clark D, Guess HA. Evaluation of the General Practice Research Database congenital heart defects prevalence: comparison to United Kingdom national systems. Birth Defects Res A: Clin Mol Teratol. 2007;79(4):309-16
282. EUROCAT. Malformation Coding Guides. 2017. Available from: http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/malformationcodingguides.
283. EUROCAT Central Registry. Eurocat Guide 1.4, Section 3.3: EUROCAT subgroups of congenital anomalies. 2016 [on 23.9.16]. Available from: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/Section%203.3-%2027_Oct2016.pdf.
284. Public Health England. Surveillance of influenza and other respiratory viruses, including novel respiratory viruses, in the United Kingdom: Winter 2012/13. 2013
285. Public Health England. Surveillance of influenza and other respiratory viruses in the United Kingdom: Winter 2015 to 2016. 2015.
286. Charlton RA, Cunnington MC, de Vries CS, Weil JG. Data resources for investigating drug exposure during pregnancy and associated outcomes: the General Practice Research Database (GPRD) as an alternative to pregnancy registries. Drug Saf. 2008;31(1):39-51
287. NHS England. eDischarge summaries. 2019. Available from: https://digital.nhs.uk/services/transfer-of-care-initiative/edischarge-summaries.
288. Baker R, Tata LJ, Kendrick D, Orton E. Identification of incident poisoning, fracture and burn events using linked primary care, secondary care and mortality data from England: implications for research and surveillance. Inj Prev. 2016 Feb;22(1):59-67
289. Crooks CJ, Card TR, West J. Defining upper gastrointestinal bleeding from linked primary and secondary care data and the effect on occurrence and 28 day mortality. BMC Health Serv Res. 2012 Nov 13;12:392
290. McDonald L, Sammon CJ, Samnaliev M, Ramagopalan S. Under-recording of hospital bleeding events in UK primary care: a linked Clinical Practice Research Datalink and Hospital Episode Statistics study. Clin Epidemiol. 2018;10:1155-68
291. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ. 2013 May 20;346:f2350
292. Hammad TA, Margulis AV, Ding Y, Strazzeri MM, Epperly H. Determining the predictive value of Read codes to identify congenital cardiac malformations in the UK Clinical Practice Research Datalink. Pharmacoepidemiology and drug safety. 2013;22(11):1233-8
293. Wurst KE, Ephross SA, Loehr J, Clark DW, Guess H. The utility of the general practice research database to examine selected congenital heart defects: a validation study. Pharmacoepidemiology and drug safety. 2007;16(8):867-77
294. EUROCAT. Prevalence chats and tables. 2019. Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en.
295. EUROCAT. Data Quality Indicators 2011-2015. 2018. Available from: http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators
296. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. American journal of obstetrics and gynecology. 2012 Sep;207(3 Suppl):S3-8
297. Fell DB, Azziz-Baumgartner E, Baker MG, Batra M, Beauté J, Beutels P, et al. Influenza epidemiology and immunization during pregnancy: Final report of a World Health Organization working group. Vaccine. 2017;35(43):5738-50
298. Thompson MG, Kwong JC, Regan AK, Katz MA, Drews SJ, Azziz-Baumgartner E, et al. Influenza Vaccine Effectiveness in Preventing Influenza-associated Hospitalizations During Pregnancy: A Multi-country Retrospective Test Negative Design Study, 2010-2016. Clinical infectious diseases. 2018 Oct 11;68(9):1444-53

299. World Health Organization. Vaccines against influenza WHO position paper - November 2012. 2012. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23210147.
300. Yuen CYS, Tarrant M. Determinants of uptake of influenza vaccination among pregnant women–a systematic review. Vaccine. 2014;32(36):4602-13
301. Bishop C, Small N, Mason D, Corry P, Wright J, Parslow RC, et al. Improving case ascertainment of congenital anomalies: findings from a prospective birth cohort with detailed primary care record linkage. BMJ Paediatrics Open. 2017;1(1)
302. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ. 2013;346:f2350
303. Jain A, van Hoek AJ, Walker JL, Mathur R, Smeeth L, Thomas SL. Identifying social factors amongst older individuals in linked electronic health records: An assessment in a population based study. PloS one. 2017;12(11):e0189038
304. Centers for Disease Control and Prevention. What are birth defects? 2019. Available from: https://www.cdc.gov/ncbddd/birthdefects/facts.html.
305. National Institute for Health and Clinical Excellence: Guidance. Antenatal Care: Routine Care for the Healthy Pregnant Woman London. 2008. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21370514.
306. Health Protection Agency. Surveillance of influenza and other respiratory viruses in the UK: 2010-2011 report. 2011
307. Public Health England. Surveillance of influenza and other respiratory viruses in the United Kingdom: Winter 2013 to 2014. 2014
308. Public Health England. Surveillance of influenza and other respiratory viruses in the United Kingdom: Winter 2014 to 2015. 2015
309. Public Health England. Surveillance of influenza and other respiratory viruses in the United Kingdom: Winter 2015 to 2016. 2016
310. National Health Service. 20-week scan. 2018. Available from: https://www.nhs.uk/conditions/pregnancy-and-baby/20-week-scan/.
311. Public Health England. Screening key performance indicators: latest data publications. 2019. Available from: https://phescreening.blog.gov.uk/2020/01/10/screening-key-performance-indicators-latest-data-publications/.
312. Sammon CJ, Snowball J, McGrogan A, de Vries CS. Evaluating the hazard of foetal death following H1N1 influenza vaccination; a population based cohort study in the UK GPRD. PloS one. 2012 Dec 20;7(12):e51734
313. Massin MM, Dessy H. Delayed recognition of congenital heart disease. Postgrad Med J. 2006 Jul;82(969):468-70
314. Walsh LK, Donelle J, Dodds L, Hawken S, Wilson K, Benchimol EI, et al. Health outcomes of young children born to mothers who received 2009 pandemic H1N1 influenza vaccination during pregnancy: retrospective cohort study. BMJ. 2019 Jul 10;366:l4151
315. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. Clin Epidemiol. 2015;7:449-90
316. Cooper WO, Hernandez-Diaz S, Gideon P, Dyer SM, Hall K, Dudley J, et al. Positive predictive value of computerized records for major congenital malformations. Pharmacoepidemiol Drug Saf. 2008 May;17(5):455-60
317. Palmsten K, Huybrechts KF, Kowal MK, Mogun H, Hernandez-Diaz S. Validity of maternal and infant outcomes within nationwide Medicaid data. Pharmacoepidemiol Drug Saf. 2014 Jun;23(6):646-55
318. Kharbanda EO, Vazquez-Benitez G, Romitti PA, Naleway AL, Cheetham TC, Lipkind HS, et al. Identifying birth defects in automated data sources in the Vaccine Safety Datalink. Pharmacoepidemiol Drug Saf. 2017 Apr;26(4):412-20
319. Audit Commission. Improving data quality in the NHS: Annual report on the PbR assurance programme. 2010. Available from:

https://webarchive.nationalarchives.gov.uk/20150406162523/http://archive.audit-commission.gov.uk/auditcommission/sitecollectiondocuments/Downloads/26082010pbrnhsdataqualityreport.pdf.
320. CAPITA. The quality of clinical coding in the NHS. 2014. Available from: https://www.chks.co.uk/userfiles/files/The_quality_of_clinical_coding_in_the_NHS.pdf.
321. Department of Health and Social Care. Abortion Statistics, England and Wales: 2018. 2019. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/808556/Abortion_Statistics__England_and_Wales_2018__1_.pdf.
322. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. International journal of epidemiology. 2019 Dec 1;48(6):1740-g

# Appendices

## Appendix 1 – Systematic review search strategy

The search strategy used in Medline is provided as an example, below. The systematic review was a component of a wider search strategy that included publications in the US and Europe and also examined additional diagnoses such as pervasive developmental disorders.

| Search # | Search term (keyword/free text or MeSH) |
|---|---|
| 1 | Malformatio* |
| 2 | Congenital |
| 3 | Birth defect* |
| 4 | Developmental adj5 defect* |
| 5 | Developmental adj5 anomal* |
| 6 | Developmental adj5 abnormalit* |
| 7 | Developmental adj5 disabilit* |
| 8 | Developmental adj5 disorder* |
| 9 | Developmental adj5 deform* |
| 10 | Minor anomal* |
| 11 | Minor abnormalit* |
| 12 | Minor disorde* |
| 13 | Minor defect* |
| 14 | Minor deform* |
| 15 | Major anomal* |
| 16 | Major abnormalit* |
| 17 | Major disorde* |
| 18 | Major defect* |
| 19 | Major deform* |
| 20 | Teratogen* |
| 21 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 |
| 22 | Septal defect* |
| 23 | Transposition* of great vessel* |
| 24 | Tetralog* of fallot |
| 25 | Pulmonary valve stenos* |
| 26 | Coarction of aorta |
| 27 | Hypoplastic left heart |
| 28 | Patent ductus arteriosus |
| 29 | Limb adj3 defect* |
| 30 | Clubfoot |
| 31 | Club-foot |
| 32 | Talipes |
| 33 | Polydactyl* |
| 34 | Syndactyl* |
| 35 | Neural tube defect* |
| 36 | Hydrocephal* |
| 37 | Anencephal* |
| 38 | Microcephal* |
| 39 | Spina bifida |
| 40 | Hypospadia* |
| 41 | Oesophageal atresia* |
| 42 | Anorectal atresia* |
| 43 | Anorectal stenos* |

| Search # | Search term (keyword/free text or MeSH) |
|---|---|
| 44 | Diaphragmatic hernia* |
| 45 | Abdominal wall defect* |
| 46 | Gastroschisis |
| 47 | Omphalocele |
| 48 | Oro-facial cleft* |
| 49 | Orofacial cleft* |
| 50 | Skeletal dysplasia* |
| 51 | Cleft lip |
| 52 | Cleft palate |
| 53 | Craniosynostos* |
| 54 | Vascular disruption anomal* |
| 55 | 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 |
| 56 | Asymmetric skull* |
| 57 | Plagiocephal* |
| 58 | Microtia* |
| 59 | Anotia* |
| 60 | Microtia-anotia* |
| 61 | Patent foramen ovale* |
| 62 | Hemangioma* |
| 63 | 56 or 57 or 58 or 59 or 60 or 61 or 62 |
| | |
| 64 | Exp Teratogens/ |
| 65 | Prenatal Exposure Delayed Effects/ |
| 66 | Teratogenesis/ |
| 67 | Exp Congenital Abnormalities/ |
| 68 | 64 or 65 or 66 or 67 |
| 69 | 21 or 55 or 63 |
| 70 | 68 OR 69 |
| 71 | Electronic healt* record* |
| 72 | Electronic medical record* |
| 73 | Electronic clinical record* |
| 74 | Electronic patient record* |
| 75 | Digital healt* record* |
| 76 | Digital medical record* |
| 77 | Digital clinical record* |
| 78 | Digital patient record* |
| 79 | Computeri#ed healt* record* |
| 80 | Computeri#ed medical record* |
| 81 | Computeri#ed clinical record* |
| 82 | Computeri#ed patient record* |
| 83 | EHR |
| 84 | EHRs |
| 85 | EMR |
| 86 | EMRs |
| 87 | HMO |
| 88 | HMOs |
| 89 | Longitudinal medical record* |
| 90 | Longitudinal healt* record* |
| 91 | Longitudinal clinical record* |
| 92 | Health-care data* |
| 93 | Healthcare data* |

| Search # | Search term (keyword/free text or MeSH) |
|---|---|
| 94 | Medical record* data* |
| 95 | Health record* data* |
| 96 | Clinical record* data* |
| 97 | Longitudinal healt* data* |
| 98 | Longitudinal clinical data* |
| 99 | Longitudinal medical data* |
| 100 | Administrative adj3 data* |
| 101 | Automated adj3 data* |
| 102 | Administrative claim* |
| 103 | Claim* data* |
| 104 | CPRD |
| 105 | GPRD |
| 106 | Clinical Practice Research Datalink |
| 107 | General Practice Research Database |
| 108 | The Health Improvement Network |
| 109 | QResearch |
| 110 | ResearchOne |
| 111 | IMS Health |
| 112 | Medicaid |
| 113 | Kaiser Permanente |
| 114 | Hospital Episode Statistics |
| 115 | Primary care data* |
| 116 | Primary care record* |
| 117 | Routinely collected data |
| 118 | Read cod* |
| 119 | Clinical cod* |
| 120 | Medical cod* |
| 121 | ICD-9* |
| 122 | ICD9* |
| 123 | ICD-10* |
| 124 | ICD10* |
| 125 | 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 r 121 or 122 or 123 or 124 |
| 126 | Electronic Health Records/ |
| 127 | Medical Records System, Computerized/ |
| 128 | Medicaid/ |
| 129 | Administrative Claims, Healthcare/ |
| 130 | Health Maintenance Organizations/ |
| 131 | Databases, Factual/ |
| 132 | International Classification of Diseases |
| 133 | Clinical Coding |
| 134 | 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 |
| 135 | 125 or 134 |
| 136 | 135 AND 70 |
| 137 | Limits: English and Human |
| 138 | Autism (free text) |
| 139 | Autistic* (free text) |
| 140 | Autistic Disorder/ (Mesh) |
| 141 | Autism Spectrum Disorder/ (MesH) |
| 142 | 138 or 139 or 140 or 141 |
| 143 | 142 or 70 |

| Search # | Search term (keyword/free text or MeSH) |
|---|---|
| 144 | 143 AND 135 |
| 145 | 144 NOT 136 |
| 146 | English Language and Humans |

# Appendix 2 – Code lists for identifying major congenital malformations

## Read codes

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7H19511 | Closure of exomphalos | | Abdominal Wall |
| J32..11 | Omphalocele | | Abdominal Wall |
| J321000 | Omphalocele with obstruction | | Abdominal Wall |
| J323000 | Simple omphalocoele | | Abdominal Wall |
| J32y000 | Unspecified omphalocoele | | Abdominal Wall |
| PG7..00 | Abdominal wall anomalies | | Abdominal Wall |
| PG70.00 | Exomphalos | | Abdominal Wall |
| PG71.00 | Gastroschisis | | Abdominal Wall |
| PG7y.00 | Other specified anomaly of abdominal wall | | Abdominal Wall |
| PG7z.00 | Abdominal wall anomaly nos | | Abdominal Wall |
| P70..00 | Patent ductus arteriosus | If gest. age <37 weeks | Heart |
| P70..11 | Botalli's patent ductus | If gest. age <37 weeks | Heart |
| P551.00 | Patent foramen ovale | Yes | Heart |
| P721500 | Persistent right aortic arch | Yes | Heart |
| P74z500 | Persistent left superior vena cava | Yes | Heart |
| 7A01.00 | Open correction of patent ductus arteriosus | | Heart |
| 7A01.11 | Open correction of patent ductus arteriosus (PDA) | | Heart |
| 7A01000 | Division of patent ductus arteriosus | | Heart |
| 7A01100 | Ligation of patent ductus arteriosus | | Heart |
| 7A01200 | Closure of patent ductus arteriosus NEC | | Heart |
| 7A01300 | Revision of correction of patent ductus arteriosus | | Heart |
| 7A01y00 | Other specified open correction of patent ductus arteriosus | | Heart |
| 7A01z00 | Open correction of patent ductus arteriosus NOS | | Heart |
| 7A02000 | Percut transluminal prosth occlusion patent ductus arterios | | Heart |
| 7A02011 | Percut translum prosth occlus patent ductus arteriosus (PDA) | | Heart |
| G543100 | Pulmonary stenosis, non-rheumatic | | Heart |
| G543300 | Pulmonary stenosis, cause unspecified | | Heart |
| G543311 | Pulmonary stenosis, cause unspecified | | Heart |
| P602.00 | Congenital pulmonary stenosis | | Heart |
| P602z00 | Congenital pulmonary stenosis NOS | | Heart |
| 14AV.00 | History of ventricular septal defect | | Heart |
| 14H1.00 | H/O: cardiac anomaly | | Heart |
| 14H1.11 | H/O: heart anomaly | | Heart |
| 2126800 | Ostium secundum atrial septal defect resolved | | Heart |
| 24M..00 | Spontaneous closure of ventricular septal defect | | Heart |
| 33B8.00 | Detection of cardiac shunt | | Heart |
| 66g..00 | Congenital heart condition monitoring | | Heart |
| 7902.00 | Correction of tetralogy of Fallot | | Heart |
| 7902.11 | Repair of tetralogy of Fallot | | Heart |
| 7902000 | Correct Fallot tetralogy- valved right ventr outflow conduit | | Heart |
| 7902100 | Correct Fallot tetralogy- right ventric outflow conduit NEC | | Heart |
| 7902200 | Correct Fallot tetralogy- right ventricular outflow patch | | Heart |
| 7902300 | Revision of correction of tetralogy of Fallot | | Heart |
| 7902400 | Repair of tetralogy of Fallot using transannular patch | | Heart |
| 7902500 | Repair of tetralogy of Fallot with absent pulmonary valve | | Heart |
| 7902600 | Repair Fallot-type pulmonary atresia aortopulmonary collater | | Heart |
| 7902y00 | Other specified correction of tetralogy of Fallot | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7902z00 | Correction of tetralogy of Fallot NOS | | Heart |
| 7902z11 | Repair of tetralogy of Fallot NOS | | Heart |
| 7903.00 | Atrial inversion ops for transposition of great vessels | | Heart |
| 7903.11 | Mustard interatrial tr venous return | | Heart |
| 7903.12 | Senning correction for transposition of great vessels | | Heart |
| 7903.13 | Atrial inversion operations for transposition of great art | | Heart |
| 7903000 | Atrium reconstruction atrial patch for transpos great vessel | | Heart |
| 7903100 | Atrium reconstruction atrial wall for transpos great vessels | | Heart |
| 7903y00 | Atrial inversion op for transposition of great vessels OS | | Heart |
| 7903z00 | Atrial inversion op for transposition of great vessels NOS | | Heart |
| 7904.00 | Other correction of transposition of great vessels | | Heart |
| 7904000 | Repositioning of transposed great vessels | | Heart |
| 7904200 | Left ventricle aorta tunnel right ventricle pul art val con | | Heart |
| 7904300 | Atrial switch and arterial switch | | Heart |
| 7904y00 | Other correction of transposition of great vessels OS | | Heart |
| 7904z00 | Other correction of transposition of great vessels NOS | | Heart |
| 7905.00 | Correction of total anomalous pulmonary venous connection | | Heart |
| 7905000 | Correct total anomal pulm venous connect to supracard vessel | | Heart |
| 7905100 | Correct total anomal pulm venous connect to coronary sinus | | Heart |
| 7905y00 | Correction of total anomalous pulmonary venous connection OS | | Heart |
| 7905z00 | Correction total anomalous pulmonary venous connection NOS | | Heart |
| 7906.00 | Closure of defect of atrioventricular septum | | Heart |
| 7906.11 | Repair of defect of the atrioventricular septum | | Heart |
| 7906000 | Close defect atrioventric septum using dual prosthetic patch | | Heart |
| 7906011 | Rep defect atrioventricular septum dual prosthetic patches | | Heart |
| 7906100 | Close defect atrioventric septum using prosthetic patch NEC | | Heart |
| 7906111 | Repair defect atrioventricular septum prosthetic patch NEC | | Heart |
| 7906200 | Closure defect atrioventricular septum using tissue graft | | Heart |
| 7906211 | Repair defect of atrioventricular septum using tissue graft | | Heart |
| 7906300 | Closure of persistent ostium primum | | Heart |
| 7906311 | Repair of persistent ostium primum | | Heart |
| 7906400 | Primary closure of defect of atrioventricular septum NEC | | Heart |
| 7906500 | Revision of closure of defect of atrioventricular septum | | Heart |
| 7906y00 | Other specified closure of defect of atrioventricular septum | | Heart |
| 7906z00 | Closure of defect of atrioventricular septum NOS | | Heart |
| 7907.00 | Closure of defect of interatrial septum | | Heart |
| 7907.11 | Repair of defect of interatrial septum | | Heart |
| 7907000 | Closure defect of interatrial septum using prosthetic patch | | Heart |
| 7907011 | Repair defect of interatrial septum using prosthetic patch | | Heart |
| 7907100 | Closure defect of interatrial septum using pericardial patch | | Heart |
| 7907111 | Repair defect of interatrial septum using pericardial patch | | Heart |
| 7907200 | Closure defect of interatrial septum using tissue graft NEC | | Heart |
| 7907300 | Primary closure of defect of interatrial septum NEC | | Heart |
| 7907311 | Primary repair of defect of interatrial septum NEC | | Heart |
| 7907400 | Revision of closure of defect of interatrial septum | | Heart |
| 7907y00 | Other specified closure of defect of interatrial septum | | Heart |
| 7907z00 | Closure of defect of interatrial septum NOS | | Heart |
| 7908.00 | Closure of defect of interventricular septum | | Heart |
| 7908.11 | Repair of defect of interventricular septum | | Heart |
| 7908000 | Close defect interventricular septum using prosthetic patch | | Heart |
| 7908011 | Repair defect interventricular septum us prosthetic patch | | Heart |
| 7908100 | Close defect interventricular septum using pericardial patch | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7908111 | Repair defect interventricular septum us pericardial patch | | Heart |
| 7908200 | Close defect interventricular septum using tissue graft NEC | | Heart |
| 7908300 | Primary closure of defect of interventricular septum NEC | | Heart |
| 7908311 | Primary repair of defect of interventricular septum NEC | | Heart |
| 7908400 | Revision of closure of defect of interventricular septum | | Heart |
| 7908500 | Closure of multiple interventricular septal defects | | Heart |
| 7908511 | Repair of multiple interventricular septal defects | | Heart |
| 7908600 | Closure interventricular septal defect us intraop trans pros | | Heart |
| 7908611 | Repair interventricular septal defect us intraop trans pros | | Heart |
| 7908y00 | Other specified closure of defect of interventricular septum | | Heart |
| 7908z00 | Closure of defect of interventricular septum NOS | | Heart |
| 7909.00 | Closure of defect of unspecified septum of heart | | Heart |
| 7909.11 | Repair of defect of unspecified septum of heart | | Heart |
| 7909000 | Closure of defect of heart septum using prosthetic patch NEC | | Heart |
| 7909100 | Closure defect of heart septum using pericardial patch NEC | | Heart |
| 7909300 | Primary closure of defect of septum of heart NEC | | Heart |
| 7909y00 | Other specified closure of defect unspecified heart septum | | Heart |
| 7909z00 | Closure of defect of unspecified septum of heart NOS | | Heart |
| 7909z11 | Repair of defect of unspecified septum of heart NOS | | Heart |
| 790A.00 | Other open operations on septum of heart | | Heart |
| 790A000 | Open enlargement of defect of atrial septum | | Heart |
| 790A100 | Open atrial septostomy | | Heart |
| 790A111 | Atrial septostomy NEC | | Heart |
| 790A200 | Open atrial septum fenestration | | Heart |
| 790A300 | Atrial septectomy | | Heart |
| 790A400 | Atrial septation procedure | | Heart |
| 790A600 | Surgical atrial septation | | Heart |
| 790Ay00 | Other specified other open operation on septum of heart | | Heart |
| 790Az00 | Other open operation on septum of heart NOS | | Heart |
| 790B.00 | Closed operations on septum of heart | | Heart |
| 790B000 | Closed enlargement of defect of atrial septum | | Heart |
| 790B011 | Blalock creation of defect in atrial septum | | Heart |
| 790B012 | Hanlon creation of defect in atrial septum | | Heart |
| 790B100 | Closed atrial septostomy | | Heart |
| 790By00 | Other specified closed operation on septum of heart | | Heart |
| 790Bz00 | Closed operation on septum of heart NOS | | Heart |
| 790F.00 | Refashioning of atrium | | Heart |
| 790F000 | Correction of persistent sinus venosus | | Heart |
| 790F100 | Correction of partial anomalous pulmonary venous drainage | | Heart |
| 790F200 | Repair of cor triatriatum | | Heart |
| 790F300 | Repair of coronary sinus abnormality | | Heart |
| 790Fy00 | Other specified refashioning of atrium | | Heart |
| 790J.00 | Other repair of transposition of great arteries | | Heart |
| 790J000 | Repositioning of transposed great arteries | | Heart |
| 790Jz00 | Other repair of transposition of great arteries NOS | | Heart |
| 790K.00 | Repair of double outlet ventricle | | Heart |
| 790K100 | Repair of Fallot-type double outlet right ventricle | | Heart |
| 790K200 | Repair of double outlet right ventricle | | Heart |
| 790L.00 | Transluminal closure of defect of septum | | Heart |
| 790L000 | Percutan transluminal closure defect intervent sept us pros | | Heart |
| 790L111 | Percutaneous translum repair defect intervent septum NEC | | Heart |
| 790L200 | Percutan translum closure defect interatr septum us prosth | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 790L300 | Percutan transluminal closure defect interatrial septum NEC | | Heart |
| 790L311 | Percutan transluminal repair defect interatrial septum NEC | | Heart |
| 790L400 | Percut translum closure defect unspecified septum us prosth | | Heart |
| 790Ly00 | Other specified transluminal closure of defect of septum | | Heart |
| 790Lz00 | Transluminal closure of defect of septum NOS | | Heart |
| 790M.00 | Repair of univentricular heart | | Heart |
| 790M000 | Total cavopulmonary con extrac inf cav vein pulmon art con | | Heart |
| 790M100 | Total cavopulmonary connection with lateral atrial tunnel | | Heart |
| 790M200 | Radical aortopulmonary reconstr systemic-to-pulmon art shunt | | Heart |
| 790M400 | Biventricular repair of hypoplastic left heart syndrome | | Heart |
| 790M500 | Takedown of total cavopulmonary connection | | Heart |
| 790M600 | Conversion atrial pulmonary anastomosis total pulmon connect | | Heart |
| 790M700 | Aortopulm reconstruct with systemic to pulmon arterial shunt | | Heart |
| 790My00 | Other specified repair of univentricular heart | | Heart |
| 790Mz00 | Repair of univentricular heart NOS | | Heart |
| 790N000 | Relief of right ventricular outflow tract obstruction | | Heart |
| 790N100 | Repair of double chambered right ventricle | | Heart |
| 790N400 | Relief of left ventricular outflow tract obstruction | | Heart |
| 790N500 | Myectomy of left ventricular outflow tract | | Heart |
| 791A000 | Infundibulectomy of heart using patch | | Heart |
| 791A100 | Infundibulectomy of heart NEC | | Heart |
| 791A200 | Repair of subaortic stenosis | | Heart |
| 791A300 | Repair of supraaortic stenosis | | Heart |
| 791B400 | Closure of aortic sinus of Valsalva fistula | | Heart |
| 791B500 | Repair of aortic sinus of Valsalva aneurysm | | Heart |
| 7927000 | Repair of arteriovenous fistula of coronary artery | | Heart |
| 7927300 | Transposition of coronary artery NEC | | Heart |
| 792B200 | Repair of arteriovenous malformation of coronary artery | | Heart |
| 7934700 | Percutaneous transluminal ablation congenit heart malformat | | Heart |
| 7A0..00 | Great vessels and pulmonary artery operations | | Heart |
| 7A0..11 | Great vessel operations | | Heart |
| 7A00.00 | Open operations for combined abnormality of great vessels | | Heart |
| 7A00000 | Correction of persistent truncus arteriosus | | Heart |
| 7A00200 | Repair of hemitruncus arteriosus | | Heart |
| 7A00300 | Closure of aortopulmonary window | | Heart |
| 7A00400 | Repair anomalous pulmonary artery origin ascending aorta | | Heart |
| 7A00y00 | Open operation for combined abnormality of great vessels OS | | Heart |
| 7A00z00 | Open operation for combined abnormality of great vessels NOS | | Heart |
| 7A02.00 | Transluminal operations on abnormality of great vessel | | Heart |
| 7A02100 | Percutaneous transluminal stent implantation arterial duct | | Heart |
| 7A02y00 | Transluminal operation on abnormality of great vessel OS | | Heart |
| 7A02z00 | Transluminal operation on abnormality of great vessel NOS | | Heart |
| 7A03.00 | Creation interposition tube prosth shunt aorta to pulm art | | Heart |
| 7A03000 | Creation interpos tube prosth shunt asc aorta to main pulm a | | Heart |
| 7A03100 | Create interpos tube prosth shunt asc aorta to right pulm a | | Heart |
| 7A03200 | Creation interpos tube prosth shunt asc aorta to left pulm a | | Heart |
| 7A03y00 | Create interpos tube prosth shunt fr aorta to pulm artery OS | | Heart |
| 7A03z00 | Create interpos tube prosth shunt aorta to pulm artery NOS | | Heart |
| 7A04.00 | Other connection from aorta to pulmonary artery | | Heart |
| 7A04000 | Creation of aortopulmonary window | | Heart |
| 7A04100 | Creation of anastomosis ascending aorta to main pulm art NEC | | Heart |
| 7A04200 | Creation anastomosis ascending aorta to right pulm art NEC | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7A04211 | Waterson anastomosis ascending aorta to right pulmonary art | | Heart |
| 7A05.00 | Create interpos tube prosth shunt subclavian art to pulm art | | Heart |
| 7A05000 | Create interpos tube prosth shunt R subclavian a to R pulm a | | Heart |
| 7A05100 | Create interpos tube prosth shunt L subclavian a to L pulm a | | Heart |
| 7A05200 | Closure prosthetic shunt pulmonary artery subclavian artery | | Heart |
| 7A06.00 | Other connection from subclavian artery to pulmonary artery | | Heart |
| 7A06000 | Creation anastomosis right subclav art to right pulm art NEC | | Heart |
| 7A06100 | Creation anastomosis left subclav art to left pulm art NEC | | Heart |
| 7A06200 | Creation anastomosis subclavian artery to pulmonary art NEC | | Heart |
| 7A06211 | Blalock anastomosis of subclavian artery to pulmonary artery | | Heart |
| 7A06212 | Taussig anastomosis of subclavian artery to pulmonary artery | | Heart |
| 7A06300 | Revision anastomosis subclavian artery to pulmonary artery | | Heart |
| 7A06500 | Perc trans ball dilat anas bet pulmon artery subclav artery | | Heart |
| 7A06600 | Perc translu occlusion anast pulmonary artery subclavian art | | Heart |
| 7A07.00 | Other connection to pulmonary artery | | Heart |
| 7A07000 | Creation of anastomosis from vena cava to pulmonary artery | | Heart |
| 7A07011 | Creation Glenn anastomosis from vena cava to pulmonary art | | Heart |
| 7A07y00 | Other specified other connection to pulmonary artery | | Heart |
| 7A07z00 | Other connection to pulmonary artery NOS | | Heart |
| 7A08200 | Repair of anomalous pulmonary artery NEC | | Heart |
| 7A08300 | Repair of pulmonary arterial sling | | Heart |
| 7A09000 | Application of band to pulmonary artery | | Heart |
| 7A09100 | Adjustment of band to pulmonary artery | | Heart |
| 7A09200 | Removal of band from pulmonary artery | | Heart |
| 7A09500 | Pulmonary artery ligation | | Heart |
| 7A0A.00 | Transluminal operations on pulmonary artery | | Heart |
| 7A0A700 | Percut transluminal insertion of stent into pulmonary artery | | Heart |
| 7A0Ay00 | Other specified transluminal operation on pulmonary artery | | Heart |
| 7A0Az00 | Transluminal operation on pulmonary artery NOS | | Heart |
| 7A0B.00 | Open operations on both pulmonary arteries | | Heart |
| 7A0C.00 | Operation on major systemic to pulmonary collateral arteries | | Heart |
| 7A0C000 | Major systemic to pulmonary collateral artery occlusion | | Heart |
| 7A0C100 | Pulmonary unifocalisation | | Heart |
| 7A0C400 | Percut translumin stent major systemic pulmon collateral art | | Heart |
| 7A0y.00 | Great vessel or pulmonary artery operations OS | | Heart |
| 7A0z.00 | Great vessel and pulmonary artery operations NOS | | Heart |
| 7A18111 | Hamilton repair coarctation of aorta using subclavian flap | | Heart |
| 7A18600 | Repair of interrupted aortic arch | | Heart |
| 7A63500 | Repair of anomalous caval vein connection | | Heart |
| 7A6K000 | Repair of pulmonary vein stenosis | | Heart |
| 9RD0.00 | Transfer of care from paediatric congenital heart service | | Heart |
| D410200 | Polycythaemia due to cyanotic heart disease | | Heart |
| G11..00 | Mitral valve diseases | | Heart |
| G110.00 | Mitral stenosis | | Heart |
| G112.00 | Mitral stenosis with insufficiency | | Heart |
| G112.12 | Mitral stenosis with incompetence | | Heart |
| G112.13 | Mitral stenosis with regurgitation | | Heart |
| G113.00 | Nonrheumatic mitral valve stenosis | | Heart |
| G114.00 | Ruptured mitral valve cusp | | Heart |
| G11z.00 | Mitral valve disease NOS | | Heart |
| G13..00 | Diseases of mitral and aortic valves | | Heart |
| G130.00 | Mitral and aortic stenosis | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| G131.00 | Mitral stenosis and aortic insufficiency | | Heart |
| G131.13 | Mitral stenosis and aortic incompetence | | Heart |
| G131.14 | Mitral stenosis and aortic regurgitation | | Heart |
| G132.00 | Mitral insufficiency and aortic stenosis | | Heart |
| G132.12 | Mitral incompetence and aortic stenosis | | Heart |
| G132.13 | Mitral regurgitation and aortic stenosis | | Heart |
| G133.00 | Mitral and aortic incompetence | | Heart |
| G133.11 | Mitral and aortic insufficiency | | Heart |
| G133.12 | Mitral and aortic regurgitation | | Heart |
| G13y.00 | Multiple mitral and aortic valve involvement | | Heart |
| G13z.00 | Mitral and aortic valve disease NOS | | Heart |
| G140.00 | Tricuspid valve disease NEC | | Heart |
| G140300 | Tricuspid stenosis, cause unspecified | | Heart |
| G140400 | Tricuspid insufficiency, cause unspecified | | Heart |
| G140412 | Tricuspid incompetence, cause unspecified | | Heart |
| G140413 | Tricuspid regurgitation, cause unspecified | | Heart |
| G140500 | Tricuspid stenosis and insufficiency, cause unspecified | | Heart |
| G140514 | Tricuspid stenosis and regurgitation, cause unspecified | | Heart |
| G420.00 | Arteriovenous fistula of pulmonary vessels | | Heart |
| G54..11 | Heart valve disorders - non rheumatic | | Heart |
| G540.00 | Mitral valve incompetence | | Heart |
| G540.12 | Mitral valve insufficiency | | Heart |
| G540000 | Mitral incompetence, non-rheumatic | | Heart |
| G540100 | Mitral incompetence, cause unspecified | | Heart |
| G541011 | Aortic insufficiency, non-rheumatic | | Heart |
| G541012 | Aortic regurgitation, non-rheumatic | | Heart |
| G541211 | Aortic insufficiency alone, cause unspecified | | Heart |
| G541212 | Aortic regurgitation alone, cause unspecified | | Heart |
| G541400 | Aortic valve stenosis with insufficiency | | Heart |
| G542000 | Tricuspid incompetence, non-rheumatic | | Heart |
| G542011 | Tricuspid insufficiency, non-rheumatic | | Heart |
| G542100 | Tricuspid stenosis, non-rheumatic | | Heart |
| G542200 | Nonrheumatic tricuspid valve stenosis with insufficiency | | Heart |
| G542X00 | Nonrheumatic tricuspid valve disorder, unspecified | | Heart |
| G543.00 | Pulmonary valve disorders | | Heart |
| G543400 | Pulmonary valve stenosis with insufficiency | | Heart |
| G543z00 | Pulmonary valve disorders NOS | | Heart |
| G54z000 | Incompetence of unspecified heart valve | | Heart |
| G54z014 | Insufficiency of unspecified heart valve | | Heart |
| G553.00 | Endocardial fibroelastosis | | Heart |
| Gyu1000 | [X]Other mitral valve diseases | | Heart |
| Gyu1200 | [X]Other tricuspid valve diseases | | Heart |
| Gyu5500 | [X]Other nonrheumatic mitral valve disorders | | Heart |
| Gyu5600 | [X]Other aortic valve disorders | | Heart |
| Gyu5800 | [X]Other pulmonary valve disorders | | Heart |
| L258.00 | Fetus with cardiovascular abnormality | | Heart |
| P5...00 | Bulbus cordis and cardiac septal closure anomalies | | Heart |
| P5...11 | Cardiac septal defects | | Heart |
| P5...12 | Congenital heart disease, septal and bulbar anomalies | | Heart |
| P5...13 | Heart septal defects | | Heart |
| P50..00 | Common aorto-pulmonary trunk | | Heart |
| P50..11 | Aortic septal defect | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P50..12 | Common truncus | | Heart |
| P500.00 | Absent septum between aorta and pulmonary artery | | Heart |
| P500.11 | Persistent truncus arteriosus | | Heart |
| P500.12 | Truncus arteriosus | | Heart |
| P501.00 | Aortic septal defect | | Heart |
| P501.11 | Aortopulmonary window | | Heart |
| P501.12 | Aorticopulmonary septal defect | | Heart |
| P502.00 | Persistent truncus arteriosus | | Heart |
| P502.11 | Truncus arteriosus | | Heart |
| P50z.00 | Common aorto-pulmonary trunk NOS | | Heart |
| P51..00 | Transposition of great vessels | | Heart |
| P510.00 | Total great vessel transposition | | Heart |
| P511.00 | Double outlet right ventricle | | Heart |
| P511100 | Dextratransposition of aorta | | Heart |
| P511200 | Incomplete great vessel transposition | | Heart |
| P511300 | Taussig-Bing syndrome | | Heart |
| P511z00 | Double outlet right ventricle NOS | | Heart |
| P512.00 | Corrected great vessel transposition | | Heart |
| P51y.00 | Other specified transposition of great vessels | | Heart |
| P51y.11 | Transposition of aorta | | Heart |
| P51z.00 | Great vessel transposition NOS | | Heart |
| P51z.11 | Transposition of arterial trunk NEC | | Heart |
| P52..00 | Tetralogy of Fallot | | Heart |
| P520.00 | Tetralogy of Fallot, unspecified | | Heart |
| P520.11 | Ventricular septal defect in Fallot's tetralogy | | Heart |
| P520.12 | Dextraposition of aorta in Fallot's tetralogy | | Heart |
| P521.00 | Pentalogy of Fallot | | Heart |
| P52z.00 | Tetralogy of Fallot NOS | | Heart |
| P53..00 | Common ventricle | | Heart |
| P54..00 | Ventricular septal defect | | Heart |
| P540.00 | Ventricular septal defect, unspecified | | Heart |
| P541.00 | Interventricular septal defect | | Heart |
| P542.00 | Left ventricle to right atrial communication | | Heart |
| P543.00 | Eisenmenger's complex | | Heart |
| P544.00 | Gerbode's defect | | Heart |
| P545.00 | Roger's disease | | Heart |
| P54y.00 | Other specified ventricular septal defect | | Heart |
| P54z.00 | Ventricular septal defect NOS | | Heart |
| P55..00 | Ostium secundum atrial septal defect | | Heart |
| P550.00 | Atrial septal defect NOS | | Heart |
| P550.11 | Auricular septal defect NOS | | Heart |
| P550.12 | Interatrial septal defect NEC | | Heart |
| P550.13 | Interauricular septal defect | | Heart |
| P552.00 | Persistent ostium secundum | | Heart |
| P552.11 | Patent ostium secundum | | Heart |
| P553.00 | Lutembacher's syndrome | | Heart |
| P55y.00 | Other specified ostium secundum atrial septal defect | | Heart |
| P55y.11 | Other specified atrial septal defect | | Heart |
| P55z.00 | Ostium secundum atrial septal defect NOS | | Heart |
| P56..00 | Endocardial cushion defects | | Heart |
| P561.00 | Ostium primum defect | | Heart |
| P561.11 | Persistent ostium primum | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P56y.00 | Other specified endocardial cushion defects | | Heart |
| P56z.00 | Endocardial cushion defects NOS | | Heart |
| P56z000 | Common atrium | | Heart |
| P56z011 | Cor triloculare biventriculare | | Heart |
| P56z100 | Common atrioventricular canal | | Heart |
| P56z200 | Common atrioventricular-type ventricular septal defect | | Heart |
| P56zz00 | Endocardial cushion defects NOS | | Heart |
| P58..00 | Double outlet left ventricle | | Heart |
| P59..00 | Isomerism of atrial appendages | | Heart |
| P5X..00 | Congenital malforms of cardiac chambers+connections unsp | | Heart |
| P5y..00 | Other heart bulb and septal closure defect | | Heart |
| P5z..00 | Heart bulb or septal closure defects NOS | | Heart |
| P6...00 | Other congenital heart anomalies | | Heart |
| P60..00 | Pulmonary valve anomalies | | Heart |
| P600.00 | Pulmonary valve anomaly, unspecified | | Heart |
| P601.00 | Congenital atresia of the pulmonary valve | | Heart |
| P601000 | Hypoplasia of pulmonary valve | | Heart |
| P601z00 | Congenital atresia of pulmonary valve NOS | | Heart |
| P602100 | Congenital fusion of pulmonary valve segment | | Heart |
| P603.00 | Right hypoplastic heart syndrome | | Heart |
| P603.11 | Pseudotruncus arteriosus | | Heart |
| P60z.00 | Other pulmonary valve anomalies | | Heart |
| P60z000 | Congenital insufficiency of the pulmonary valve | | Heart |
| P60z100 | Fallot's trilogy | | Heart |
| P60zz00 | Other pulmonary valve anomaly NOS | | Heart |
| P61..00 | Congenital tricuspid atresia and stenosis | | Heart |
| P610.00 | Congenital tricuspid atresia | | Heart |
| P611.00 | Congenital tricuspid stenosis | | Heart |
| P61z.00 | Congenital tricuspid atresia or stenosis NOS | | Heart |
| P62..00 | Ebstein's anomaly | | Heart |
| P63..00 | Congenital aortic valve stenosis | | Heart |
| P64..00 | Congenital aortic valve insufficiency | | Heart |
| P640.00 | Congenital aortic valve insufficiency, unspecified | | Heart |
| P641.00 | Bicuspid aortic valve | | Heart |
| P64z.00 | Congenital aortic valve insufficiency NOS | | Heart |
| P65..00 | Congenital mitral stenosis | | Heart |
| P65..11 | Duroziez's disease | | Heart |
| P650.00 | Congenital mitral stenosis, unspecified | | Heart |
| P651.00 | Fused commissure of the mitral valve | | Heart |
| P652.00 | Parachute deformity of the mitral valve | | Heart |
| P65z.00 | Congenital mitral stenosis NOS | | Heart |
| P66..00 | Congenital mitral insufficiency | | Heart |
| P67..00 | Hypoplastic left heart syndrome | | Heart |
| P68..00 | Congenital heart disease | | Heart |
| P69..00 | Left ventricular outflow tract obstruction | | Heart |
| P6W..00 | Congenital malformation of aortic and mitral valves unsp | | Heart |
| P6X..00 | Congenital malformation of tricuspid valve, unspecified | | Heart |
| P6y..00 | Other specified heart anomalies | | Heart |
| P6y0.00 | Subaortic stenosis | | Heart |
| P6y1.00 | Cor triatriatum | | Heart |
| P6y2.00 | Pulmonary infundibular stenosis | | Heart |
| P6y3.00 | Obstructive heart anomaly NEC | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P6y3000 | Uhl's disease | | Heart |
| P6y3100 | Right ventricular outflow tract obstruction | | Heart |
| P6y3z00 | Obstructive heart anomaly NEC NOS | | Heart |
| P6y4.00 | Coronary artery anomaly | | Heart |
| P6y4000 | Congenital absence of coronary artery | | Heart |
| P6y4100 | Single coronary artery | | Heart |
| P6y4300 | Coronary artery from pulmonary trunk | | Heart |
| P6y4400 | Anomalous coronary artery communication | | Heart |
| P6y4411 | Congenital coronary arterio-venous fistula | | Heart |
| P6y4500 | Congenital coronary aneurysm | | Heart |
| P6y4600 | Congenital stricture of coronary artery | | Heart |
| P6y4z00 | Coronary artery anomaly NOS | | Heart |
| P6y5.00 | Congenital heart block | | Heart |
| P6y5000 | Congenital heart block, unspecified | | Heart |
| P6y5100 | Congenital complete atrio-ventricular heart block | | Heart |
| P6y5200 | Congenital incomplete atrio-ventricular heart block | | Heart |
| P6y5z00 | Congenital heart block NOS | | Heart |
| P6y6.00 | Heart and cardiac apex malposition | | Heart |
| P6y6.11 | Ectopic heart | | Heart |
| P6y6000 | Dextrocardia | | Heart |
| P6y6100 | Levocardia | | Heart |
| P6y6111 | Laevocardia | | Heart |
| P6y6200 | Mesocardia | | Heart |
| P6y6300 | Ectopia cordis | | Heart |
| P6y6400 | Abdominal heart | | Heart |
| P6y6z00 | Heart or cardiac apex malposition NOS | | Heart |
| P6y7.00 | Myocardial bridge of coronary artery | | Heart |
| P6y8.00 | Congenital dextroposition of heart | | Heart |
| P6yy.00 | Other specified heart anomalies | | Heart |
| P6yy.11 | Hypoplastic aortic orifice or valve | | Heart |
| P6yy.12 | Hypoplasia of heart NOS | | Heart |
| P6yy000 | Atresia of cardiac vein | | Heart |
| P6yy100 | Hypoplasia of cardiac vein | | Heart |
| P6yy200 | Congenital cardiomegaly | | Heart |
| P6yy300 | Congenital left ventricular diverticulum | | Heart |
| P6yy400 | Congenital pericardial defect | | Heart |
| P6yy411 | Congenital absence of pericardium | | Heart |
| P6yy500 | Congenital anomaly of myocardium | | Heart |
| P6yy600 | Congenital aneurysm of heart | | Heart |
| P6yy700 | Atresia of heart valve NEC | | Heart |
| P6yy900 | Congenital epicardial cyst | | Heart |
| P6yyA00 | Hemicardia | | Heart |
| P6yyB00 | Supernumerary heart valve cusps NEC | | Heart |
| P6yyz00 | Other specified heart anomalies NOS | | Heart |
| P6z..00 | Congenital heart anomaly NOS | | Heart |
| P6z0.00 | Unspecified anomaly of heart valve | | Heart |
| P6z1.00 | Anomalous bands of heart | | Heart |
| P6z1000 | Anomalous atrial bands | | Heart |
| P6z1100 | Anomalous ventricular bands | | Heart |
| P6z2.00 | Acyanotic congenital heart disease NOS | | Heart |
| P6z3.00 | Cyanotic congenital heart disease NOS | | Heart |
| P6z3.11 | Blue baby | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P6zz.00 | Congenital heart anomaly NOS | | Heart |
| P71..00 | Coarctation of aorta | | Heart |
| P710.00 | Hypoplasia of aortic arch, unspecified | | Heart |
| P711.00 | Preductal coarctation of aorta | | Heart |
| P711.13 | Preductal aortic stenosis | | Heart |
| P712.00 | Postductal coarctation of aorta | | Heart |
| P712.12 | Postductal interruption of aorta | | Heart |
| P712.13 | Postductal aortic stenosis | | Heart |
| P713.00 | Interruption of aortic arch | | Heart |
| P713.11 | Stenosis of aortic arch | | Heart |
| P71z.00 | Coarctation of aorta NOS | | Heart |
| P72..00 | Other anomalies of aorta | | Heart |
| P72..11 | Anomalies of the aorta excluding coarction | | Heart |
| P720.00 | Anomaly of aorta, unspecified | | Heart |
| P721.00 | Aortic arch anomalies | | Heart |
| P721000 | Anomalous origin of the aortic arch | | Heart |
| P721100 | Dextraposition of aorta | | Heart |
| P721111 | Overriding aorta | | Heart |
| P721200 | Double aortic arch | | Heart |
| P721211 | Vascular ring | | Heart |
| P721300 | Kommerell's diverticulum | | Heart |
| P721600 | Vascular ring, aorta | | Heart |
| P721700 | Overriding aorta | | Heart |
| P721z00 | Aortic arch anomalies NOS | | Heart |
| P722.00 | Atresia and stenosis of aorta | | Heart |
| P722100 | Aplasia of aorta | | Heart |
| P722200 | Hypoplasia of aorta | | Heart |
| P722300 | Stricture of aorta | | Heart |
| P722400 | Supra-valvular aortic stenosis | | Heart |
| P722411 | Congenital stenosis of ascending aorta | | Heart |
| P722500 | Atresia of aorta | | Heart |
| P722z00 | Atresia or stenosis of aorta NOS | | Heart |
| P72z.00 | Other anomalies of aorta NOS | | Heart |
| P72z000 | Aneurysm of sinus of Valsalva | | Heart |
| P72z100 | Congenital aneurysm of aorta | | Heart |
| P72z111 | Congenital dilatation of aorta | | Heart |
| P72zz00 | Other anomaly of aorta NOS | | Heart |
| P73..00 | Pulmonary artery anomalies | | Heart |
| P730.00 | Pulmonary artery anomaly, unspecified | | Heart |
| P731.00 | Pulmonary artery agenesis | | Heart |
| P731.11 | Congenital absence of pulmonary artery | | Heart |
| P732.00 | Pulmonary artery atresia | | Heart |
| P733.00 | Coarctation of the pulmonary artery | | Heart |
| P734.00 | Hypoplasia of the pulmonary artery | | Heart |
| P735.00 | Stenosis of pulmonary artery | If gest. age <37 weeks | Heart |
| P735.11 | Congenital stricture of pulmonary artery | | Heart |
| P736.00 | Pulmonary arterio-venous aneurysm | | Heart |
| P736.11 | Pulmonary arterio-venous fistula | | Heart |
| P736.12 | Pulmonary arterio-venous malformation | | Heart |
| P737.00 | Pulmonary artery aneurysm | | Heart |
| P737.11 | Dilatation of pulmonary artery | | Heart |
| P738.00 | Atresia of pulmonary artery with septal defect | | Heart |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P73y.00 | Other specified anomaly of pulmonary artery | | Heart |
| P73z.00 | Pulmonary artery anomaly NOS | | Heart |
| P74..00 | Anomalies of great veins | | Heart |
| P740.00 | Anomaly of great veins, unspecified | | Heart |
| P740000 | Anomaly of the pulmonary veins, unspecified | | Heart |
| P740100 | Anomaly of the vena cava, unspecified | | Heart |
| P741.00 | Total anomalous pulmonary venous return - TAPVR | | Heart |
| P741000 | Subdiaphragmatic total anomalous pulmonary venous return | | Heart |
| P741100 | Supradiaphragmatic total anomalous pulmonary venous return | | Heart |
| P741z00 | Total anomalous pulmonary venous return NOS | | Heart |
| P742.00 | Partial anomalous pulmonary venous return | | Heart |
| P742.11 | Anomalous termination of right pulmonary vein | | Heart |
| P743.00 | Anomalous portal vein termination | | Heart |
| P744.00 | Portal vein - hepatic artery fistula | | Heart |
| P74z.00 | Other great vein anomalies | | Heart |
| P74z.11 | Persistent left posterior cardinal vein | | Heart |
| P74z000 | Absence of inferior vena cava | | Heart |
| P74z100 | Absence of superior vena cava | | Heart |
| P74z200 | Stenosis of inferior vena cava | | Heart |
| P74z300 | Stenosis of superior vena cava | | Heart |
| P74z600 | Scimitar syndrome | | Heart |
| P74z700 | Transposition of pulmonary veins | | Heart |
| P74z800 | Atresia of pulmonary vein | | Heart |
| P74zz00 | Other great vein anomaly NOS | | Heart |
| P8y0.00 | Abnormal pericardio-pleural communication | | Heart |
| Pyu2100 | [X]Other congenital malformations of cardiac septa | | Heart |
| Pyu2200 | [X]Other congenital malformations of pulmonary valve | | Heart |
| Pyu2500 | [X]Other specified congenital malformations of the heart | | Heart |
| Pyu2600 | [X]Other congenital malformations of aorta | | Heart |
| Pyu2700 | [X]Other congenital malformations of pulmonary artery | | Heart |
| Pyu2F00 | [X]Congenital malforms of cardiac chambers+connections unsp | | Heart |
| Pyu2G00 | [X]Congenital malformation of tricuspid valve, unspecified | | Heart |
| Pyu2H00 | [X]Congenital malformation of aortic and mitral valves unsp | | Heart |
| Q48y100 | Congenital cardiac failure | | Heart |
| ZV15100 | [V]Personal history of heart or great vessel operation | | Heart |
| 2565.00 | O/e - macroglossia | Yes | Digestive |
| 7523100 | Incision of frenulum of tongue | Yes | Digestive |
| 7523111 | Frenotomy of tongue | Yes | Digestive |
| 7523112 | Release of tongue tie | Yes | Digestive |
| 7523400 | Excision of frenulum of tongue | Yes | Digestive |
| 760K.11 | Repair of oesophageal hiatus hernia | Yes | Digestive |
| 760K.12 | Repair of hiatus hernia | Yes | Digestive |
| 760K000 | Repair of oesophageal hiatus using thoracic approach | Yes | Digestive |
| 760K011 | Allison repair of oesophageal hiatus hernia | Yes | Digestive |
| 760K012 | Mason repair of oesophageal hiatus hernia | Yes | Digestive |
| 760K200 | Repair of oesophageal hiatus using abdominal approach | Yes | Digestive |
| 760K400 | Boerema repair of hiatus hernia | Yes | Digestive |
| 760K500 | Laparoscopic repair of hiatus hernia | Yes | Digestive |
| 760L312 | Hill repair of hiatus hernia and gastropexy | Yes | Digestive |
| 7641000 | Excision of meckel diverticulum | Yes | Digestive |
| 7H11.11 | Primary inguinal herniorrhaphy | Yes | Digestive |
| J34..11 | Hiatus hernia | Yes | Digestive |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| J344.00 | Hiatus hernia with gangrene | Yes | Digestive |
| J345.00 | Hiatus hernia with obstruction | Yes | Digestive |
| J346.00 | Hiatus hernia - irreducible | Yes | Digestive |
| J347.00 | Simple hiatus hernia | Yes | Digestive |
| J348.00 | Sliding hiatus hernia | Yes | Digestive |
| J34z000 | Hiatus hernia nos | Yes | Digestive |
| PA0..00 | Tongue tie - ankyloglossia | Yes | Digestive |
| PA0..11 | Ankyloglossia | Yes | Digestive |
| PA0..12 | Tongue tie | Yes | Digestive |
| PA13.00 | Fissure of tongue | Yes | Digestive |
| PA14.00 | Macroglossia | Yes | Digestive |
| PA14.11 | Congenital tongue hypertrophy | Yes | Digestive |
| PA24.00 | Congenital fistula of lip | Yes | Digestive |
| PA25100 | High arched palate | Yes | Digestive |
| PA28.00 | Ranula, congenital | Yes | Digestive |
| PA5..00 | Congenital hypertrophic pyloric stenosis | Yes | Digestive |
| PA50.00 | Congenital pyloric hypertrophy | Yes | Digestive |
| PA51.00 | Congenital pyloric spasm | Yes | Digestive |
| PA51.11 | Congenital pylorospasm | Yes | Digestive |
| PA52.00 | Congenital pyloric stenosis | Yes | Digestive |
| PA52.11 | Congenital pyloric stricture | Yes | Digestive |
| PA6..00 | Congenital hiatus hernia | Yes | Digestive |
| PB0..00 | Meckel's diverticulum | Yes | Digestive |
| PB00.00 | Meckel's diverticulum, unspecified | Yes | Digestive |
| PB01.00 | Displaced meckel's diverticulum | Yes | Digestive |
| PB0z.00 | Meckel's diverticulum nos | Yes | Digestive |
| 7523200 | Freeing of adhesions of tongue | | Digestive |
| 7523500 | Glossopexy | | Digestive |
| 7606000 | Closure of tracheooesophageal fistula | | Digestive |
| 7606011 | Excision of tracheooesophageal fistula | | Digestive |
| 7606100 | Closure of fistula of oesophagus nec | | Digestive |
| 7606200 | Correction of congenital atresia of oesophagus | | Digestive |
| 7607000 | Exteriorisation of pouch of oesophagus | | Digestive |
| 7608200 | Division of web of oesophagus | | Digestive |
| 760D400 | Fibreoptic endoscopic dilation of web of oesophagus | | Digestive |
| 760G400 | Dilation of web of oesophagus using rigid oesophagoscope | | Digestive |
| 760K.00 | Repair of diaphragmatic hernia | | Digestive |
| 760K100 | Repair of diaphragmatic hernia using thoracic approach nec | | Digestive |
| 760K300 | Repair of diaphragmatic hernia using abdominal approach nec | | Digestive |
| 760Ky00 | Other specified repair of diaphragmatic hernia | | Digestive |
| 760Kz00 | Repair of diaphragmatic hernia nos | | Digestive |
| 761B100 | Repair of congenital atresia of pylorus | | Digestive |
| 7726y11 | Duhamel hirschsprung abdoperin | | Digestive |
| 7726y12 | Soave endorectal pull through op for hirschsprung's disease | | Digestive |
| 7726y13 | Swenson hirschsprung proctect | | Digestive |
| 7733300 | Reanastomosis rectum-anal canal correct cong rectal atresia | | Digestive |
| 7838000 | Division of annular pancreas | | Digestive |
| 7H0D300 | Repair of congenital diaphragmatic hernia | | Digestive |
| J074.00 | Fistula of salivary gland | | Digestive |
| J074000 | Fistula of parotid gland | | Digestive |
| J074100 | Fistula of submandibular gland | | Digestive |
| J074200 | Fistula of sublingual gland | | Digestive |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| J074z00 | Fistula of salivary gland nos | | Digestive |
| J085200 | Fistula of lip | | Digestive |
| J10y200 | Tracheo-oesophageal fistula | | Digestive |
| J34..00 | Diaphragmatic hernia | | Digestive |
| J340.00 | Diaphragmatic hernia with gangrene | | Digestive |
| J341.00 | Diaphragmatic hernia with obstruction | | Digestive |
| J342.00 | Diaphragmatic hernia - irreducible | | Digestive |
| J343.00 | Simple diaphragmatic hernia | | Digestive |
| J34y.00 | Unspecified diaphragmatic hernia | | Digestive |
| J34z.00 | Diaphragmatic hernia nos | | Digestive |
| J50z200 | Stenosis of intestine nos | | Digestive |
| J50z300 | Stricture of intestine nos | | Digestive |
| J527100 | Secondary megacolon - congenital | | Digestive |
| J572.00 | Stenosis of rectum and anus | | Digestive |
| J572000 | Stenosis of rectum | | Digestive |
| J572111 | Anal stenosis | | Digestive |
| J572z00 | Stenosis of rectum and anus nos | | Digestive |
| PA...00 | Other congenital upper alimentary tract anomalies | | Digestive |
| PA1..00 | Other tongue anomalies | | Digestive |
| PA10.00 | Anomaly of tongue, unspecified | | Digestive |
| PA11.00 | Aglossia | | Digestive |
| PA12.00 | Congenital adhesions of tongue | | Digestive |
| PA13.11 | Bifid tongue | | Digestive |
| PA13.12 | Double tongue | | Digestive |
| PA15.00 | Microglossia | | Digestive |
| PA15.11 | Hypoplasia of tongue | | Digestive |
| PA15.12 | Short tongue | | Digestive |
| PA16.00 | Dislocation of tongue | | Digestive |
| PA17.00 | Cleft tongue | | Digestive |
| PA18.00 | Congenital plicated tongue | | Digestive |
| PA1z.00 | Other tongue anomalies nos | | Digestive |
| PA2..00 | Other specified mouth and pharynx anomalies | | Digestive |
| PA20.00 | Congenital absence of salivary gland | | Digestive |
| PA21.00 | Accessory salivary gland | | Digestive |
| PA22.00 | Atresia, salivary duct | | Digestive |
| PA23.00 | Congenital salivary gland fistula | | Digestive |
| PA25.00 | Other mouth anomalies | | Digestive |
| PA25.11 | Fordyce's disease of mouth | | Digestive |
| PA25000 | Congenital absence of uvula | | Digestive |
| PA25y00 | Other congenital anomaly of palate | | Digestive |
| PA25z00 | Other mouth anomalies nos | | Digestive |
| PA26.00 | Diverticulum of pharynx | | Digestive |
| PA26.11 | Pharyngeal pouch | | Digestive |
| PA27.00 | Other pharynx anomalies | | Digestive |
| PA27000 | Imperforate pharynx | | Digestive |
| PA27z00 | Other pharynx anomalies nos | | Digestive |
| PA29.00 | Other anomalies of salivary glands or ducts | | Digestive |
| PA29.11 | Displacement of wharton's duct | | Digestive |
| PA2A.00 | Other anomalies of lip | | Digestive |
| PA2Az00 | Other anomaly of lip nos | | Digestive |
| PA2z.00 | Other mouth and pharynx anomalies nos | | Digestive |
| PA3..00 | Oesophageal atresia, stenosis and fistula | | Digestive |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PA3..11 | Congenital oesophageal ring | | Digestive |
| PA30.00 | Atresia of oesophagus | | Digestive |
| PA31.00 | Congenital oesophageal stricture | | Digestive |
| PA31.11 | Congenital oesophageal stenosis | | Digestive |
| PA32.00 | Congenital oesophageal fistula | | Digestive |
| PA32000 | Oesophagobronchial fistula | | Digestive |
| PA32100 | Oesophagotracheal fistula | | Digestive |
| PA32111 | Congenital tracheo-oesophageal fistula | | Digestive |
| PA32z00 | Congenital oesophageal fistula nos | | Digestive |
| PA33.00 | Imperforate oesophagus | | Digestive |
| PA34.00 | Webbed oesophagus | | Digestive |
| PA35.00 | Congenital absence of oesophagus | | Digestive |
| PA36.00 | Cong.absence of oesophagus with tracheo-oesophageal fistula | | Digestive |
| PA37.00 | Atresia of oesophagus with tracheo-oesophageal fistula | | Digestive |
| PA3y.00 | Other specified oesophageal atresia, stenosis or fistula | | Digestive |
| PA3z.00 | Oesophageal atresia, stenosis or fistula nos | | Digestive |
| PA4..00 | Other specified oesophageal anomalies | | Digestive |
| PA40.00 | Congenital dilatation of oesophagus | | Digestive |
| PA42.00 | Congenital diverticulum of oesophagus | | Digestive |
| PA43.00 | Congenital duplication of oesophagus | | Digestive |
| PA44.00 | Giant oesophagus | | Digestive |
| PA45.00 | Congenital oesophageal pouch | | Digestive |
| PA4z.00 | Other specified oesophageal anomaly nos | | Digestive |
| PA5y.00 | Other specified congenital pyloric obstruction | | Digestive |
| PA5z.00 | Congenital pyloric obstruction nos | | Digestive |
| PA7..00 | Other specified stomach anomalies | | Digestive |
| PA70.00 | Congenital cardiospasm | | Digestive |
| PA70.11 | Congenital achalasia of cardia | | Digestive |
| PA71.00 | Congenital hourglass stomach | | Digestive |
| PA73.00 | Congenital stomach diverticulum | | Digestive |
| PA74.00 | Duplication of stomach | | Digestive |
| PA75.00 | Megalogastria | | Digestive |
| PA76.00 | Microgastria | | Digestive |
| PA77.00 | Transposition of stomach | | Digestive |
| PA78.00 | Ectopic gastric mucosa | | Digestive |
| PA7z.00 | Other specified stomach anomaly nos | | Digestive |
| PAy..00 | Other specified upper alimentary tract anomaly | | Digestive |
| PAz..00 | Upper alimentary tract anomalies nos | | Digestive |
| PAz0.00 | Unspecified anomalies of mouth and pharynx | | Digestive |
| PAz1.00 | Unspecified anomalies of oesophagus | | Digestive |
| PAz2.00 | Unspecified anomalies of stomach | | Digestive |
| PAzz.00 | Anomalies of upper alimentary tract nos | | Digestive |
| PAzz.11 | Malformation of throat | | Digestive |
| PB...00 | Other congenital digestive system anomaly | | Digestive |
| PB0..12 | Persistent vitelline duct | | Digestive |
| PB03.00 | Persistent omphalomesenteric duct | | Digestive |
| PB03.11 | Persistent vitelline duct | | Digestive |
| PB1..00 | Small intestine atresia and stenosis | | Digestive |
| PB10.00 | Atresia of small intestine | | Digestive |
| PB10000 | Atresia of small intestine, unspecified | | Digestive |
| PB10100 | Atresia of duodenum | | Digestive |
| PB10200 | Atresia of ileum | | Digestive |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PB10300 | Atresia of jejunum | | Digestive |
| PB10z00 | Small intestine atresia nos | | Digestive |
| PB11200 | Congenital absence of ileum | | Digestive |
| PB12.00 | Congenital obstruction of small intestine | | Digestive |
| PB13.00 | Congenital stenosis of small intestine | | Digestive |
| PB13000 | Congenital stenosis of duodenum | | Digestive |
| PB13100 | Congenital stenosis of jejunum | | Digestive |
| PB13200 | Congenital stenosis of ileum | | Digestive |
| PB13z00 | Congenital stenosis of small intestine nos | | Digestive |
| PB13z11 | Congenital stricture of small intestine | | Digestive |
| PB14.00 | Imperforate jejunum | | Digestive |
| PB1z.00 | Small intestine atresia or stenosis nos | | Digestive |
| PB2..00 | Atresia and stenosis of large intestine/rectum/anal canal | | Digestive |
| PB2..11 | Atresia large intestine | | Digestive |
| PB2..12 | Stenosis large intestine | | Digestive |
| PB20.00 | Congenital absence of large intestine | | Digestive |
| PB20000 | Congenital absence of anus | | Digestive |
| PB20100 | Congenital absence of appendix | | Digestive |
| PB20200 | Congenital absence of rectum | | Digestive |
| PB20211 | Agenesis of rectum | | Digestive |
| PB20300 | Congenital absence of anus with fistula | | Digestive |
| PB20400 | Congenital absence of rectum with fistula | | Digestive |
| PB20411 | Agenesis of rectum with fistula | | Digestive |
| PB21.00 | Atresia of large intestine | | Digestive |
| PB21000 | Atresia of anus | | Digestive |
| PB21100 | Atresia of colon | | Digestive |
| PB21200 | Atresia of rectum | | Digestive |
| PB21300 | Atresia of appendix | | Digestive |
| PB21400 | Atresia of anus with fistula | | Digestive |
| PB21500 | Atresia of rectum with fistula | | Digestive |
| PB22.00 | Congenital obstruction of large intestine | | Digestive |
| PB22.11 | Congenital stenosis of large intestine | | Digestive |
| PB23.00 | Congenital occlusion of anus | | Digestive |
| PB23.11 | Anal septum | | Digestive |
| PB23000 | Congenital occlusion of anus with fistula | | Digestive |
| PB23z00 | Congenital occlusion of anus nos | | Digestive |
| PB24.00 | Congenital stricture of anus | | Digestive |
| PB24.11 | Congenital anal stricture | | Digestive |
| PB24000 | Congenital stricture of anus with fistula | | Digestive |
| PB24011 | Congenital stenosis of anus with fistula | | Digestive |
| PB24100 | Congenital stricture of anus without mention of fistula | | Digestive |
| PB24111 | Congenital stenosis of anus without mention of fistula | | Digestive |
| PB24z00 | Congenital stricture of anus nos | | Digestive |
| PB25.00 | Congenital stricture of rectum | | Digestive |
| PB25.11 | Congenital rectal stricture | | Digestive |
| PB25000 | Congenital stricture of rectum with fistula | | Digestive |
| PB25011 | Congenital stenosis of rectum with fistula | | Digestive |
| PB25111 | Congenital stenosis of rectum without mention of fistula | | Digestive |
| PB25z00 | Congenital stricture of rectum nos | | Digestive |
| PB26.00 | Imperforate anus | | Digestive |
| PB26000 | Imperforate anus with fistula | | Digestive |
| PB26z00 | Imperforate anus nos | | Digestive |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PB27.00 | Imperforate rectum | | Digestive |
| PB27000 | Imperforate rectum with fistula | | Digestive |
| PB2z.00 | Atresia and stenosis of large intestine/rectum/anus nos | | Digestive |
| PB3..00 | Hirschsprung's disease and allied congenital conditions | | Digestive |
| PB3..11 | Aganglionosis | | Digestive |
| PB30.00 | Hirschsprung's disease | | Digestive |
| PB30000 | Long segment hirschsprung's disease | | Digestive |
| PB30100 | Short segment hirschsprung's disease | | Digestive |
| PB30z00 | Hirschsprung's disease nos | | Digestive |
| PB31.00 | Idiopathic congenital megacolon | | Digestive |
| PB33.00 | Total intestinal aganglionosis | | Digestive |
| PB33.11 | Aganglionic macrocolon | | Digestive |
| PB33.12 | Congenital aganglionic megacolon | | Digestive |
| PB3z.00 | Hirschsprung's disease and allied congenital conditions nos | | Digestive |
| PB4..00 | Intestinal fixation anomalies | | Digestive |
| PB40.00 | Congenital intestinal adhesions | | Digestive |
| PB40000 | Congenital omental adhesions | | Digestive |
| PB40100 | Jackson's membrane | | Digestive |
| PB40200 | Congenital peritoneal adhesions | | Digestive |
| PB40211 | Congenital peritoneal bands | | Digestive |
| PB40z00 | Congenital intestinal adhesions nos | | Digestive |
| PB41.00 | Malrotation of colon and caecum | | Digestive |
| PB41000 | Malrotation of colon | | Digestive |
| PB41100 | Malrotation of caecum | | Digestive |
| PB41z00 | Malrotation of colon or caecum nos | | Digestive |
| PB42.00 | Universal mesentery | | Digestive |
| PB43.00 | Other anomalies of mesentery | | Digestive |
| PB4y.00 | Other specified intestinal fixation anomaly | | Digestive |
| PB4z.00 | Intestinal fixation anomaly nos | | Digestive |
| PB4z.11 | Malfixation of gut nec | | Digestive |
| PB4z.12 | Malrotation of gut | | Digestive |
| PB4z.13 | Malrotation of intestine | | Digestive |
| PB5..00 | Other anomalies of intestine | | Digestive |
| PB50.00 | Congenital diverticulum of colon | | Digestive |
| PB51.00 | Dolichocolon | | Digestive |
| PB52.00 | Duplication of intestine | | Digestive |
| PB52000 | Duplication of intestine, unspecified | | Digestive |
| PB52100 | Duplication of anus | | Digestive |
| PB52300 | Duplication of caecum | | Digestive |
| PB52z00 | Duplication of intestine nos | | Digestive |
| PB52z11 | Congenital redundant rectal mucosa | | Digestive |
| PB52z12 | Congenital redundant colon | | Digestive |
| PB53.00 | Transposition of intestine | | Digestive |
| PB53000 | Transposition of intestine, unspecified | | Digestive |
| PB53100 | Transposition of appendix | | Digestive |
| PB53200 | Transposition of caecum | | Digestive |
| PB53300 | Transposition of colon | | Digestive |
| PB53z00 | Transposition of intestine nos | | Digestive |
| PB54.00 | Ectopic anus | | Digestive |
| PB56.00 | Megaloduodenum | | Digestive |
| PB57.00 | Microcolon | | Digestive |
| PB58.00 | Persistent cloaca | | Digestive |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PB58.11 | Anal fusion | | Digestive |
| PB59.00 | Congenital anal fistula | | Digestive |
| PB5A.00 | Enterogenous cyst | | Digestive |
| PB5X.00 | Congenital malformation of intestine, unspecified | | Digestive |
| PB5z.00 | Other intestine anomalies nos | | Digestive |
| PB5z.11 | Congenital volvulus | | Digestive |
| PB5z000 | Congenital faecal fistula | | Digestive |
| PB6..00 | Liver and biliary system anomalies | | Digestive |
| PB6..11 | Bile duct anomalies | | Digestive |
| PB6..12 | Biliary anomalies | | Digestive |
| PB6..13 | Gallbladder anomalies | | Digestive |
| PB6..14 | Liver anomalies | | Digestive |
| PB60.00 | Liver and biliary system anomalies, unspecified | | Digestive |
| PB60000 | Liver anomaly, unspecified | | Digestive |
| PB60100 | Gallbladder anomaly, unspecified | | Digestive |
| PB60200 | Bile duct anomaly, unspecified | | Digestive |
| PB60z00 | Unspecified liver and biliary system anomaly nos | | Digestive |
| PB61.00 | Biliary atresia | | Digestive |
| PB61000 | Congenital absence of bile duct | | Digestive |
| PB61200 | Congenital obstruction of bile duct | | Digestive |
| PB61300 | Congenital stricture of bile duct | | Digestive |
| PB61311 | Congenital stricture of common bile duct | | Digestive |
| PB61400 | Atresia of bile duct | | Digestive |
| PB61411 | Intrahepatic atresia of bile duct | | Digestive |
| PB61412 | Extrahepatic atresia of bile duct | | Digestive |
| PB61500 | Congenital absence of hepatic ducts | | Digestive |
| PB61600 | Atresia of hepatic ducts | | Digestive |
| PB61z00 | Biliary atresia nos | | Digestive |
| PB62.00 | Congenital cystic liver disease | | Digestive |
| PB62.11 | Congenital hepatic cyst | | Digestive |
| PB62000 | Congenital polycystic liver disease | | Digestive |
| PB62100 | Fibrocystic liver disease | | Digestive |
| PB62z00 | Congenital cystic liver disease nos | | Digestive |
| PB63000 | Congenital absence of gallbladder | | Digestive |
| PB63011 | Agenesis of gallbladder | | Digestive |
| PB63100 | Congenital absence of liver lobe | | Digestive |
| PB63300 | Riedel's lobe liver | | Digestive |
| PB64000 | Duplication of biliary duct | | Digestive |
| PB64100 | Duplication of cystic duct | | Digestive |
| PB64200 | Duplication of gallbladder | | Digestive |
| PB64311 | Accessory liver | | Digestive |
| PB6y.00 | Other liver and biliary anomalies | | Digestive |
| PB6y000 | Congenital choledochal cyst | | Digestive |
| PB6y100 | Congenital hepatomegaly | | Digestive |
| PB6y200 | Congenital floating gallbladder | | Digestive |
| PB6y400 | Intrahepatic gallbladder | | Digestive |
| PB6y500 | Hypoplasia of gallbladder | | Digestive |
| PB6y600 | Atrophy of left lobe of liver | | Digestive |
| PB6y700 | Congenital dilation of bile duct | | Digestive |
| PB6y800 | Congenital diverticulum of bile duct | | Digestive |
| PB6y900 | Liver hyperplasia | | Digestive |
| PB6yw00 | Other congenital anomaly of liver | | Digestive |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PB6yw12 | Abnormal liver lobulation | | Digestive |
| PB6yw13 | Trilobular liver | | Digestive |
| PB6yx00 | Other congenital anomaly of gallbladder | | Digestive |
| PB6yy00 | Other congenital anomaly of hepatic or bile ducts | | Digestive |
| PB6yz00 | Other liver or biliary system anomalies nos | | Digestive |
| PB6z.00 | Liver or biliary system anomalies nos | | Digestive |
| PB7..00 | Anomalies of pancreas | | Digestive |
| PB72.00 | Hypoplasia of pancreas | | Digestive |
| PB73.00 | Accessory pancreas | | Digestive |
| PB74.00 | Annular pancreas | | Digestive |
| PB75.00 | Ectopic pancreas | | Digestive |
| PB76.00 | Pancreatic heterotopia | | Digestive |
| PB77.00 | Pancreatic cyst, congenital | | Digestive |
| PB7y.00 | Other specified anomalies of pancreas | | Digestive |
| PB7z.00 | Anomalies of pancreas nos | | Digestive |
| PBy..00 | Other specified digestive system anomalies | | Digestive |
| PBy0.00 | Congenital absence of digestive system nos | | Digestive |
| PBy1.00 | Duplication of digestive system nos | | Digestive |
| PBy2.00 | Congenital malposition of digestive system nos | | Digestive |
| PBy2.11 | Ectopic digestive organs nos | | Digestive |
| PByz.00 | Other specified digestive system anomalies nos | | Digestive |
| PBz..00 | Digestive system anomalies nos | | Digestive |
| PG61.00 | Congenital diaphragmatic hernia | | Digestive |
| Pyu5000 | [X]other congenital malformations of tongue | | Digestive |
| Pyu5100 | [X]Congenital malformations of palate, NEC | | Digestive |
| Pyu5200 | [X]Other congenital malformations of mouth | | Digestive |
| Pyu5700 | [X]Cong absence/atresia/stenos oth spec parts small intest | | Digestive |
| Pyu5D00 | [X]Other congenital malformations of bile ducts | | Digestive |
| Pyu5E00 | [X]Other congenital malformations of liver | | Digestive |
| Pyu5F00 | [X]Other congen malformation of pancreas & pancreatic duct | | Digestive |
| Q435000 | Perinatal jaundice due to congenital obstruction bile duct | | Digestive |
| 7300200 | Excision of preauricular abnormality | Yes | Ear, Face & Neck |
| 7302200 | Pinnaplasty | Yes | Ear, Face & Neck |
| 7302211 | Bat ear pinnaplasty | Yes | Ear, Face & Neck |
| 7302212 | Correction of prominent ear | Yes | Ear, Face & Neck |
| 7302213 | Mustarde pinnaplasty | Yes | Ear, Face & Neck |
| 7302214 | Revision pinnaplasty | Yes | Ear, Face & Neck |
| 7H67100 | Operation on branchial cleft nec | Yes | Ear, Face & Neck |
| 7H67200 | Excision of branchial cyst | Yes | Ear, Face & Neck |
| 7H67300 | Closure of branchial fistula | Yes | Ear, Face & Neck |
| 7H67w00 | Other specified operation on branchial cleft | Yes | Ear, Face & Neck |
| 7H67x00 | Operation on branchial cleft nos | Yes | Ear, Face & Neck |
| J085300 | Hypertrophy of lip | Yes | Ear, Face & Neck |
| P402100 | Stenosis of external auditory canal | Yes | Ear, Face & Neck |
| P402111 | Congenital stricture of external auditory canal | Yes | Ear, Face & Neck |
| P402112 | Congenital stricture of osseous meatus | Yes | Ear, Face & Neck |
| P41..00 | Accessory ear auricle | Yes | Ear, Face & Neck |
| P41..11 | Polyotia | Yes | Ear, Face & Neck |
| P410.00 | Supernumerary ear | Yes | Ear, Face & Neck |
| P411.00 | Accessory tragus | Yes | Ear, Face & Neck |
| P412.00 | Supernumerary ear lobule | Yes | Ear, Face & Neck |
| P413.00 | Preauricular appendage, tag or lobule | Yes | Ear, Face & Neck |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P413.11 | Preauricular appendage | Yes | Ear, Face & Neck |
| P413.12 | Preauricular tag | Yes | Ear, Face & Neck |
| P413.13 | Preauricular lobule | Yes | Ear, Face & Neck |
| P414.00 | Other ear appendage or tag | Yes | Ear, Face & Neck |
| P414.11 | Other ear appendage | Yes | Ear, Face & Neck |
| P414.12 | Other ear tag | Yes | Ear, Face & Neck |
| P41z.00 | Accessory ear auricle nos | Yes | Ear, Face & Neck |
| P421.00 | Macrotia - abnormally big ears | Yes | Ear, Face & Neck |
| P421.11 | Congenital big ears | Yes | Ear, Face & Neck |
| P422.00 | Microtia - abnormally small ears | Yes | Ear, Face & Neck |
| P422.11 | Congenital small ears | Yes | Ear, Face & Neck |
| P42z000 | Congenital bat ear | Yes | Ear, Face & Neck |
| P42z100 | Darwin's tubercle | Yes | Ear, Face & Neck |
| P42z200 | Congenital pointed ear | Yes | Ear, Face & Neck |
| P42z300 | Congenital prominent auricle | Yes | Ear, Face & Neck |
| P42z400 | Congenital ridge ear | Yes | Ear, Face & Neck |
| P42z500 | Other mis-shapen ear | Yes | Ear, Face & Neck |
| P42z511 | Aztec ear | Yes | Ear, Face & Neck |
| P42z512 | Cat ear | Yes | Ear, Face & Neck |
| P42z513 | Vulcan ear | Yes | Ear, Face & Neck |
| P42z600 | Misplaced ears | Yes | Ear, Face & Neck |
| P42z611 | Low-set ears | Yes | Ear, Face & Neck |
| P44..00 | Branchial cleft, cyst or fistula; preauricular sinus | Yes | Ear, Face & Neck |
| P440.00 | Branchial cleft sinus and fistula | Yes | Ear, Face & Neck |
| P440.11 | Branchial cleft | Yes | Ear, Face & Neck |
| P440.12 | Branchial cleft sinus | Yes | Ear, Face & Neck |
| P440000 | Branchial cleft vestige, unspecified | Yes | Ear, Face & Neck |
| P440100 | Branchial cleft external sinus | Yes | Ear, Face & Neck |
| P440200 | Branchial cleft internal sinus | Yes | Ear, Face & Neck |
| P440300 | Branchial cleft fistula | Yes | Ear, Face & Neck |
| P440z00 | Branchial cleft vestige nos | Yes | Ear, Face & Neck |
| P441.00 | Branchial cleft cyst | Yes | Ear, Face & Neck |
| P442.00 | Cervical auricle | Yes | Ear, Face & Neck |
| P443.00 | Preauricular sinus and fistula | Yes | Ear, Face & Neck |
| P443000 | Preauricular sinus | Yes | Ear, Face & Neck |
| P443100 | Preauricular fistula | Yes | Ear, Face & Neck |
| P443z00 | Preauricular sinus or fistula nos | Yes | Ear, Face & Neck |
| P444.00 | Preauricular cyst | Yes | Ear, Face & Neck |
| P44y.00 | Other branchial cleft anomalies | Yes | Ear, Face & Neck |
| P44z.00 | Branchial cleft,cyst,or fistula preauricular anomaly os/nos | Yes | Ear, Face & Neck |
| P44z000 | Fistula of congenital auricle | Yes | Ear, Face & Neck |
| P44z100 | Cervicoaural fistula | Yes | Ear, Face & Neck |
| P44zz00 | Branchial cleft, cyst or fistula preauricular anomaly nos | Yes | Ear, Face & Neck |
| P4y0.00 | Macrocheilia | Yes | Ear, Face & Neck |
| P4y0.11 | Lip hypertrophy | Yes | Ear, Face & Neck |
| P4y1.00 | Microcheilia | Yes | Ear, Face & Neck |
| P4y2.00 | Macrostomia | Yes | Ear, Face & Neck |
| P4y3.00 | Microstomia | Yes | Ear, Face & Neck |
| Pyu1E00 | [X]other branchial cleft malformations | Yes | Ear, Face & Neck |
| 7306100 | Reconstruction of external auditory canal | | Ear, Face & Neck |
| 7306111 | Pattee reconstruction of external auditory canal | | Ear, Face & Neck |
| 7308.00 | Attachment of auricular prosthesis | | Ear, Face & Neck |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7308000 | Insertion of fixtures for auricular prosthesis stage 1 | | Ear, Face & Neck |
| 7308100 | Insertion of fixtures for auricular prosthesis stage 2 | | Ear, Face & Neck |
| 7308300 | Attention to fixtures for auricular prosthesis | | Ear, Face & Neck |
| 7K6T000 | Release of webbing of neck | | Ear, Face & Neck |
| J040.15 | Micrognathism | | Ear, Face & Neck |
| J040300 | Mandibular micrognathism | | Ear, Face & Neck |
| J040800 | Maxillary micrognathism | | Ear, Face & Neck |
| J040B00 | Micrognathism unspecified | | Ear, Face & Neck |
| P4...00 | Ear, face and neck congenital anomalies | | Ear, Face & Neck |
| P40..00 | Ear anomalies with hearing impairment | | Ear, Face & Neck |
| P400.00 | Ear anomalies with hearing impaired, unspecified | | Ear, Face & Neck |
| P401.00 | Congenital absence of external ear | | Ear, Face & Neck |
| P401000 | Congenital absence of external ear, unspecified | | Ear, Face & Neck |
| P401011 | Absence of ear nos | | Ear, Face & Neck |
| P401100 | Absence of external auditory canal | | Ear, Face & Neck |
| P401200 | Ear auricle and external auditory canal absent | | Ear, Face & Neck |
| P401211 | Congenital absence ear auricle | | Ear, Face & Neck |
| P401300 | Congenital absence of auricle | | Ear, Face & Neck |
| P401z00 | Absence of external ear nos | | Ear, Face & Neck |
| P402.00 | Other external ear anomaly with hearing impairment | | Ear, Face & Neck |
| P402000 | Atresia of external auditory canal | | Ear, Face & Neck |
| P402z00 | Other external ear anomaly with hearing impairment nos | | Ear, Face & Neck |
| P403.00 | Middle ear anomaly, excluding ossicles | | Ear, Face & Neck |
| P403000 | Ear osseous meatus atresia | | Ear, Face & Neck |
| P403z00 | Middle ear anomaly nec nos | | Ear, Face & Neck |
| P404.00 | Anomaly of ossicles | | Ear, Face & Neck |
| P404000 | Congenital fusion of ear ossicles | | Ear, Face & Neck |
| P404z00 | Anomaly of ossicles nos | | Ear, Face & Neck |
| P405.00 | Inner ear anomalies | | Ear, Face & Neck |
| P405z00 | Inner ear anomalies nos | | Ear, Face & Neck |
| P40z.00 | Other and unspecified ear anomaly with hearing impaired | | Ear, Face & Neck |
| P40z.11 | Deafness due to congenital anomaly nec | | Ear, Face & Neck |
| P40z000 | Congenital absence of ear nos | | Ear, Face & Neck |
| P40zz00 | Ear anomaly with hearing impaired nos | | Ear, Face & Neck |
| P42..00 | Other specified ear anomalies | | Ear, Face & Neck |
| P420.00 | Congenital ear lobe absence | | Ear, Face & Neck |
| P423.00 | Eustachian tube anomalies | | Ear, Face & Neck |
| P423100 | Congenital stenosis of eustachian tube | | Ear, Face & Neck |
| P423z00 | Eustachian tube anomalies nos | | Ear, Face & Neck |
| P42z.00 | Other specified ear anomalies nos | | Ear, Face & Neck |
| P42zz00 | Other ear anomalies nos | | Ear, Face & Neck |
| P43..00 | Congenital ear anomaly nos | | Ear, Face & Neck |
| P45..00 | Congenital webbing of neck | | Ear, Face & Neck |
| P451.00 | Pterygium colli | | Ear, Face & Neck |
| P45z.00 | Congenital webbing of neck nos | | Ear, Face & Neck |
| P4y..00 | Other specified face and neck anomalies | | Ear, Face & Neck |
| P4y4.00 | Congenital absence of chin | | Ear, Face & Neck |
| P4y5.00 | Mid-facial hypoplasia | | Ear, Face & Neck |
| P4yz.00 | Other specified face and neck anomalies nos | | Ear, Face & Neck |
| P4z..00 | Congenital face or neck anomaly nos | | Ear, Face & Neck |
| P4z0.00 | Congenital anomaly of neck nos | | Ear, Face & Neck |
| P4z1.00 | Congenital anomaly of face nos | | Ear, Face & Neck |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PE0..11 | Face congenital deformities | | Ear, Face & Neck |
| Pyu1.00 | [X]congenital malformations of eye, ear, face and neck | | Ear, Face & Neck |
| Pyu1900 | [X]other congenital malformations of middle ear | | Ear, Face & Neck |
| Pyu1A00 | [X]congenital malformation of inner ear | | Ear, Face & Neck |
| Pyu1B00 | [X]malformation of ear with impairment of hearing, unspec | | Ear, Face & Neck |
| Pyu1D00 | [X]other specified congenital malformations of ear | | Ear, Face & Neck |
| Pyu1F00 | [X]other specified congenital malformations of face & neck | | Ear, Face & Neck |
| F4E4600 | Other blepharophimosis | Yes | Eye |
| P361.00 | Congenital eyelid deformity | Yes | Eye |
| P361000 | Ablepharon -absent eyelids | Yes | Eye |
| P361100 | Accessory eyelid | Yes | Eye |
| P361200 | Congenital entropion | Yes | Eye |
| P361300 | Congenital ectropion | Yes | Eye |
| P361400 | Congenital blepharophimosis | Yes | Eye |
| P361500 | Coloboma of eyelids | Yes | Eye |
| P361z00 | Congenital eyelid deformity nos | Yes | Eye |
| P362.00 | Other specified congenital eyelid anomalies | Yes | Eye |
| P362000 | Agenesis of cilia | Yes | Eye |
| P362100 | Agenesis of eyelid | Yes | Eye |
| P362200 | Fused eyelids | Yes | Eye |
| P362z00 | Other specified congenital eyelid anomalies nos | Yes | Eye |
| P364300 | Stenosis or stricture of lacrimal duct | Yes | Eye |
| P364y00 | Other specified congenital anomaly of lacrimal passages | Yes | Eye |
| P364z00 | Congenital anomaly of lacrimal passages nos | Yes | Eye |
| P36z000 | Accessory eye muscles | Yes | Eye |
| P36z100 | Hypoplasia of eye muscle | Yes | Eye |
| p341.11 | Arcus juvenilis | Yes | Eye |
| p364200 | Accessory lacrimal canal | Yes | Eye |
| 1482.00 | H/o: glaucoma | | Eye |
| 2BB4.00 | O/e - retinal microaneurysms | | Eye |
| 7255411 | Insertion molteno implantation tube in anterior chamber eye | | Eye |
| 7258600 | Excision of pupillary membrane | | Eye |
| 7259.00 | Operations following glaucoma surgery | | Eye |
| 7259000 | Needling of bleb following glaucoma surgery | | Eye |
| 7259100 | Injection of bleb following glaucoma surgery | | Eye |
| 7259200 | Revision of bleb nec following glaucoma surgery | | Eye |
| 7259300 | Removal of releasable suture following glaucoma surgery | | Eye |
| 7259400 | Laser suture lysis following glaucoma surgery | | Eye |
| 7259y00 | Other specified operations following glaucoma surgery | | Eye |
| 7259z00 | Operations following glaucoma surgery nos | | Eye |
| 7275.00 | Pan retinal photocoagulation for glaucoma | | Eye |
| 8D35.00 | Spectacles for aphakia | | Eye |
| F404211 | Glaucoma - absolute | | Eye |
| F421800 | Retinal microaneurysms nos | | Eye |
| F442100 | Glaucomatocyclitic crises | | Eye |
| F447700 | Pupillary membranes nos | | Eye |
| F45..00 | Glaucoma | | Eye |
| F450.00 | Borderline glaucoma | | Eye |
| F450000 | Unspecified preglaucoma | | Eye |
| F450100 | Open angle glaucoma with borderline intraocular pressure | | Eye |
| F450200 | Borderline glaucoma with anatomical narrow angle | | Eye |
| F450300 | Borderline glaucoma steroid responder | | Eye |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| F450z00 | Borderline glaucoma nos | | Eye |
| F451.00 | Open-angle glaucoma | | Eye |
| F451000 | Unspecified open-angle glaucoma | | Eye |
| F451100 | Primary open-angle glaucoma | | Eye |
| F451111 | Simple chronic glaucoma | | Eye |
| F451200 | Low tension glaucoma | | Eye |
| F451211 | Normal pressure glaucoma | | Eye |
| F451300 | Pigmentary glaucoma | | Eye |
| F451400 | Glaucoma of childhood | | Eye |
| F451500 | Open-angle glaucoma residual stage | | Eye |
| F451z00 | Open-angle glaucoma nos | | Eye |
| F452.00 | Primary angle-closure glaucoma | | Eye |
| F452.11 | Closed angle glaucoma | | Eye |
| F452000 | Unspecified primary angle-closure glaucoma | | Eye |
| F452100 | Intermittent primary angle-closure glaucoma | | Eye |
| F452200 | Acute primary angle-closure glaucoma | | Eye |
| F452300 | Chronic primary angle-closure glaucoma | | Eye |
| F452400 | Primary angle-closure glaucoma residual stage | | Eye |
| F452z00 | Primary angle-closure glaucoma nos | | Eye |
| F454000 | Glaucoma due to chamber angle anomaly | | Eye |
| F454100 | Glaucoma due to iris anomaly | | Eye |
| F454200 | Glaucoma due to other anterior segment anomaly | | Eye |
| F455.00 | Glaucoma associated with disorders of the lens | | Eye |
| F455000 | Phacolytic glaucoma | | Eye |
| F455100 | Pseudoexfoliation glaucoma | | Eye |
| F455z00 | Glaucoma associated with disorders of the lens nos | | Eye |
| F456100 | Glaucoma due to pupillary block | | Eye |
| F45y.00 | Other specified forms of glaucoma | | Eye |
| F45yz00 | Other specified glaucoma nos | | Eye |
| F45z.00 | Glaucoma nos | | Eye |
| F463100 | Glaucomatous subcapsular flecks | | Eye |
| F4B..00 | Corneal opacity and other disorders of cornea | | Eye |
| F4B0.00 | Corneal scars and opacities | | Eye |
| F4B0000 | Unspecified corneal opacity | | Eye |
| F4B0100 | Minor opacity of cornea | | Eye |
| F4B0200 | Peripheral opacity of cornea | | Eye |
| F4B0300 | Central opacity of cornea | | Eye |
| F4B0z00 | Corneal scar or opacity nos | | Eye |
| F4E6.00 | Blepharochalasis | | Eye |
| F4H1400 | Optic disc glaucomatous atrophy | | Eye |
| F4H2200 | Coloboma of optic disc | | Eye |
| F4K3.00 | Aphakia and other disorders of lens | | Eye |
| F4K3000 | Aphakia | | Eye |
| F4K3z00 | Aphakia and other disorders of lens nos | | Eye |
| F4K4100 | Anisocoria - unequal pupil diameter | | Eye |
| FyuG.00 | [X]glaucoma | | Eye |
| FyuG000 | [X]other glaucoma | | Eye |
| P3...00 | Congenital eye anomalies | | Eye |
| P30..00 | Anophthalmos | | Eye |
| P300.00 | Clinical anophthalmos, unspecified | | Eye |
| P300100 | Agenesis of eye | | Eye |
| P300200 | Congenital absence of eye | | Eye |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P300z00 | Anophthalmos nos | | Eye |
| P301.00 | Congenital cystic eyeball | | Eye |
| P303.00 | Congenital absence of eyes | | Eye |
| P30z.00 | Anophthalmos nos | | Eye |
| P31..00 | Microphthalmos | | Eye |
| P310.00 | Microphthalmos, unspecified | | Eye |
| P310000 | Dysplasia of eye | | Eye |
| P310100 | Hypoplasia of eye | | Eye |
| P310200 | Rudimentary eye | | Eye |
| P310z00 | Unspecified microphthalmos nos | | Eye |
| P311.00 | Simple microphthalmos | | Eye |
| P312.00 | Microphthalmos with other eye anomaly | | Eye |
| P31z.00 | Microphthalmos nos | | Eye |
| P32..00 | Buphthalmos | | Eye |
| P320000 | Congenital glaucoma | | Eye |
| P320011 | Newborn glaucoma | | Eye |
| P320z00 | Unspecified buphthalmos nos | | Eye |
| P321.00 | Simple buphthalmos | | Eye |
| P32z.00 | Buphthalmos nos | | Eye |
| P33..00 | Congenital cataract and lens anomalies | | Eye |
| P33..11 | Congenital lens anomaly | | Eye |
| P330.00 | Congenital cataract, unspecified | | Eye |
| P332000 | Cortical cataract - congenital | | Eye |
| P333.00 | Nuclear cataract - congenital | | Eye |
| P334000 | Total congenital cataract | | Eye |
| P334z00 | Total or subtotal congenital cataract nos | | Eye |
| P335.00 | Congenital aphakia | | Eye |
| P335.11 | Congenital absence of lens | | Eye |
| P336.00 | Anomalies of lens shape | | Eye |
| P336200 | Coloboma of lens | | Eye |
| P336z00 | Anomalies of lens shape nos | | Eye |
| P337.00 | Congenital ectopic lens | | Eye |
| P337.11 | Congenital displaced lens | | Eye |
| P337.12 | Congenital dislocation of lens | | Eye |
| P33y.00 | Other specified congenital cataract or lens anomaly | | Eye |
| P33y100 | Congenital membranous cataract | | Eye |
| P33yz00 | Other congenital cataract or lens anomaly nos | | Eye |
| P33z.00 | Congenital cataract or lens anomaly nos | | Eye |
| P340.00 | Corneal size and shape anomalies | | Eye |
| P340000 | Microcornea | | Eye |
| P340z00 | Corneal size or shape anomalies nos | | Eye |
| P341.00 | Congenital corneal opacities | | Eye |
| P341000 | Congenital corneal opacity with visual deficit | | Eye |
| P341100 | Congenital corneal opacity without visual deficit | | Eye |
| P341z00 | Congenital corneal opacities nos | | Eye |
| P344.11 | Goniodysgenesis | | Eye |
| P344000 | Congenital anisocoria | | Eye |
| P344100 | Atresia of pupil | | Eye |
| P344200 | Coloboma of iris | | Eye |
| P344300 | Corectopia | | Eye |
| P344400 | Polycoria | | Eye |
| P344z00 | Other iris or ciliary body anomalies nos | | Eye |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P35..00 | Posterior chamber congenital anomalies | | Eye |
| P350.00 | Vitreous anomalies | | Eye |
| P350000 | Congenital vitreous opacity | | Eye |
| P350z00 | Vitreous anomalies nos | | Eye |
| P351.00 | Fundus coloboma | | Eye |
| P352.00 | Congenital chorioretinal degeneration | | Eye |
| P353000 | Congenital folds of the posterior segment | | Eye |
| P353100 | Congenital cysts of the posterior segment | | Eye |
| P355.00 | Other congenital retinal changes | | Eye |
| P355000 | Coloboma of retina | | Eye |
| P355100 | Congenital retinal fold | | Eye |
| P355200 | Congenital hypertrophy of retinal pigment epithelium | | Eye |
| P355z00 | Other congenital retinal changes nos | | Eye |
| P356.00 | Specified optic disc anomalies | | Eye |
| P356.11 | Optic disc congenital anomalies | | Eye |
| P356000 | Congenital optic disc coloboma | | Eye |
| P356z00 | Specified optic disc anomaly nos | | Eye |
| P357000 | Congenital retinal aneurysm | | Eye |
| P358.00 | Specified anomalies of choroid | | Eye |
| P358000 | Coloboma of choroid | | Eye |
| P358z00 | Specified anomaly of choroid nos | | Eye |
| P35y.00 | Other specified congenital anomalies of posterior chamber | | Eye |
| P35z.00 | Congenital anomalies of posterior chamber nos | | Eye |
| P36..00 | Congenital anomalies of eyelid, lacrimal system and orbit | | Eye |
| P360.00 | Congenital ptosis | | Eye |
| P360.11 | Blepharoptosis | | Eye |
| P362300 | Hypoplasia of eyelid | | Eye |
| P363.00 | Congenital lacrimal gland anomalies | | Eye |
| P364.00 | Congenital lacrimal passage anomalies | | Eye |
| P364.11 | Congenital blocked tear duct | | Eye |
| P364000 | Agenesis of lacrimal apparatus | | Eye |
| P364011 | Congenital absence of lacrimal apparatus | | Eye |
| P364100 | Agenesis of punctum lacrimale | | Eye |
| P364111 | Congenital absence of punctum lacrimale | | Eye |
| P364400 | Congenital blocked tear duct | | Eye |
| P365.00 | Congenital orbit anomalies | | Eye |
| P36z.00 | Other/unspecified anomalies of eyelid/lacrimal system/orbit | | Eye |
| P36zz00 | Eyelid, lacrimal system and orbit congenital anomalies nos | | Eye |
| P37..00 | Macrophthalmos | | Eye |
| P3y..00 | Other specified eye anomalies | | Eye |
| P3yz.00 | Other eye anomalies nos | | Eye |
| P3z..00 | Congenital eye anomalies nos | | Eye |
| Pyu1100 | [X]other congenital malformations of lacrimal apparatus | | Eye |
| Pyu1200 | [X]other anophthalmos | | Eye |
| Pyu1300 | [X]other congenital lens malformations | | Eye |
| Pyu1400 | [X]other congenital malformations of iris | | Eye |
| Pyu1600 | [X]other congenital malforms of anterior segment of eye | | Eye |
| Pyu1800 | [X]other specified congenital malformations of eye | | Eye |
| p321.11 | Enlarged eye nos | | Eye |
| p331.00 | Capsular and subcapsular cataract | | Eye |
| p331000 | Capsular cataract | | Eye |
| p331100 | Subcapsular cataract | | Eye |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| p331z00 | Capsular or subcapsular cataract nos | | Eye |
| p332.00 | Cortical and zonular cataract | | Eye |
| p332100 | Zonular cataract | | Eye |
| p332z00 | Cortical or zonular cataract nos | | Eye |
| p335.12 | Agenesis of lens | | Eye |
| p33y000 | Blue dot cataract | | Eye |
| p34..00 | Anterior chamber anomalies | | Eye |
| p340100 | Congenital keratoconus | | Eye |
| p340200 | Cornea plana | | Eye |
| p342.00 | Specified anterior chamber anomalies | | Eye |
| p342z00 | Specified anterior chamber anomalies nos | | Eye |
| p344500 | Hypoplasia of iris | | Eye |
| p344600 | Aplasia of iris | | Eye |
| p345.00 | Specified anomalies of sclera | | Eye |
| p345z00 | Specified anomaly of sclera nos | | Eye |
| p34z.00 | Anterior segment anomalies nos | | Eye |
| PC6..00 | Hypospadias and epispadias | | Genital/Urinary |
| PC6z.00 | Hypospadias or epispadias nos | | Genital/Urinary |
| 7C08600 | Correction of hydrocele of infancy | Yes | Genital |
| 7D14.00 | Excision of band of vagina | Yes | Genital |
| 7D14000 | Laser excision of septum of vagina | Yes | Genital |
| 7D14100 | Excision of septum of vagina nec | Yes | Genital |
| 7D14200 | Excision of transverse vaginal septum high | Yes | Genital |
| 7D14300 | Excision of transverse vaginal septum low | Yes | Genital |
| 7D14400 | Excision of transverse vaginal septum vertical | Yes | Genital |
| 7D14y00 | Other specified excision of band of vagina | Yes | Genital |
| 7D14z00 | Excision of band of vagina nos | Yes | Genital |
| 7H10200 | Ligation of patent processus vaginalis | Yes | Genital |
| K562z11 | Vaginal band | Yes | Genital |
| PC04.00 | Developmental ovarian cyst | Yes | Genital |
| PC41200 | Congenital cyst of vulva | Yes | Genital |
| PC42.00 | Imperforate hymen | Yes | Genital |
| PC4y600 | Congenital absence of vulva | Yes | Genital |
| PC4y700 | Agenesis of vulva | Yes | Genital |
| PC4yB11 | Imperforate vagina | Yes | Genital |
| PC4yD11 | Fusion of labia | Yes | Genital |
| PC4yE00 | Congenital labial adhesions | Yes | Genital |
| PC4yy12 | Hypertrophy of clitoris | Yes | Genital |
| PCy2000 | Hypoplasia of penis | Yes | Genital |
| PCy7.00 | Congenital lateral curvature of penis | Yes | Genital |
| PCyw.00 | Other congenital anomaly of testis or scrotum | Yes | Genital |
| PCyy000 | Hooded penis | Yes | Genital |
| PCyy100 | Webbed penis | Yes | Genital |
| Q476.00 | Congenital hydrocele | Yes | Genital |
| Q476.11 | Patent processus vaginalis | Yes | Genital |
| 7B41000 | Other hypospadias repair | | Genital |
| 7B41011 | Byars hypospadias repair | | Genital |
| 7B41012 | Cecil reconstruction of urethra | | Genital |
| 7B41013 | Denis - browne hypospadias repair | | Genital |
| 7B41014 | Ombredanne hypospadias repair | | Genital |
| 7B41015 | Van der meulen hypospadias repair | | Genital |
| 7B41016 | Young hypospadias repair | | Genital |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7B41017 | First stage hypospadias repair | | Genital |
| 7B41018 | Second stage hypospadias repair | | Genital |
| 7B41700 | Magpi hypospadias repair | | Genital |
| 7B41800 | Duckett hypospadias repair | | Genital |
| 7C04200 | Excision of cyst of male hydatid of morgagni | | Genital |
| 7C09700 | Excision of appendix of testis | | Genital |
| 7C09711 | Excision of male hydatid of morgagni | | Genital |
| 7C25400 | Correction of chordee | | Genital |
| 7C25411 | Release of chordee | | Genital |
| 7D1A200 | Repair of rectovaginal fistula | | Genital |
| 7E0D014 | Endoscopic resection of uterine septum | | Genital |
| 7E1A200 | Excision of hydatid of morgagni | | Genital |
| 7L0B200 | Excision of ovotestis | | Genital |
| K521200 | Rectovaginal fistula | | Genital |
| K562.00 | Stricture or atresia of the vagina | | Genital |
| K562.12 | Atresia of vagina | | Genital |
| K562300 | Atresia of vagina | | Genital |
| K562z00 | Stricture or atresia of the vagina nos | | Genital |
| PC...00 | Congenital genital organ anomalies | | Genital |
| PC0..00 | Anomalies of ovaries | | Genital |
| PC00.00 | Congenital absence of ovary | | Genital |
| PC00.11 | Agenesis of ovary | | Genital |
| PC02.00 | Ectopic ovary | | Genital |
| PC05.00 | Congenital torsion of ovary | | Genital |
| PC0y.00 | Other specified congenital anomalies of ovaries | | Genital |
| PC0y.11 | Congenital ovarian dysplasia | | Genital |
| PC0z.00 | Congenital anomalies of ovaries nos | | Genital |
| PC1..00 | Fallopian tube and broad ligament anomalies | | Genital |
| PC10.00 | Fallopian tube and broad ligament anomalies, unspecified | | Genital |
| PC11.00 | Embryonic cyst of fallopian tube and broad ligament | | Genital |
| PC11.11 | Cyst of mesenteric remnant | | Genital |
| PC11000 | Epoophoron cyst | | Genital |
| PC11100 | Fimbrial cyst | | Genital |
| PC11200 | Gartner's duct cyst | | Genital |
| PC11211 | Persistent gartner's duct | | Genital |
| PC11300 | Parovarian cyst | | Genital |
| PC11z00 | Embryonic cyst of fallopian tube or broad ligament nos | | Genital |
| PC1y.00 | Other fallopian tube and broad ligament anomalies | | Genital |
| PC1y000 | Congenital absence of fallopian tube | | Genital |
| PC1y100 | Accessory fallopian tube | | Genital |
| PC1y200 | Atresia of fallopian tube | | Genital |
| PC1y300 | Absent broad ligament | | Genital |
| PC1y400 | Accessory broad ligament | | Genital |
| PC1yz00 | Other fallopian tube or broad ligament anomalies nos | | Genital |
| PC1z.00 | Fallopian tube or broad ligament anomalies nos | | Genital |
| PC2..00 | Doubling of uterus | | Genital |
| PC20.00 | Doubling of uterus, unspecified | | Genital |
| PC21.00 | Didelphic uterus | | Genital |
| PC22.00 | Doubling of uterus, including cervix and vagina | | Genital |
| PC2z.00 | Doubling of uterus nos | | Genital |
| PC3..00 | Other anomalies of uterus | | Genital |
| PC30.00 | Congenital absence of uterus | | Genital |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PC31.00 | Agenesis of uterus | | Genital |
| PC32.00 | Aplasia of uterus | | Genital |
| PC33.00 | Bicornuate uterus | | Genital |
| PC34.00 | Uterus unicornis | | Genital |
| PC35.00 | Displaced uterus | | Genital |
| PC35.11 | Congenital prolapse of uterus | | Genital |
| PC36.00 | Fistulae involving uterus with digestive or urinary tract | | Genital |
| PC36100 | Uterovesical fistula, congenital | | Genital |
| PC36z00 | Fistula involving uterus with digestive or urinary tract nos | | Genital |
| PC3y.00 | Other specified anomalies of uterus | | Genital |
| PC3z.00 | Anomalies of uterus nos | | Genital |
| PC4..00 | Cervical, vaginal and external female genital anomalies | | Genital |
| PC40.00 | Cervical/vaginal/external female genital anomalies, unspec | | Genital |
| PC41.00 | Embryonic cyst of cervix/vagina/external female genitalia | | Genital |
| PC41000 | Congenital cyst of canal of nuck | | Genital |
| PC41011 | Patent canal of nuck | | Genital |
| PC41100 | Embryonal cyst of vagina | | Genital |
| PC41300 | Embryonic cyst of cervix | | Genital |
| PC41z00 | Embryonic cyst cervix/vagina/external female genitalia nos | | Genital |
| PC43.00 | Rectovaginal fistula, congenital | | Genital |
| PC4y.00 | Other cervical, vaginal and external female genital anomaly | | Genital |
| PC4y000 | Congenital absence of cervix | | Genital |
| PC4y100 | Agenesis of cervix | | Genital |
| PC4y200 | Congenital absence of clitoris | | Genital |
| PC4y400 | Congenital absence of vagina | | Genital |
| PC4y411 | Rudimentary vagina | | Genital |
| PC4y500 | Agenesis of vagina | | Genital |
| PC4y611 | Congenital absence of labium major | | Genital |
| PC4y612 | Congenital absence of labium minor | | Genital |
| PC4y800 | Congenital stenosis of cervical canal | | Genital |
| PC4y900 | Congenital stenosis of vagina | | Genital |
| PC4y911 | Congenital stricture of vagina | | Genital |
| PC4yA00 | Atresia of cervix | | Genital |
| PC4yB00 | Atresia of vagina | | Genital |
| PC4yC00 | Congenital vaginal cyst nec | | Genital |
| PC4yD00 | Fusion of vulva | | Genital |
| PC4yv00 | Other congenital anomaly of cervix | | Genital |
| PC4yw00 | Other congenital anomaly of vagina | | Genital |
| PC4yw11 | Vaginal septum | | Genital |
| PC4yx00 | Other congenital anomaly of vulva | | Genital |
| PC4yy00 | Other congenital anomaly of clitoris | | Genital |
| PC4yy11 | Hooded clitoris | | Genital |
| PC4yz00 | Other cervical/vaginal/external female genital anomaly nos | | Genital |
| PC4z.00 | Cervical, vaginal and external female genital anomaly nos | | Genital |
| PC60.00 | Hypospadias | | Genital |
| PC60000 | Hypospadias, penile | | Genital |
| PC60100 | Hypospadias, penoscrotal | | Genital |
| PC60200 | Hypospadias, perineal | | Genital |
| PC60300 | Hypospadias, balanic | | Genital |
| PC60311 | Hypospadias, glanular | | Genital |
| PC60312 | Hypospadias, glandular | | Genital |
| PC62.00 | Congenital chordee | | Genital |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PC7..00 | Indeterminate sex and pseudohermaphroditism | | Genital |
| PC70.00 | True hermaphroditism | | Genital |
| PC70.11 | Ovotestis | | Genital |
| PC71.00 | Male pseudohermaphroditism | | Genital |
| PC72.00 | Female pseudohermaphroditism | | Genital |
| PC7z.00 | Indeterminate sex or pseudohermaphroditism nos | | Genital |
| PC7z000 | Indeterminate sex nos | | Genital |
| PC7z011 | Intersex nec | | Genital |
| PC7z100 | Pseudohermaphrodite nos | | Genital |
| PC7z111 | False hermaphrodite | | Genital |
| PC8..00 | Congenital anomaly of male genital system | | Genital |
| PC80.00 | Other specified congenital anomaly of male genital system | | Genital |
| PCy..00 | Other specified genital organ anomaly | | Genital |
| PCy0.00 | Absence of genital organ nec | | Genital |
| PCy0000 | Congenital absence of penis | | Genital |
| PCy0200 | Congenital absence of spermatic cord | | Genital |
| PCy0300 | Congenital absence of vas deferens | | Genital |
| PCy0z00 | Genital organ absence nec nos | | Genital |
| PCy1.00 | Congenital aplasia of genital organ nec | | Genital |
| PCy1000 | Congenital aplasia of prostate | | Genital |
| PCy1200 | Congenital aplasia of testicle | | Genital |
| PCy1300 | Congenital aplasia of scrotum | | Genital |
| PCy1400 | Aplasia of penis | | Genital |
| PCy2.00 | Hypoplasia of genital organ nec | | Genital |
| PCy2100 | Hypoplasia of testis | | Genital |
| PCy2200 | Hypoplasia of scrotum | | Genital |
| PCy2z00 | Hypoplasia of genital organ nec nos | | Genital |
| PCy3.00 | Atresia of genital organ nec | | Genital |
| PCy3000 | Atresia of ejaculatory duct | | Genital |
| PCy3z00 | Atresia of genital organ nec nos | | Genital |
| PCy4.00 | Anarchism | | Genital |
| PCy4.11 | Congenital absence of both testes | | Genital |
| PCy4.12 | Testicular agenesis, bilateral | | Genital |
| PCy5.00 | Monarchism | | Genital |
| PCy5.11 | Congenital absence of testis, unilateral | | Genital |
| PCy5.12 | Testicular agenesis, unilateral | | Genital |
| PCy6.00 | Polyorchism | | Genital |
| PCy8.00 | Fusion of testes | | Genital |
| PCyA.00 | Cysts of embryonic remnants nec | | Genital |
| PCyA000 | Hydatid cyst of Morgagni | | Genital |
| PCyA100 | Wolffian duct cyst | | Genital |
| PCyA200 | Hydatid cyst of morgagni - male | | Genital |
| PCyA300 | Hydatid cyst of morgagni - female | | Genital |
| PCyA400 | Wolffian duct cyst – male | | Genital |
| PCyA500 | Wolffian duct cyst – female | | Genital |
| PCyA600 | Cyst of embryonic remnant - male | | Genital |
| PCyA700 | Cyst of embryonic remnant - female | | Genital |
| PCyB.00 | Doubling of vagina | | Genital |
| PCyx.00 | Other congenital anomaly of vas deferens or prostate | | Genital |
| PCyy.00 | Other congenital anomaly of penis | | Genital |
| PCyyz00 | Other congenital anomaly of penis nos | | Genital |
| PCyz.00 | Other specified genital organ anomaly nos | | Genital |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PCz..00 | Genital organ anomaly nos | | Genital |
| PDyz100 | Hypospadias, female | | Genital |
| Pyu6.00 | [X]congenital malformations of genital organs | | Genital |
| Pyu6300 | [X]other congenital malformations of uterus and cervix | | Genital |
| Pyu6400 | [X]other congenital malformations of vagina | | Genital |
| Pyu6600 | [X]other specified congenital malform of female genitalia | | Genital |
| Pyu6700 | [X]other specified hypospadias | | Genital |
| Pyu6800 | [X]other congenital malformations of testis and scrotum | | Genital |
| Pyu6A00 | [X]other congenital malformations of penis | | Genital |
| Pyu6B00 | [X]other specified congenit malform of male genital organs | | Genital |
| pe8yz11 | Specified intrauterine postural deformity nec | | Genital |
| 2371 | O/e - pigeon chest | Yes | Limb |
| 2373 | O/e - funnel chest | Yes | Limb |
| 7L0L300 | Correction of curly fifth toe | Yes | Limb |
| 7L0L400 | Correction of congenital crossed toes | Yes | Limb |
| 7L0N000 | Cranio-orbital remodelling for plagiocephaly | Yes | Limb |
| 7h01000 | Correction of pectus deformity of chest wall | Yes | Limb |
| 7h01011 | Correction of pectus carinatum | Yes | Limb |
| 7h01012 | Correction of pectus excavatum | Yes | Limb |
| 7h01100 | Insertion of silicone implant correction of pectus excavatum | Yes | Limb |
| 7k02500 | Correction of metatarsus varus | Yes | Limb |
| 7k02511 | Herndon correction of metatarsus varus | Yes | Limb |
| 7k02512 | Heymann correction of metatarsus varus | Yes | Limb |
| 7k51200 | Syndactylisation of lesser toes | Yes | Limb |
| 7l0j700 | Correction of congenital vertical talus | Yes | Limb |
| 7l0k300 | Separation of tarsal coalition | Yes | Limb |
| 7l0l500 | Reduction of macrodactyly of toe | Yes | Limb |
| 7l0ly00 | Correction of minor congenital deformity of foot os | Yes | Limb |
| 7l0lz00 | Correction of minor congenital deformity of foot nos | Yes | Limb |
| PE06.00 | Congenital nasal septum deviation | Yes | Limb |
| PE07.00 | Congenital bent or squashed nose | Yes | Limb |
| n34..00 | Flat foot | Yes | Limb |
| n340000 | Hypermobile flat foot | Yes | Limb |
| n340100 | Rigid flat foot | Yes | Limb |
| n340200 | Peroneal spastic flat foot | Yes | Limb |
| n34z.00 | Flat foot nos | Yes | Limb |
| n357.00 | Crossover toe | Yes | Limb |
| n358.00 | Mallet toe | Yes | Limb |
| n35a.00 | Over-riding 5th toe | Yes | Limb |
| n361.00 | Mallet finger | Yes | Limb |
| n364011 | Knock knee | Yes | Limb |
| n364111 | Bow legged | Yes | Limb |
| n36yh00 | Deformity of talus | Yes | Limb |
| n36yj00 | Deformity of other tarsal bone | Yes | Limb |
| n36yk00 | Deformity of metatarsal | Yes | Limb |
| n36yl00 | Deformity of phalanx of toe | Yes | Limb |
| pe00.00 | Asymmetry of face | Yes | Limb |
| pe01.00 | Compression facies | Yes | Limb |
| pe03.00 | Depressions in skull | Yes | Limb |
| pe04.00 | Dolichocephaly | Yes | Limb |
| pe05.00 | Plagiocephaly | Yes | Limb |
| pe05.11 | Asymmetric head | Yes | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pe1..00 | Congenital sternomastoid torticollis | Yes | Limb |
| pe1..11 | Congenital wry neck | Yes | Limb |
| pe3..00 | Congenital dislocation and subluxation of the hip | Yes | Limb |
| pe31.00 | Congenital subluxation of hip | Yes | Limb |
| pe31000 | Unilateral congenital subluxation of hip | Yes | Limb |
| pe31011 | Unstable hip | Yes | Limb |
| pe31012 | Preluxation of hip | Yes | Limb |
| pe31013 | Predislocation status of hip at birth | Yes | Limb |
| pe31014 | Congenital instability of hip joint | Yes | Limb |
| pe31100 | Bilateral congenital subluxation of hip | Yes | Limb |
| pe31z00 | Congenital subluxation of hip nos | Yes | Limb |
| pe32.00 | Congenital dislocation one hip with subluxation other hip | Yes | Limb |
| pe35.00 | Unstable hip | Yes | Limb |
| pe35000 | Unilateral unstable hip | Yes | Limb |
| pe35100 | Bilateral unstable hip | Yes | Limb |
| pe4..00 | Genu recurvatum and long leg bone bowing | Yes | Limb |
| pe4..11 | Congenital leg bone bowing | Yes | Limb |
| pe40.00 | Congenital genu recurvatum | Yes | Limb |
| pe42.00 | Congenital bowing of femur | Yes | Limb |
| pe43.00 | Congenital bowing of tibia and fibula | Yes | Limb |
| pe43000 | Congenital bowing of tibia | Yes | Limb |
| pe43100 | Congenital bowing of fibula | Yes | Limb |
| pe44.00 | Congenital bowing of long leg bone, unspecified | Yes | Limb |
| pe44.11 | Bow legs nos | Yes | Limb |
| pe4z.00 | Genu recurvatum and long leg bone bowing nos | Yes | Limb |
| pe5..00 | Varus deformities of feet | Yes | Limb |
| pe52.00 | Metatarsus primus varus | Yes | Limb |
| pe53.00 | Congenital metatarsus varus | Yes | Limb |
| pe54.00 | Congenital metatarsus adductus | Yes | Limb |
| pe5z.00 | Varus foot deformity nos | Yes | Limb |
| pe6..00 | Valgus deformities of feet | Yes | Limb |
| pe60.00 | Congenital talipes valgus | Yes | Limb |
| pe60.11 | Congenital clubfoot – valgus | Yes | Limb |
| pe61.00 | Congenital pes planus | Yes | Limb |
| pe61.11 | Congenital flat foot | Yes | Limb |
| pe61.13 | Rigid flat foot | Yes | Limb |
| pe61.14 | Spastic flat foot | Yes | Limb |
| pe61000 | Congenital vertical talus | Yes | Limb |
| pe62.00 | Congenital talipes calcaneovalgus | Yes | Limb |
| pe6y.00 | Other valgus foot deformities | Yes | Limb |
| pe6y000 | Congenital talipes equinovalgus | Yes | Limb |
| pe6y100 | Congenital planovalgus | Yes | Limb |
| pe6yz00 | Other valgus foot deformity nos | Yes | Limb |
| pe6z.00 | Valgus foot deformity nos | Yes | Limb |
| pe6z.11 | Congenital metatarsus valgus | Yes | Limb |
| pe71.00 | Talipes cavus | Yes | Limb |
| pe71.12 | Pes cavus | Yes | Limb |
| pe72.00 | Congenital pes cavus | Yes | Limb |
| pe74.00 | Short achilles tendon, congenital | Yes | Limb |
| pe7y000 | Asymmetric talipes | Yes | Limb |
| pe7y300 | Congenital positional talipes | Yes | Limb |
| pe80.00 | Pectus excavatum, congenital | Yes | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pe80.11 | Congenital funnel chest | Yes | Limb |
| pe81.00 | Pectus carinatum, congenital | Yes | Limb |
| pe81.11 | Congenital pigeon chest | Yes | Limb |
| pe8y100 | Congenital chest wall deformity nec | Yes | Limb |
| pf13100 | Simple syndactyly lesser toes | Yes | Limb |
| pf56.00 | Accessory carpal bones | Yes | Limb |
| pf5y100 | Congenital cubitus valgus | Yes | Limb |
| pf64100 | Congenital genu valgum - knock-knee | Yes | Limb |
| pf64200 | Congenital genu varum - bowleg | Yes | Limb |
| pf65.00 | Macrodactylia of toes | Yes | Limb |
| pf65000 | Macrodactyly of toes - simple | Yes | Limb |
| pf66100 | Congenital hallux varus | Yes | Limb |
| pf66200 | Congenital hammer toe | Yes | Limb |
| pf66400 | Congenital crossed toes | Yes | Limb |
| pf66411 | Congenital overlapping toes | Yes | Limb |
| pf66500 | Congenital curly toes | Yes | Limb |
| pf66600 | Brachyphalangia of little toe | Yes | Limb |
| pf67400 | Tarsal coalitions | Yes | Limb |
| pf67a00 | Complex tarsal coalition | Yes | Limb |
| pf6y500 | Congenital valgus ankle | Yes | Limb |
| pyu8200 | [X]other congenital valgus deformities of feet | Yes | Limb |
| z1ni.00 | Talipes strapping | Yes | Limb |
| 14h5.00 | H/o: cong. Dislocation – hip | | Limb |
| 7L0D.00 | Correction of congenital deformity of shoulder or upper arm | | Limb |
| 7L0Dy00 | Correction of congenital deformity shoulder or upper arm OS | | Limb |
| 7L0Dz00 | Correction of congenital deformity shoulder or upper arm NOS | | Limb |
| 7L0F400 | Amputation of duplicate thumb | | Limb |
| 7L0F500 | Amputation of supernumerary finger NEC | | Limb |
| 7L0H.00 | Correction of congenital deformity of leg | | Limb |
| 7L0H900 | Tibiofibular synostosis for congenital deformity | | Limb |
| 7L0Hy00 | Other specified correction of congenital deformity of leg | | Limb |
| 7L0Hz00 | Correction of congenital deformity of leg NOS | | Limb |
| 7L0K400 | Triple arthrodesis for correction of congenital deformity | | Limb |
| 7L0K500 | Dilwyn Evans proc for correction of congenital deformity | | Limb |
| 7L0L200 | Amputation of supernumerary toe | | Limb |
| 7L0N.00 | Correction of complex craniofacial deformity | | Limb |
| 7L0N200 | Cranio-orbital remodelling, unspecified | | Limb |
| 7L0N500 | Correction of oblique facial cleft | | Limb |
| 7L0Nz00 | Correction of complex craniofacial deformity NOS | | Limb |
| 7j44y00 | Instrumental correction of deformity of spine os | | Limb |
| 7j44z00 | Instrumental correction deformity of spine nos | | Limb |
| 7j45.00 | Other correction of deformity of spine | | Limb |
| 7j45y00 | Other specified correction of deformity of spine | | Limb |
| 7j45z00 | Correction of deformity of spine nos | | Limb |
| 7l0d000 | Reduction of sprengel deformity | | Limb |
| 7l0e.00 | Correction of congenital deformity of forearm | | Limb |
| 7l0e200 | Centralisation carpus- correctn congenital deformity forearm | | Limb |
| 7l0e300 | Revisn release radius- correctn congenital deformity forearm | | Limb |
| 7l0e400 | Revisn release ulna- correction congenital deformity forearm | | Limb |
| 7l0e500 | Correction of congenital absence of radius | | Limb |
| 7l0e600 | Radialialization correction for radial club hand | | Limb |
| 7l0ey00 | Correction of congenital deformity of forearm os | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7l0ez00 | Correction of congenital deformity of forearm nos | | Limb |
| 7l0f.00 | Correction of congenital deformity of hand | | Limb |
| 7l0f200 | Correction of syndactyly of fingers using skin graft | | Limb |
| 7l0f300 | Correction of syndactyly of fingers using skin expander | | Limb |
| 7l0fa00 | Realignment of congenital ulnar drift | | Limb |
| 7l0ff00 | Correction of radial polydactyly | | Limb |
| 7l0fg00 | Excision of radial digit & skeletal repair for polydactyly | | Limb |
| 7l0fh00 | Excision of ulnar digit and skeletal repair for polydactyly | | Limb |
| 7l0fj00 | Correction of macrodactyly | | Limb |
| 7l0fk00 | Reconstruction of radial club hand | | Limb |
| 7l0fy00 | Other specified correction of congenital deformity of hand | | Limb |
| 7l0fz00 | Correction of congenital deformity of hand nos | | Limb |
| 7l0g.00 | Correction of congenital deformity of hip | | Limb |
| 7l0g000 | Open reduction of congenital dislocation of hip | | Limb |
| 7l0g011 | Ferguson open reduction of congenital deformity of hip | | Limb |
| 7l0g012 | Ludloff open reduction of congenital deformity of hip | | Limb |
| 7l0g100 | Primary osteotomy pelvis correction congenital deformity hip | | Limb |
| 7l0g200 | Secndry arthroplasty hip for correctn congenital deformity | | Limb |
| 7l0g300 | Intraartic soft tiss proced correct congenital deformity hip | | Limb |
| 7l0g500 | Osteotomy of ilium correction of congenital deformity of hip | | Limb |
| 7l0g600 | Femoral osteotomy for correction congenital deformity of hip | | Limb |
| 7l0g700 | Pelvic osteotomy for congenital deformity of hip | | Limb |
| 7l0g800 | Salter osteotomy for congenital deformity of hip | | Limb |
| 7l0g900 | Pemberton osteotomy for congenital deformity of hip | | Limb |
| 7l0ga00 | Chiari osteotomy for congenital deformity of hip | | Limb |
| 7l0gb00 | Colonna osteotomy for congenital deformity of hip | | Limb |
| 7l0gc00 | Shelf procedure for correction congenital deformity of hip | | Limb |
| 7l0gy00 | Other specified correction of congenital deformity of hip | | Limb |
| 7l0gz00 | Correction of congenital deformity of hip nos | | Limb |
| 7l0gz11 | Adams correction of congenital dislocation of hip | | Limb |
| 7l0h000 | Open reduction of congenital dislocation of knee | | Limb |
| 7l0h800 | Open reduction congenital dislocation of patella | | Limb |
| 7l0j.00 | Primary correction of congenital deformity of foot | | Limb |
| 7l0j.11 | Primary correction of club foot | | Limb |
| 7l0j.12 | Primary correction of talipes | | Limb |
| 7l0j000 | Release pantalar joints correction congenital deformity foot | | Limb |
| 7l0j011 | Turco soft tissue release for club foot | | Limb |
| 7l0j100 | Post release foot joints for correction congenital deformity | | Limb |
| 7l0j200 | Medial release foot joints- correction congenital deformity | | Limb |
| 7l0j211 | Dillwyn operation for club foot | | Limb |
| 7l0j212 | Evans operation for club foot | | Limb |
| 7l0j213 | Medial release of joints of foot for correction of club foot | | Limb |
| 7l0j214 | Perkins operation for club foot | | Limb |
| 7l0j300 | Anterior release foot joints correction congenital deformity | | Limb |
| 7l0j400 | Posteromedial release of clubfoot | | Limb |
| 7l0j500 | Combined posteromedial + posterolateral release of clubfoot | | Limb |
| 7l0j600 | Lateral release for congenital deformity of foot | | Limb |
| 7l0j800 | Complete subtalar release of clubfoot | | Limb |
| 7l0jy00 | Primary correction of congenital deformity of foot os | | Limb |
| 7l0jz00 | Primary correction of congenital deformity of foot nos | | Limb |
| 7l0k.00 | Other correction of congenital deformity of foot | | Limb |
| 7l0k.11 | Other operations for club foot | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7l0k.12 | Other correction of talipes | | Limb |
| 7l0k100 | Wedge tarsectomy for correction congenital deformity of foot | | Limb |
| 7l0ky00 | Other correction of congenital deformity of foot os | | Limb |
| 7l0kz00 | Other correction of congenital deformity of foot nos | | Limb |
| 7l0l.00 | Correction of minor congenital deformity of foot | | Limb |
| 7l0l100 | Release of syndactyly of toes | | Limb |
| PE0..00 | Skull, face and jaw congenital deformities | | Limb |
| PE0..12 | Jaw congenital deformities | | Limb |
| PE0z.00 | Skull, face or jaw congenital deformities NOS | | Limb |
| PE22.00 | Congenital postural scoliosis | | Limb |
| PE2z.11 | Congenital postural curvature of spine nos | | Limb |
| PF01200 | Radial polydactyly Wassel 3 | | Limb |
| PF4y.00 | Sympus | | Limb |
| PF5y011 | Cleidocranial dysplasia | | Limb |
| PF6C300 | Other specified reduction deformities of unspecified limb | | Limb |
| PG0y.12 | Cranial dysostosis nec | | Limb |
| Pyu8000 | [X]Other congenital deformities of hip | | Limb |
| Pyu8400 | [X]other congenital deformities of skull, face and jaw | | Limb |
| f233.11 | Congenital spastic foot | | Limb |
| n233000 | Arthrogryposis | | Limb |
| n233011 | Arthrogryposis multiplex congenita. | | Limb |
| n363400 | Persistent femoral anteversion | | Limb |
| n36y300 | Deformity of clavicle | | Limb |
| n36y400 | Deformity of scapula | | Limb |
| n36y500 | Deformity of humerus | | Limb |
| n36y600 | Deformity of radius | | Limb |
| n36y700 | Deformity of ulna | | Limb |
| n36y800 | Deformity of carpal bone | | Limb |
| n36y900 | Deformity of metacarpal | | Limb |
| n36ya00 | Deformity of phalanx of finger/thumb | | Limb |
| n36yb00 | Deformity of pelvis | | Limb |
| n36yc00 | Deformity of femur | | Limb |
| n36yd00 | Deformity of patella | | Limb |
| n36ye00 | Deformity of tibia | | Limb |
| n36yf00 | Deformity of fibula | | Limb |
| n36yg00 | Deformity of calcaneum | | Limb |
| pe...00 | Certain congenital musculoskeletal deformities | | Limb |
| pe...11 | Congenital musculoskeletal deformities | | Limb |
| pe0..13 | Skull congenital deformities | | Limb |
| pe2..00 | Congenital spine deformity | | Limb |
| pe20.00 | Congenital spine deformity, unspecified | | Limb |
| pe2z.00 | Congenital spine deformity nos | | Limb |
| pe30.00 | Congenital dislocation of hip | | Limb |
| pe30000 | Unilateral congenital dislocation of hip | | Limb |
| pe30100 | Bilateral congenital dislocation of hip | | Limb |
| pe30z00 | Congenital dislocation of hip nos | | Limb |
| pe34.00 | Dysplastic hip | | Limb |
| pe34000 | Unilateral dysplastic hip | | Limb |
| pe34100 | Bilateral dysplastic hip | | Limb |
| pe3z.00 | Congenital dislocation of hip nos | | Limb |
| pe41.00 | Congenital dislocation of knee | | Limb |
| pe41100 | Congenital dislocation of knee grade ii | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pe41300 | Congenital dislocation of patella | | Limb |
| pe50.00 | Congenital talipes varus | | Limb |
| pe50.11 | Pes varus | | Limb |
| pe50.12 | Congenital clubfoot – varus | | Limb |
| pe51.00 | Congenital talipes equinovarus | | Limb |
| pe5x.00 | Complex varus foot deformities | | Limb |
| pe5y.00 | Other specified varus feet deformity | | Limb |
| pe5y000 | Congenital talipes calcaneovarus | | Limb |
| pe5yz00 | Other specified varus foot deformity nos | | Limb |
| pe7..00 | Other deformities of feet | | Limb |
| pe70.00 | Talipes, unspecified | | Limb |
| pe70.11 | Clubfoot nos | | Limb |
| pe71.11 | Congenital claw toe | | Limb |
| pe73.00 | Congenital claw foot | | Limb |
| pe7y.00 | Other specified foot deformity | | Limb |
| pe7y100 | Congenital talipes calcaneus | | Limb |
| pe7y200 | Congenital talipes equinus | | Limb |
| pe7yz00 | Other specified foot deformity nos | | Limb |
| pe7z.00 | Feet deformities nos | | Limb |
| pe8y000 | Congenital club hand | | Limb |
| pe8y011 | Congenital club fingers | | Limb |
| pe8y111 | Congenital thoracic wall deformity nec | | Limb |
| pe8y200 | Congenital dislocation of elbow | | Limb |
| pe8y300 | Congenital flexion contractures of leg | | Limb |
| pe8y400 | Congenital spade-like hand | | Limb |
| pe8y500 | Guerin - stern syndrome | | Limb |
| pe8y600 | Congenital flexion contracture of hip | | Limb |
| pe8y700 | Congenital abduction contracture of hip | | Limb |
| pe8y800 | Congenital flexion contracture of knee | | Limb |
| pe8y900 | Congenital short quadriceps | | Limb |
| pe8ya00 | Congenital dislocation of radial head | | Limb |
| pe9..00 | Other musc skeletal deformity | | Limb |
| pe9..11 | Other congenital musculoskeletal deformity | | Limb |
| pf...00 | Other congenital limb anomalies | | Limb |
| pf0..00 | Polydactyly - supernumerary digits | | Limb |
| pf00.00 | Supernumerary digits, unspecified | | Limb |
| pf01.00 | Accessory fingers | | Limb |
| pf01000 | Radial polydactyly wassel 1 | | Limb |
| pf01100 | Radial polydactyly wassel 2 | | Limb |
| pf01300 | Radial polydactyly wassel 4 | | Limb |
| pf01700 | Central polydactyly | | Limb |
| pf01800 | Ulnar polydactyly | | Limb |
| pf02.00 | Accessory toes | | Limb |
| pf02000 | Accesory hallux | | Limb |
| pf02100 | Accessory little toe | | Limb |
| pf02200 | Other accessory toe | | Limb |
| pf03.00 | Accessory thumbs | | Limb |
| pf0z.00 | Polydactyly nos | | Limb |
| pf1..00 | Syndactyly - webbing of digits | | Limb |
| pf10.00 | Syndactyly of multiple digits, unspecified | | Limb |
| pf11.00 | Syndactyly of fingers without bone fusion | | Limb |
| pf11.11 | Webbed fingers | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pf11000 | Simple syndactyly - 1st web | | Limb |
| pf11100 | Simple syndactyly - 2nd to 4th web | | Limb |
| pf12.00 | Syndactyly of fingers with bone fusion | | Limb |
| pf12.11 | Fused fingers | | Limb |
| pf12.12 | Osseous syndactyly of fingers | | Limb |
| pf13.00 | Syndactyly of toes without bone fusion | | Limb |
| pf13.11 | Webbed toes | | Limb |
| pf13000 | Simple syndactyly of toes 1st web space | | Limb |
| pf14.00 | Syndactyly of toes with bone fusion | | Limb |
| pf14.11 | Fused toes | | Limb |
| pf14.12 | Conjoined toes | | Limb |
| pf14.13 | Syndactyly of toes with bone fusion | | Limb |
| pf14100 | Osseous syndactyly lesser toes | | Limb |
| pf15.00 | Polysyndactyly | | Limb |
| pf1z.00 | Syndactyly nos | | Limb |
| pf1z.11 | Polysyndactyly | | Limb |
| pf1z.12 | Symphalangism | | Limb |
| pf2..00 | Reduction deformity of upper limb | | Limb |
| pf2..11 | Arm reduction deformity | | Limb |
| pf20.00 | Congenital shortening of arm, unspecified | | Limb |
| pf20.11 | Brachymelia of arm | | Limb |
| pf20100 | Ectromelia of upper limb nos | | Limb |
| pf20200 | Hemimelia of upper limb nos | | Limb |
| pf20z00 | Unspecified congenital shortening of arm nos | | Limb |
| pf21.00 | Transverse deficiency of arm | | Limb |
| pf21.11 | Congenital absence part of arm | | Limb |
| pf21000 | Transverse deficiency of arm,unspecified | | Limb |
| pf21100 | Transverse deficiency of arm, phalangeal level, all fingers | | Limb |
| pf21200 | Transverse deficiency of arm, forearm level | | Limb |
| pf21300 | Transverse deficiency of arm, shoulder level(amelia) | | Limb |
| pf21400 | Congenital amputation of upper limb | | Limb |
| pf21500 | Transverse deficiency of arm, elbow level(hemimelia) | | Limb |
| pf21600 | Transverse deficiency of arm, wrist level(hemimelia) | | Limb |
| pf21611 | Acheiria | | Limb |
| pf21612 | Rudimentary hand | | Limb |
| pf21613 | Congenital absence of hand | | Limb |
| pf21z00 | Transverse deficiency of arm nos | | Limb |
| pf21z11 | Agenesis of hand | | Limb |
| pf22.00 | Longitudinal deficiency of arm nec | | Limb |
| pf22000 | Phocomelia of upper limb nos | | Limb |
| pf22100 | Rudimentary arm | | Limb |
| pf22z00 | Longitudinal deficiency of arm nec nos | | Limb |
| pf23.00 | Congenital absence upper arm and forearm with hand present | | Limb |
| pf23.11 | Complete phocomelia of upper limb | | Limb |
| pf24.00 | Congenital absence of upper arm only | | Limb |
| pf24.11 | Proximal phocomelia of upper limb | | Limb |
| pf25.00 | Congenital absence of forearm only | | Limb |
| pf25.11 | Distal phocomelia of upper limb | | Limb |
| pf26.00 | Agenesis of radial ray | | Limb |
| pf26.11 | Congenital absence of radius | | Limb |
| pf26000 | Hypoplasia of radius | | Limb |
| pf26100 | Partial radial absence | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pf26200 | Total radial absence | | Limb |
| pf26300 | Absent thumb | | Limb |
| pf26400 | Hypoplastic thumb-blauth 1 | | Limb |
| pf26500 | Hypoplastic thumb-blauth 2 | | Limb |
| pf26600 | Hypoplastic thumb-blauth 3 | | Limb |
| pf26700 | Hypoplastic thumb-blauth 4 | | Limb |
| pf26800 | Hypoplastic thumb-blauth 5 | | Limb |
| pf27.00 | Agenesis of ulna | | Limb |
| pf27000 | Partial defect of ulna | | Limb |
| pf27100 | Total absence of ulna | | Limb |
| pf27200 | Ulnar and humeroulnar synostosis | | Limb |
| pf28.00 | Agenesis of carpals and metacarpals | | Limb |
| pf28.11 | Transverse arrest of carpals and metacarpals | | Limb |
| pf28000 | Transverse arrest carpal level | | Limb |
| pf28100 | Transverse arrest metacarpal 1st ray | | Limb |
| pf28200 | Transverse arrest metacarpal other | | Limb |
| pf29.00 | Congenital absence of finger | | Limb |
| pf29.12 | Transverse arrest of phalanges | | Limb |
| pf29000 | Transverse arrest phalangeal level 1st ray | | Limb |
| pf29100 | Transverse arrest phalangeal level 2nd ray | | Limb |
| pf29300 | Transverse arrest phalangeal level 4th ray | | Limb |
| pf29400 | Transverse arrest phalangeal level 5th ray | | Limb |
| pf29z00 | Congenital absence finger nos | | Limb |
| pf2y.00 | Other specified reduction deformities of upper limb | | Limb |
| pf2z.00 | Reduction deformity of upper limb nos | | Limb |
| pf2z.11 | Hypoplasia of upper limb | | Limb |
| pf3..00 | Reduction deformity of lower limb | | Limb |
| pf3..11 | Leg reduction deformity | | Limb |
| pf30.00 | Congenital shortening of leg, unspecified | | Limb |
| pf30.11 | Brachymelia of leg | | Limb |
| pf30000 | Ectromelia of lower limb nos | | Limb |
| pf30100 | Hemimelia of lower limb nos | | Limb |
| pf30z00 | Unspecified congenital leg shortening nos | | Limb |
| pf31.00 | Transverse deficiency of leg | | Limb |
| pf31100 | Transverse deficiency lower limb - ankle level | | Limb |
| pf31112 | Hemimelia - ankle level | | Limb |
| pf31200 | Congenital absence of leg and foot | | Limb |
| pf31311 | Amelia - lower limb | | Limb |
| pf31500 | Transverse deficiency lower limb - knee level | | Limb |
| pf31511 | Hemimelia - knee level | | Limb |
| pf32.00 | Longitudinal reduction deformity of lower limb nec | | Limb |
| pf32.11 | Phocomelia of lower limb nos | | Limb |
| pf33.00 | Congenital absence of thigh and lower leg with foot present | | Limb |
| pf33.11 | Complete phocomelia of lower limb | | Limb |
| pf34.00 | Congenital absence of thigh only | | Limb |
| pf34.11 | Proximal phocomelia of lower limb | | Limb |
| pf34000 | Proximal femoral focal deficiency | | Limb |
| pf34100 | Congenital short femur | | Limb |
| pf35.00 | Congenital absence of lower leg only | | Limb |
| pf35.11 | Distal phocomelia of lower limb | | Limb |
| pf36.00 | Agenesis of tibia | | Limb |
| pf36200 | Congenital tibial deficiency type iii | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pf37.00 | Agenesis of fibula | | Limb |
| pf37100 | Congenital fibular deficiency type ii | | Limb |
| pf38.00 | Agenesis of tarsals and metatarsals | | Limb |
| pf38000 | Agenesis of talus | | Limb |
| pf38200 | Agenesis of other tarsal bone | | Limb |
| pf38500 | Agenesis of 5th metatarsal | | Limb |
| pf38600 | Agenesis of other metatarsal | | Limb |
| pf38700 | Agenesis of 4th and 5th metatarsals | | Limb |
| pf39.00 | Congenital absence of toe | | Limb |
| pf39000 | Congenital absence of great toe | | Limb |
| pf39100 | Congenital absence of 5th toe | | Limb |
| pf39200 | Congenital absence of other lesser toe | | Limb |
| pf39400 | Congenital absence of other multiple toes | | Limb |
| pf3y.00 | Other specified reduction deformities of lower limb | | Limb |
| pf3z.00 | Reduction deformity of lower limb nos | | Limb |
| pf3z.11 | Hypoplasia of lower limb | | Limb |
| pf4..00 | Reduction deformity of unspecified limb | | Limb |
| pf40.00 | Congenital absence of limb nos | | Limb |
| pf41.00 | Amelia of unspecified limb | | Limb |
| pf43.00 | Hemimelia of unspecified limb | | Limb |
| pf44.00 | Phocomelia of unspecified limb | | Limb |
| pf45.00 | Congenital amputation of unspecified limb | | Limb |
| pf46.00 | Longitudinal reduction deformity of unspecified limb | | Limb |
| pf47.00 | Congenital absence of digits nos | | Limb |
| pf47.11 | Adactyly | | Limb |
| pf4y000 | Brachymelia nos | | Limb |
| pf4z.00 | Reduction deformity of unspecified limb nos | | Limb |
| pf4z.11 | Brachydactyly nos | | Limb |
| pf4z.12 | Withered limb | | Limb |
| pf4z.13 | Hypoplasia of limb nos | | Limb |
| pf5..00 | Other upper limb and shoulder anomaly | | Limb |
| pf50.00 | Upper limb anomaly, unspecified | | Limb |
| pf51.00 | Congenital deformity of clavicle | | Limb |
| pf51.11 | Clavicle agenesis | | Limb |
| pf52.00 | Congenital elevation of scapula | | Limb |
| pf52.11 | Sprengel's deformity | | Limb |
| pf53.00 | Radio-ulnar synostosis | | Limb |
| pf53000 | Proximal radioulnar synostosis | | Limb |
| pf53100 | Radioulnar synostosis and dislocation of radial head | | Limb |
| pf53200 | Distal radioulnar synostosis | | Limb |
| pf54.00 | Madelung's deformity | | Limb |
| pf57.00 | Macrodactylia (fingers) | | Limb |
| pf57000 | Macrodactyly – simple | | Limb |
| pf57100 | Macrodactyly - fatty nerve tumor | | Limb |
| pf59000 | Windblown hand | | Limb |
| pf59300 | Aberrant intrinsic muscles | | Limb |
| pf59500 | Thumb in palm deformity | | Limb |
| pf59600 | Congenital trigger thumb | | Limb |
| pf5a.00 | Other failure of differentiation, skeletal tissues of arm | | Limb |
| pf5a100 | Capitate-hamate synostosis | | Limb |
| pf5a200 | Scaphoid-lunate synostosis | | Limb |
| pf5a300 | Other carpal synostosis | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pf5a400 | Pip joint symphalangism | | Limb |
| pf5a500 | Dip joint symphalangism | | Limb |
| pf5b.00 | Other duplication of limb | | Limb |
| pf5bz00 | Duplication of limb nos | | Limb |
| pf5c.00 | Other overgrowth of upper limb | | Limb |
| pf5c100 | Overgrowth of partial upper limb | | Limb |
| pf5cz00 | Other overgrowth of limb nos | | Limb |
| pf5d100 | Undergrowth of whole hand | | Limb |
| pf5d200 | Brachymetacarpia | | Limb |
| pf5dz00 | Other undergrowth of limb nos | | Limb |
| pf5e.00 | Constriction ring syndrome of upper limb | | Limb |
| pf5e000 | Constriction ring | | Limb |
| pf5e100 | Constriction ring with lymphoedema | | Limb |
| pf5e200 | Acrosyndactyly | | Limb |
| pf5e300 | Intra-uterine amputation | | Limb |
| pf5e400 | Constriction ring with acrosyndactyly and amputation | | Limb |
| pf5f.00 | Congenital absence of both forearm and hand | | Limb |
| pf5g.00 | Congenital complete absence of upper limb(s) | | Limb |
| pf5r.00 | Other congenital anomalies of fingers | | Limb |
| pf5r000 | Triphalangeal thumb | | Limb |
| pf5r100 | Brachydactyly of fingers, unspecified | | Limb |
| pf5r400 | Flexion deformity of fingers | | Limb |
| pf5r500 | Brachydactyly-all 3 phalanges | | Limb |
| pf5r600 | Brachydactyly-missing phalanx | | Limb |
| pf5r700 | Symbrachydactyly | | Limb |
| pf5rc00 | Brachymesophalangia | | Limb |
| pf5rd00 | Congenital malformation of thumb | | Limb |
| pf5rz00 | Other anomaly of fingers nos | | Limb |
| pf5s.00 | Other congenital anomalies of hand | | Limb |
| pf5t.00 | Other congenital anomalies of wrist | | Limb |
| pf5u.00 | Other congenital anomalies of forearm | | Limb |
| pf5u000 | Radio-ulnar dysostosis | | Limb |
| pf5uz00 | Other congenital anomaly forearm nos | | Limb |
| pf5v.00 | Congenital anomalies of elbow and upper arm | | Limb |
| pf5v.11 | Cubitus nos | | Limb |
| pf5w.00 | Other congenital anomalies of shoulder | | Limb |
| pf5w.11 | Congenital deformity of scapula nec | | Limb |
| pf5x.00 | Other congenital anomalies of whole arm | | Limb |
| pf5y.00 | Other upper limb and shoulder anomaly os | | Limb |
| pf5y000 | Cleidocranial dysostosis | | Limb |
| pf5y200 | Congenital cubitus varus | | Limb |
| pf5y300 | Congenital humeral varus | | Limb |
| pf5y400 | Humeroradial synostosis | | Limb |
| pf5y500 | Humeroulnar synostosis | | Limb |
| pf5y600 | Total elbow synostosis | | Limb |
| pf5yz00 | Other upper limb and shoulder anomaly nos | | Limb |
| pf5z.00 | Upper limb or shoulder anomaly nos | | Limb |
| pf6..00 | Other lower limb and pelvic girdle anomalies | | Limb |
| pf60.00 | Lower limb anomaly, unspecified | | Limb |
| pf61.00 | Congenital coxa valga | | Limb |
| pf62.00 | Congenital coxa vara | | Limb |
| pf63.00 | Other congenital hip joint deformity | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pf63000 | Congenital anteversion of femoral neck | | Limb |
| pf63100 | Congenital hip dysplasia | | Limb |
| pf63111 | Developmental dysplasia of the hip | | Limb |
| pf63200 | Congenital acetabular dysplasia | | Limb |
| pf63x00 | Congenital deformity of hip, unspecified | | Limb |
| pf63z00 | Other congenital hip joint deformity nos | | Limb |
| pf64.00 | Congenital knee joint deformity | | Limb |
| pf64000 | Congenital absence of patella | | Limb |
| pf64300 | Rudimentary patella | | Limb |
| pf64400 | Congenital dislocation of patella | | Limb |
| pf64500 | Bipartite patella | | Limb |
| pf64z00 | Congenital knee joint deformity nos | | Limb |
| pf66.00 | Other congenital anomalies of toe | | Limb |
| pf66000 | Congenital hallux valgus | | Limb |
| pf66300 | Brachydactyly of toes | | Limb |
| pf66800 | Perodactylia of great toe | | Limb |
| pf66900 | Perodactylia of lesser toe | | Limb |
| pf66b00 | Triphalangeal great toe | | Limb |
| pf66z00 | Other toe anomalies nos | | Limb |
| pf67.00 | Congenital anomalies of foot nec | | Limb |
| pf67000 | Astragaloscaphoid synostosis | | Limb |
| pf67100 | Calcaneonavicular bar | | Limb |
| pf67200 | Coalition of calcaneous | | Limb |
| pf67300 | Talonavicular synostosis | | Limb |
| pf67700 | Accessory tarsal bones | | Limb |
| pf67800 | Talocalcaneal bar | | Limb |
| pf67900 | Naviculocuneiform bar | | Limb |
| pf67z00 | Anomalies of foot nec nos | | Limb |
| pf69.00 | Failure of differentiation of skeletal tissues of lower limb | | Limb |
| pf69000 | Congenital synostosis of lower limb bones | | Limb |
| pf6a.00 | Duplication of lower limb bone | | Limb |
| pf6b.00 | Congenital overgrowth of lower limb | | Limb |
| pf6b200 | Congenital overgrowth of foot | | Limb |
| pf6b300 | Congen overgrowth of whole lower limb | | Limb |
| pf6c.00 | Congenital undergrowth of lower limb | | Limb |
| pf6c000 | Congenital undergrowth of proximal part of limb | | Limb |
| pf6c100 | Congenital undergrowth of distal part of limb | | Limb |
| pf6d.00 | Constriction ring syndrome of lower limb | | Limb |
| pf6d000 | Constriction ring of lower limb | | Limb |
| pf6d200 | Intrauterine amputation of lower limb | | Limb |
| pf6d300 | Constriction ring syndrome of lower limb with amputation | | Limb |
| pf6e.00 | Congenital absence of thigh and lower leg with foot present | | Limb |
| pf6v.00 | Other congenital anomalies of lower leg | | Limb |
| pf6w.00 | Other congenital anomalies of upper leg | | Limb |
| pf6x.00 | Other congenital anomalies of pelvis | | Limb |
| pf6xz00 | Other congenital anomalies of pelvis nos | | Limb |
| pf6y.00 | Other lower limb anomalies | | Limb |
| pf6y000 | Congenital angulation of tibia | | Limb |
| pf6y100 | Congenital deformity of ankle joint | | Limb |
| pf6y200 | Congenital deformity of sacroiliac joint | | Limb |
| pf6y300 | Congenital fusion of sacroiliac joint | | Limb |
| pf6y400 | Congenital varus ankle | | Limb |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pf6y600 | Congenital pseudarthrosis of tibia | | Limb |
| pf6yz00 | Other lower limb and pelvic girdle anomaly nos | | Limb |
| pfy..00 | Other specified anomalies of unspecified limb | | Limb |
| pfy0.00 | Arthrogryposis multiplex congenita | | Limb |
| pfy4.00 | Other arthrogryposis syndromes | | Limb |
| pfyz.00 | Other anomaly of unspecified limb nos | | Limb |
| pfz..00 | Congenital anomaly of unspecified limb nos | | Limb |
| pg...00 | Other congenital musculoskeletal anomalies | | Limb |
| pg0..00 | Skull and face bone anomalies | | Limb |
| pg0..11 | Face bone anomalies | | Limb |
| pg1..00 | Anomalies of spine | | Limb |
| pg10.00 | Anomaly of spine, unspecified | | Limb |
| pg1y.00 | Other anomaly of spine | | Limb |
| pg1yz00 | Other anomaly of spine nos | | Limb |
| pg1z.00 | Anomalies of spine nos | | Limb |
| pyu8100 | [X]other congenital varus deformities of feet | | Limb |
| pyu8300 | [X]other congenital deformities of feet | | Limb |
| pyu8500 | [X]other congenital deformities of chest | | Limb |
| pyu8700 | [X]other reduction defects of upper limb(s) | | Limb |
| pyu8a00 | [X]other congen malform upper limb(s), inlc shoulder girdle | | Limb |
| pyu8c00 | [X]other specified congenital malformations of limb(s) | | Limb |
| pyu8m00 | [X]other congenital malforms of the musculoskeletal system | | Limb |
| pyu8n00 | [X]congenital deformity of hip, unspecified | | Limb |
| zv49000 | [V]deficiencies of limbs problems | | Limb |
| p240.00 | Congenital cerebral cyst | Yes | Nervous System |
| p240000 | Single congenital cerebral cyst | Yes | Nervous System |
| p240z00 | Congenital cerebral cyst nos | Yes | Nervous System |
| p240.11 | Congenital intracerebral cyst | | Nervous System |
| 7010111 | Insertion of halber valve for spina bifida | | Nervous System |
| 7031000 | Repair of meningoencephalocele | | Nervous System |
| 7043.00 | Repair of spina bifida | | Nervous System |
| 7043100 | Closure of spinal myelomeningocele | | Nervous System |
| 7043200 | Closure of spinal meningocele | | Nervous System |
| 7043y00 | Other specified repair of spina bifida | | Nervous System |
| 7043z00 | Repair of spina bifida nos | | Nervous System |
| 7f1a300 | Drainage of hydrocephalus of fetus to facilitate delivery | | Nervous System |
| P227z00 | Anomaly of cerebrum NOS | | Nervous System |
| P23y.00 | Other specified congenital hydrocephalus | | Nervous System |
| P244.00 | Ulegyria | | Nervous System |
| P26..00 | Disorder of neuronal migration and differentiation | | Nervous System |
| P6z..11 | Chiari's malformation | | Nervous System |
| f23..00 | Congenital cerebral palsy | | Nervous System |
| f23..11 | Congenital spastic cerebral palsy | | Nervous System |
| f230.11 | Paraplegia – congenital | | Nervous System |
| f230000 | Congenital paraplegia | | Nervous System |
| f230z00 | Congenital diplegia nos | | Nervous System |
| f231.00 | Congenital hemiplegia | | Nervous System |
| f232.00 | Congenital quadriplegia | | Nervous System |
| f232.11 | Tetraplegia – congenital | | Nervous System |
| f233.00 | Congenital monoplegia | | Nervous System |
| f23y.00 | Other congenital cerebral palsy | | Nervous System |
| f23y511 | Congenital suprabulbar paresis | | Nervous System |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| f23z.00 | Congenital cerebral palsy nos | | Nervous System |
| l236.00 | Hydrocephalic disproportion | | Nervous System |
| l236000 | Hydrocephalic disproportion unspecified | | Nervous System |
| l236100 | Hydrocephalic disproportion - delivered | | Nervous System |
| l236200 | Hydrocephalic disproportion with antenatal problem | | Nervous System |
| l236z00 | Hydrocephalic disproportion nos | | Nervous System |
| l250.00 | Fetus with central nervous system malformation | | Nervous System |
| l250.11 | Suspect fetal anencephaly | | Nervous System |
| l250.12 | Suspect fetal hydrocephaly | | Nervous System |
| l250.13 | Suspect fetal spina bifida | | Nervous System |
| l250000 | Fetus with central nervous system malformation unspecified | | Nervous System |
| l250100 | Fetus with central nervous system malformation – delivered | | Nervous System |
| l250200 | Fetus with central nervous system malformation + a/n problem | | Nervous System |
| l250300 | Maternal care for suspected cns malformation in fetus | | Nervous System |
| l250400 | Maternal care for cns malformation in fetus | | Nervous System |
| l250z00 | Fetus with central nervous system malformation nos | | Nervous System |
| p0...00 | Anencephalus and similar anomalies | | Nervous System |
| p00..00 | Anencephalus | | Nervous System |
| p00..11 | Congenital absence of brain | | Nervous System |
| p000.00 | Acrania | | Nervous System |
| p001.00 | Amyelencephalus | | Nervous System |
| p002.00 | Hemicephaly | | Nervous System |
| p002.11 | Hemianencephaly | | Nervous System |
| p00y.00 | Other specified anencephalus | | Nervous System |
| p00z.00 | Anencephalus nos | | Nervous System |
| p01..00 | Craniorachischisis | | Nervous System |
| p02..00 | Iniencephaly | | Nervous System |
| p0z..00 | Anencephalus and similar anomalies nos | | Nervous System |
| p1...00 | Spina bifida | | Nervous System |
| p10..00 | Spina bifida with hydrocephalus | | Nervous System |
| p10..11 | Arnold - chiari syndrome | | Nervous System |
| p100.00 | Unspecified spina bifida with hydrocephalus | | Nervous System |
| p100000 | Spina bifida with hydrocephalus, unspecified | | Nervous System |
| p100100 | Cervical spina bifida with hydrocephalus | | Nervous System |
| p100200 | Thoracic spina bifida with hydrocephalus | | Nervous System |
| p100300 | Lumbar spina bifida with hydrocephalus | | Nervous System |
| p100z00 | Spina bifida with hydrocephalus nos | | Nervous System |
| p101.00 | Arnold - chiari syndrome | | Nervous System |
| p101.11 | Closed spina bifida with arnold-chiari malformation | | Nervous System |
| p101000 | Chiari malformation type i | | Nervous System |
| p101100 | Chiari malformation type ii | | Nervous System |
| p102.00 | Spina bifida with hydrocephalus - open | | Nervous System |
| p102.11 | Fissured spine with hydrocephalus | | Nervous System |
| p102.13 | Myelocele with hydrocephalus | | Nervous System |
| p102.14 | Rachischisis with hydrocephalus | | Nervous System |
| p102200 | Thoracic spina bifida with hydrocephalus - open | | Nervous System |
| p102300 | Lumbar spina bifida with hydrocephalus - open | | Nervous System |
| p102400 | Sacral spina bifida with hydrocephalus - open | | Nervous System |
| p102z00 | Spina bifida with hydrocephalus - open nos | | Nervous System |
| p103.00 | Spina bifida with hydrocephalus - closed | | Nervous System |
| p103300 | Lumbar spina bifida with hydrocephalus - closed | | Nervous System |
| p103400 | Sacral spina bifida with hydrocephalus - closed | | Nervous System |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| p103z11 | Thoracolumbar spina bifida with hydrocephalus – closed | | Nervous System |
| p104.00 | Spina bifida with hydrocephalus of late onset | | Nervous System |
| p105.00 | Spina bifida with stenosis of aqueduct of sylvius | | Nervous System |
| p10y.00 | Other specified spina bifida with hydrocephalus | | Nervous System |
| p10y000 | Dandy - walker syndrome with spina bifida | | Nervous System |
| p10z.00 | Spina bifida with hydrocephalus nos | | Nervous System |
| p11..00 | Spina bifida without mention of hydrocephalus | | Nervous System |
| p110000 | Spina bifida without hydrocephalus, site unspecified | | Nervous System |
| p110100 | Cervical spina bifida without mention of hydrocephalus | | Nervous System |
| p110200 | Thoracic spina bifida without mention of hydrocephalus | | Nervous System |
| p110300 | Lumbar spina bifida without mention of hydrocephalus | | Nervous System |
| p110z00 | Unspecified spina bifida without hydrocephalus nos | | Nervous System |
| p111.00 | Spinal hydromeningocele | | Nervous System |
| p112.00 | Hydromyelocele | | Nervous System |
| p113.00 | Spinal meningocele | | Nervous System |
| p113000 | Spinal meningocele of unspecified site | | Nervous System |
| p113100 | Cervical spinal meningocele | | Nervous System |
| p113200 | Thoracic spinal meningocele | | Nervous System |
| p113300 | Lumbar spinal meningocele | | Nervous System |
| p113z00 | Spinal meningocele nos | | Nervous System |
| p114.00 | Meningomyelocele | | Nervous System |
| p114000 | Meningomyelocele of unspecified site | | Nervous System |
| p114100 | Cervical meningomyelocele | | Nervous System |
| p114200 | Thoracic meningomyelocele | | Nervous System |
| p114300 | Lumbar meningomyelocele | | Nervous System |
| p114z00 | Meningomyelocele nos | | Nervous System |
| p115.00 | Myelocele | | Nervous System |
| p115100 | Cervical myelocele | | Nervous System |
| p115300 | Lumbar myelocele | | Nervous System |
| p115z00 | Myelocele nos | | Nervous System |
| p116.00 | Myelocystocele | | Nervous System |
| p116100 | Cervical myelocystocele | | Nervous System |
| p116300 | Lumbar myelocystocele | | Nervous System |
| p116z00 | Myelocystocele nos | | Nervous System |
| p117.00 | Spina bifida without hydrocephalus - open | | Nervous System |
| p117.11 | Fissured spine | | Nervous System |
| p117.12 | Rachischisis | | Nervous System |
| p117200 | Thoracic spina bifida without hydrocephalus - open | | Nervous System |
| p117300 | Lumbar spina bifida without hydrocephalus - open | | Nervous System |
| p117400 | Sacral spina bifida without hydrocephalus - open | | Nervous System |
| p117z00 | Spina bifida without hydrocephalus - open nos | | Nervous System |
| p118.00 | Spina bifida without hydrocephalus - closed | | Nervous System |
| p118000 | Unspecified spina bifida without hydrocephalus – closed | | Nervous System |
| p118100 | Cervical spina bifida without hydrocephalus - closed | | Nervous System |
| p118300 | Lumbar spina bifida without hydrocephalus - closed | | Nervous System |
| p118400 | Sacral spina bifida without hydrocephalus - closed | | Nervous System |
| p118z00 | Spina bifida without hydrocephalus - closed nos | | Nervous System |
| p11y.00 | Other specified spina bifida without hydrocephalus | | Nervous System |
| p11y.11 | Syringomyelocele | | Nervous System |
| p11z.00 | Spina bifida without mention of hydrocephalus nos | | Nervous System |
| p11z.14 | Congenital hernia of dura mater | | Nervous System |
| p1z..00 | Spina bifida nos | | Nervous System |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| p2...00 | Other nervous system congenital anomalies | | Nervous System |
| p20..00 | Encephalocele | | Nervous System |
| p20..11 | Hydroencephalocele | | Nervous System |
| p20..12 | Cephalocele | | Nervous System |
| p20..13 | Congenital cerebral hernia | | Nervous System |
| p20..14 | Congenital endaural hernia | | Nervous System |
| p20..15 | Sinus pericranii | | Nervous System |
| p200.00 | Encephalocystocele | | Nervous System |
| p201.00 | Encephalomyelocele | | Nervous System |
| p202.00 | Hydromeningocele – cranial | | Nervous System |
| p203.00 | Meningocele – cerebral | | Nervous System |
| p203.11 | Meningocele – cranial | | Nervous System |
| p204.00 | Meningoencephalocele | | Nervous System |
| p205.00 | Frontal encephalocele | | Nervous System |
| p206.00 | Nasofrontal encephalocele | | Nervous System |
| p20z.00 | Encephalocele nos | | Nervous System |
| p20z000 | Occipital encephalocele | | Nervous System |
| p20z100 | Encephalocele of other specified site | | Nervous System |
| p21..00 | Microcephalus | | Nervous System |
| p210.00 | Hydromicrocephaly | | Nervous System |
| p211.00 | Micrencephaly | | Nervous System |
| p21z.00 | Microcephalus nos | | Nervous System |
| p22..00 | Reduction deformities of brain | | Nervous System |
| p220.00 | Agenesis of brain, part unspecified | | Nervous System |
| p221.00 | Aplasia of brain, part unspecified | | Nervous System |
| p222.00 | Hypoplasia of brain, part unspecified | | Nervous System |
| p223.00 | Agyria | | Nervous System |
| p223.11 | Lissencephaly | | Nervous System |
| p224.00 | Arhinencephaly | | Nervous System |
| p225.00 | Holoprosencephaly | | Nervous System |
| p226.00 | Microgyria | | Nervous System |
| p227.00 | Anomalies of cerebrum | | Nervous System |
| p227000 | Agenesis of cerebrum | | Nervous System |
| p227100 | Congenital hypoplasia of cerebrum | | Nervous System |
| p228.00 | Anomalies of corpus callosum | | Nervous System |
| p228000 | Congenital absence of corpus callosum | | Nervous System |
| p228011 | Agenesis of corpus callosum | | Nervous System |
| p228100 | Hypoplasia of corpus callosum | | Nervous System |
| p228200 | Aplasia of corpus callosum | | Nervous System |
| p228z00 | Anomaly of corpus callosum nos | | Nervous System |
| p229.00 | Anomalies of hypothalamus | | Nervous System |
| p22a.00 | Anomalies of cerebellum | | Nervous System |
| p22a000 | Congenital absence of cerebellum | | Nervous System |
| p22a011 | Agenesis of cerebellum | | Nervous System |
| p22a100 | Hypoplasia of cerebellum | | Nervous System |
| p22a200 | Aplasia of cerebellum | | Nervous System |
| p22az00 | Anomaly of cerebellum nos | | Nervous System |
| p22y.00 | Other specified reduction deformities of brain | | Nervous System |
| p22y300 | Partial absence of septum pellucidum | | Nervous System |
| p22yz00 | Other reduction deformity of brain nos | | Nervous System |
| p22z.00 | Reduction deformities of brain nos | | Nervous System |
| p22z.11 | Cerebellar hypoplasia | | Nervous System |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| p22z.12 | Agenesis of part of brain nec | | Nervous System |
| p22z.13 | Hypoplasia of part of brain nec | | Nervous System |
| p23..00 | Congenital hydrocephalus | | Nervous System |
| p230.00 | Aqueduct of sylvius anomaly | | Nervous System |
| p230.11 | Hydrocephauls with anomaly of aqueduct of sylvius | | Nervous System |
| p230.12 | Stenosis of aqueduct of sylvius | | Nervous System |
| p230100 | Aqueduct of sylvius stenosis | | Nervous System |
| p231.00 | Foramen of magendie atresia | | Nervous System |
| p232.00 | Foramen of luschka atresia | | Nervous System |
| p233.00 | Atresia of foramina of magendie and luschka | | Nervous System |
| p233.11 | Dandy - walker syndrome | | Nervous System |
| p233.12 | Hydrocephalus with atresia of foramina of magendie+luschka | | Nervous System |
| p234.00 | Hydranencephaly | | Nervous System |
| p23z.00 | Congenital hydrocephalus nos | | Nervous System |
| p24..00 | Other specified brain anomalies | | Nervous System |
| p240100 | Multiple congenital cerebral cysts | | Nervous System |
| p240200 | Schizencephaly | | Nervous System |
| p241.00 | Macroencephaly | | Nervous System |
| p241.11 | Megalencephaly | | Nervous System |
| p241.12 | Enlarged brain | | Nervous System |
| p242.00 | Macrogyria | | Nervous System |
| p243.00 | Porencephaly | | Nervous System |
| p245.00 | Congenital adhesions of cerebral meninges | | Nervous System |
| p246.00 | Septo-optic dysplasia | | Nervous System |
| p247.00 | Dysplasia of cerebral cortex | | Nervous System |
| p248.00 | Congenital dilated lateral ventricles of brain | | Nervous System |
| p249.00 | Megalencephaly | | Nervous System |
| p24a.00 | Hemimegalencephaly | | Nervous System |
| p24z.00 | Other specified brain anomalies nos | | Nervous System |
| p25..00 | Other specified spinal cord anomalies | | Nervous System |
| p250.00 | Diastematomyelia | | Nervous System |
| p251.00 | Hydromyelia | | Nervous System |
| p252.00 | Congenital tethering of spinal cord | | Nervous System |
| p25y.00 | Other specified anomalies of spinal cord | | Nervous System |
| p25y.11 | Neuroenteric cyst | | Nervous System |
| p25y000 | Amyelia | | Nervous System |
| p25y100 | Atelomyelia | | Nervous System |
| p25y111 | Myelatelia | | Nervous System |
| p25y112 | Myelodysplasia of spinal cord | | Nervous System |
| p25y200 | Congenital anomaly of spinal meninges | | Nervous System |
| p25y300 | Defective development of the cauda equina | | Nervous System |
| p25y400 | Spinal cord hypoplasia | | Nervous System |
| p25yz00 | Other specified spinal cord anomalies nos | | Nervous System |
| p25z.00 | Spinal cord anomalies nos | | Nervous System |
| p2x..00 | Other specified nervous system anomalies | | Nervous System |
| p2x0.00 | Agenesis of nerve, unspecified | | Nervous System |
| p2x1.00 | Brachial plexus displacement | | Nervous System |
| p2x6.00 | Chiari malformation type i | | Nervous System |
| p2x7.00 | Congenital facial nerve palsy | | Nervous System |
| p2xz.00 | Other specified nervous system anomalies nos | | Nervous System |
| p2xz000 | Agenesis of nerve nec | | Nervous System |
| p2xz100 | Congenital optic atrophy | | Nervous System |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| p2y..00 | Unspec nervous system anomaly of brain/cord/nervous system | | Nervous System |
| p2y0.00 | Congenital brain anomaly | | Nervous System |
| p2y1.00 | Congenital spinal cord anomaly | | Nervous System |
| p2yz.00 | Unspecified nervous system anomaly nos | | Nervous System |
| p2z..00 | Nervous system anomalies nos | | Nervous System |
| pyu0100 | [X]other congenital hydrocephalus | | Nervous System |
| pyu0300 | [X]other specified congenital malformations of brain | | Nervous System |
| pyu0400 | [X]unspecified spina bifida with hydrocephalus | | Nervous System |
| pyu0600 | [X]other specified congenital malformations of spinal cord | | Nervous System |
| q48y500 | Megalencephaly | | Nervous System |
| 14H2.00 | H/O: cleft palate | | Orofacial Clefts |
| 14H3.00 | H/O: cleft lip | | Orofacial Clefts |
| 7409.00 | Correction of cleft lip nasal deformity | | Orofacial Clefts |
| 7409000 | Primary correction of cleft lip nasal deformity | | Orofacial Clefts |
| 7409011 | Primary correction of alar cartilage | | Orofacial Clefts |
| 7409013 | Pigott alar leap-frog correction | | Orofacial Clefts |
| 7409100 | Secondary correction of cleft lip nasal deformity | | Orofacial Clefts |
| 7409111 | Secondary correction of alar slump | | Orofacial Clefts |
| 7409113 | Skoog correction of alar slump | | Orofacial Clefts |
| 7409114 | Dibbell correction of alar slump | | Orofacial Clefts |
| 7409200 | Correction of cleft lip nasal tip deformity | | Orofacial Clefts |
| 7409211 | Alar base advancement | | Orofacial Clefts |
| 7409300 | Columella lengthening procedure unspecified | | Orofacial Clefts |
| 7409400 | Unilateral columella lengthening operation | | Orofacial Clefts |
| 7409411 | Tajima unilateral columella lengthening operation | | Orofacial Clefts |
| 7409500 | Rhinoplasty for cleft lip nasal deformity | | Orofacial Clefts |
| 7409600 | Septorhinoplasty for cleft lip nasal deformity | | Orofacial Clefts |
| 7409700 | Septoplasty for cleft lip nasal deformity | | Orofacial Clefts |
| 7502.11 | Repair of cleft lip operations | | Orofacial Clefts |
| 7502000 | Primary closure of cleft lip, unspecified | | Orofacial Clefts |
| 7502011 | Lemesurier cleft lip repair | | Orofacial Clefts |
| 7502012 | Millard cleft lip correction | | Orofacial Clefts |
| 7502014 | Tenison cleft lip repair | | Orofacial Clefts |
| 7502100 | Revision of primary closure of cleft lip | | Orofacial Clefts |
| 7502300 | Unilateral lip adhesion | | Orofacial Clefts |
| 7502400 | Bilateral lip adhesion | | Orofacial Clefts |
| 7502500 | Repair of unilateral cleft lip using straight line technique | | Orofacial Clefts |
| 7502600 | Repair unilat cleft lip - rotation advancement flp technique | | Orofacial Clefts |
| 7502611 | Millard repair unilateral cleft lip | | Orofacial Clefts |
| 7502700 | Repair of unilateral cleft lip with triangular flap | | Orofacial Clefts |
| 7502712 | Skoog repair unilateral cleft lip | | Orofacial Clefts |
| 7502713 | Tennyson repair unilateral cleft lip | | Orofacial Clefts |
| 7502800 | Repair unilateral cleft lip with quadrilateral flap | | Orofacial Clefts |
| 7502811 | Repair unilateral cleft lip with quadrilateral flap | | Orofacial Clefts |
| 7502900 | Repair of unilateral cleft lip unspecified | | Orofacial Clefts |
| 7502A00 | Repair bilateral cleft lip - rotation advancement flap tech | | Orofacial Clefts |
| 7502A11 | Rep bilat cleft lip Millard | | Orofacial Clefts |
| 7502B00 | Repair of bilateral cleft lip with quadrilateral flap | | Orofacial Clefts |
| 7502C11 | Manchester bilateral cleft lip repair | | Orofacial Clefts |
| 7502C12 | Veau type III bilateral cleft lip repair | | Orofacial Clefts |
| 7502D00 | Repair of bilateral cleft lip unspecified | | Orofacial Clefts |
| 7502E00 | Synchronous bilateral cleft lip repair | | Orofacial Clefts |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7502F00 | Asynchronous bilateral cleft lip repair | | Orofacial Clefts |
| 7525.12 | Repair of cleft palate | | Orofacial Clefts |
| 7525000 | Primary repair of cleft palate, unspecified | | Orofacial Clefts |
| 7525011 | Kilner repair of cleft palate | | Orofacial Clefts |
| 7525012 | Langenbeck repair of cleft palate | | Orofacial Clefts |
| 7525013 | Wardill repair of cleft palate | | Orofacial Clefts |
| 7525100 | Revision of repair of cleft palate | | Orofacial Clefts |
| 7525200 | Repair cleft hard palate post based axial transposition flap | | Orofacial Clefts |
| 7525212 | Wardill repair cleft palate | | Orofacial Clefts |
| 7525213 | Veau flap repair cleft palate | | Orofacial Clefts |
| 7525300 | Repair of cleft hard palate with bipedicled flaps | | Orofacial Clefts |
| 7525311 | Langenbeck repair cleft palate | | Orofacial Clefts |
| 7525400 | Repair of cleft soft palate with Z-plasty | | Orofacial Clefts |
| 7525411 | Furlow repair cleft palate | | Orofacial Clefts |
| 7525500 | Repair of anterior cleft palate with local flap | | Orofacial Clefts |
| 7525600 | Repair of anterior cleft palate with vomerine flap | | Orofacial Clefts |
| 7525700 | Repair of cleft soft palate with intra-velar veloplasty | | Orofacial Clefts |
| 7525711 | Rep anterior cleft palate local flap | | Orofacial Clefts |
| 7525800 | Repair cleft soft palate with other musculature correction | | Orofacial Clefts |
| P9...00 | Cleft palate and lip | | Orofacial Clefts |
| P90..00 | Cleft palate | | Orofacial Clefts |
| P900.00 | Cleft palate, unspecified | | Orofacial Clefts |
| P900.11 | Palatoschisis | | Orofacial Clefts |
| P901.00 | Unilateral complete cleft palate | | Orofacial Clefts |
| P901.11 | Cleft hard palate, unilateral | | Orofacial Clefts |
| P902.00 | Unilateral incomplete cleft palate | | Orofacial Clefts |
| P902.11 | Cleft uvula | | Orofacial Clefts |
| P902.12 | Cleft soft palate, unilateral | | Orofacial Clefts |
| P903.00 | Bilateral complete cleft palate | | Orofacial Clefts |
| P904.00 | Bilateral incomplete cleft palate | | Orofacial Clefts |
| P904.11 | Cleft soft palate, bilateral | | Orofacial Clefts |
| P905.00 | Central complete cleft palate | | Orofacial Clefts |
| P906.00 | Central incomplete cleft palate | | Orofacial Clefts |
| P906.11 | Cleft soft palate, central | | Orofacial Clefts |
| P907.00 | Complete cleft palate NOS | | Orofacial Clefts |
| P907.11 | Cleft hard palate NOS | | Orofacial Clefts |
| P908.00 | Incomplete cleft palate NOS | | Orofacial Clefts |
| P908.11 | Cleft soft palate NOS | | Orofacial Clefts |
| P909.00 | Cleft uvula | | Orofacial Clefts |
| P90A.00 | Cleft soft palate, bilateral | | Orofacial Clefts |
| P90B.00 | Cleft hard palate, bilateral | | Orofacial Clefts |
| P90C.00 | Cleft hard palate, unilateral | | Orofacial Clefts |
| P90z.00 | Cleft palate NOS | | Orofacial Clefts |
| P91..00 | Cleft lip (harelip) | | Orofacial Clefts |
| P91..11 | Cheiloschisis | | Orofacial Clefts |
| P91..12 | Congenital fissure of lip | | Orofacial Clefts |
| P910.00 | Cleft lip, unspecified | | Orofacial Clefts |
| P911.00 | Unilateral complete cleft lip | | Orofacial Clefts |
| P912.00 | Unilateral incomplete cleft lip | | Orofacial Clefts |
| P913.00 | Bilateral complete cleft lip | | Orofacial Clefts |
| P914.00 | Bilateral incomplete cleft lip | | Orofacial Clefts |
| P915.00 | Central cleft lip | | Orofacial Clefts |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P91z.00 | Cleft lip NOS | | Orofacial Clefts |
| P92..00 | Cleft palate with cleft lip | | Orofacial Clefts |
| P92..11 | Cheilopalatoschisis | | Orofacial Clefts |
| P920.00 | Cleft palate with cleft lip, unspecified | | Orofacial Clefts |
| P921.00 | Unilateral complete cleft palate with cleft lip | | Orofacial Clefts |
| P922.00 | Unilateral incomplete cleft palate with cleft lip | | Orofacial Clefts |
| P923.00 | Bilateral complete cleft palate with cleft lip | | Orofacial Clefts |
| P924.00 | Bilateral incomplete cleft palate with cleft lip | | Orofacial Clefts |
| P928.00 | Cleft hard palate with cleft soft palate, unilateral | | Orofacial Clefts |
| P92A.00 | Cleft hard palate with cleft lip, bilateral | | Orofacial Clefts |
| P92B.00 | Cleft hard palate with cleft lip, unilateral | | Orofacial Clefts |
| P92z.00 | Cleft palate with cleft lip NOS | | Orofacial Clefts |
| P9z..00 | Cleft palate or cleft lip NOS | | Orofacial Clefts |
| Pyu4.00 | [X]Cleft lip and cleft palate | | Orofacial Clefts |
| Pyu4000 | [X]Cleft palate, unspecified, bilateral | | Orofacial Clefts |
| Pyu4100 | [X]Unspecified cleft palate with cleft lip, bilateral | | Orofacial Clefts |
| 7H10.00 | Simple excision of inguinal hernial sac | Yes | Other |
| 7H10y00 | Other specified simple excision of inguinal hernial sac | Yes | Other |
| 7H10z00 | Simple excision of inguinal hernial sac nos | Yes | Other |
| 7H11.00 | Primary repair of inguinal hernia | Yes | Other |
| 7H11000 | Primary repair inguinal hernia using insert natural material | Yes | Other |
| 7H11100 | Prim repair inguinal hernia using insert prosthet material | Yes | Other |
| 7H11111 | Primary mesh repair of inguinal hernia | Yes | Other |
| 7H11200 | Primary repair of inguinal hernia using sutures | Yes | Other |
| 7H11211 | Bassini repair of inguinal hernia | Yes | Other |
| 7H11212 | Ferguson repair of inguinal hernia | Yes | Other |
| 7H11213 | Mcvay repair of inguinal hernia | Yes | Other |
| 7H11214 | Shouldice repair of inguinal hernia | Yes | Other |
| 7H11300 | Primary repair inguinal hernia & reduction of sliding hernia | Yes | Other |
| 7H11400 | Endoscopic primary repair of inguinal hernia | Yes | Other |
| 7H11500 | Bilateral inguinal hernia repair | Yes | Other |
| 7H11600 | Primary laparoscopic repair of inguinal hernia | Yes | Other |
| 7H11y00 | Other specified primary repair of inguinal hernia | Yes | Other |
| 7H11y11 | Halsted repair of inguinal hernia | Yes | Other |
| 7H11z00 | Primary repair of inguinal hernia nos | Yes | Other |
| 7H12.00 | Repair of recurrent inguinal hernia | Yes | Other |
| 7H12.11 | Herniorrhaphy for recurrent inguinal hernia | Yes | Other |
| 7H12000 | Repair recurr inguinal hernia using insert natural material | Yes | Other |
| 7H12100 | Repair recurr inguinal hernia using insert prosthet material | Yes | Other |
| 7H12200 | Repair of recurrent inguinal hernia using sutures | Yes | Other |
| 7H12300 | Removal prosthet material fr previous repair inguinal hernia | Yes | Other |
| 7H12y00 | Other specified repair of recurrent inguinal hernia | Yes | Other |
| 7H12z00 | Repair of recurrent inguinal hernia nos | Yes | Other |
| J30..00 | Inguinal hernia | Yes | Other |
| J30..12 | Direct inguinal hernia | Yes | Other |
| J30..13 | Indirect inguinal hernia | Yes | Other |
| J300.00 | Inguinal hernia with gangrene | Yes | Other |
| J300000 | Unilateral inguinal hernia with gangrene | Yes | Other |
| J300300 | Bilateral recurrent inguinal hernia with gangrene | Yes | Other |
| J300z00 | Inguinal hernia with gangrene nos | Yes | Other |
| J301.00 | Inguinal hernia with obstruction | Yes | Other |
| J301000 | Unilateral inguinal hernia with obstruction | Yes | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| J301100 | Unilateral recurrent inguinal hernia with obstruction | Yes | Other |
| J301200 | Bilateral inguinal hernia with obstruction | Yes | Other |
| J301z00 | Inguinal hernia with obstruction nos | Yes | Other |
| J302.00 | Inguinal hernia – irreducible | Yes | Other |
| J302000 | Unilateral inguinal hernia - irreducible | Yes | Other |
| J302100 | Unilateral recurrent inguinal hernia - irreducible | Yes | Other |
| J302200 | Bilateral inguinal hernia - irreducible | Yes | Other |
| J302300 | Bilateral recurrent inguinal hernia - irreducible | Yes | Other |
| J302z00 | Inguinal hernia - irreducible and nos | Yes | Other |
| J303.00 | Simple inguinal hernia | Yes | Other |
| J303000 | Unilateral inguinal hernia – simple | Yes | Other |
| J303011 | Left inguinal hernia | Yes | Other |
| J303012 | Right inguinal hernia | Yes | Other |
| J303100 | Unilateral recurrent inguinal hernia - simple | Yes | Other |
| J303200 | Bilateral inguinal hernia – simple | Yes | Other |
| J303300 | Bilateral recurrent inguinal hernia - simple | Yes | Other |
| J303z00 | Simple inguinal hernia nos | Yes | Other |
| J304.00 | Direct inguinal hernia | Yes | Other |
| J305.00 | Indirect inguinal hernia | Yes | Other |
| J30y.00 | Inguinal hernia unspecified | Yes | Other |
| J30y000 | Unilateral inguinal hernia unspecified | Yes | Other |
| J30y100 | Unilateral recurrent inguinal hernia unspecified | Yes | Other |
| J30y200 | Bilateral inguinal hernia unspecified | Yes | Other |
| J30y300 | Bilateral recurrent inguinal hernia unspecified | Yes | Other |
| J30yz00 | Unspecified inguinal hernia nos | Yes | Other |
| J30z.00 | Inguinal hernia nos | Yes | Other |
| PG8..00 | Congenital inguinal hernia | Yes | Other |
| P75..00 | Absence or hypoplasia of the umbilical artery | Yes | Other |
| P750.00 | Congenital absence of umbilical artery, unspecified | Yes | Other |
| P752.00 | Single umbilical artery | Yes | Other |
| P75z.00 | Absence or hypoplasia of the umbilical artery NOS | Yes | Other |
| P831600 | Laryngomalacia | Yes | Other |
| P831700 | Congenital laryngomalacia | Yes | Other |
| P83y900 | Congenital laryngeal stridor | Yes | Other |
| 7204A00 | Correction of hypertelorism with orbital osteotomies | Yes | Other |
| 7204B00 | Corr hypertelorism c orbital osteotomies+facial bipartition | Yes | Other |
| 7204C00 | Corr hypertelorism c orbital osteotomies+nasal reconstruct | Yes | Other |
| 7204D00 | Correction of hypotelorism with orbital osteotomies | Yes | Other |
| F4G4100 | Hypertelorism of orbit | Yes | Other |
| P241.13 | Macrocephaly | Yes | Other |
| PG05.00 | Hypertelorism | Yes | Other |
| PG0H.00 | Macrocephaly | Yes | Other |
| PG0y000 | Brachycephaly | Yes | Other |
| PG2..00 | Cervical rib | Yes | Other |
| PG30.00 | Congenital absence of rib | Yes | Other |
| PG33.00 | Congenital fusion of ribs | Yes | Other |
| PG34.00 | Sternum bifidum | Yes | Other |
| PG36.00 | Extra ribs | Yes | Other |
| PG36.11 | Supernumerary ribs | Yes | Other |
| PG37.00 | Mis-shapen sternum | Yes | Other |
| pe21.00 | Congenital postural lordosis | Yes | Other |
| pg17.00 | Spina bifida occulta | Yes | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| p814.00 | Deformity of nasal sinus wall | Yes | Other |
| p815.00 | Congenital notching of tip of nose | Yes | Other |
| 7136800 | Excision of accessory nipple | Yes | Other |
| PH31.11 | Vascular naevus | Yes | Other |
| PH31.12 | Naevus flammeus | Yes | Other |
| PH31000 | Birth mark, unspecified | Yes | Other |
| PH31100 | Port wine stain | Yes | Other |
| PH31200 | Strawberry naevus | Yes | Other |
| PH32.00 | Congenital pigmentary skin anomalies | Yes | Other |
| PH34.00 | Other specified birthmark | Yes | Other |
| PH34.11 | Naevus nec | Yes | Other |
| PH34000 | Naevus sebaceous | Yes | Other |
| PH35.00 | Mongolian blue spot | Yes | Other |
| PH3y.00 | Other congenital skin anomalies | Yes | Other |
| PH3y.11 | Keratosis palmaris | Yes | Other |
| PH3y000 | Congenital accessory skin tags | Yes | Other |
| PH3y600 | Keratosis palmaris et plantaris | Yes | Other |
| PH3yz00 | Other congenital skin anomaly nos | Yes | Other |
| PH3z.00 | Integument anomalies nos | Yes | Other |
| PH41.11 | Beaded hair | Yes | Other |
| PH43.00 | Persistent lanugo | Yes | Other |
| PH4z.00 | Specified hair anomalies nos | Yes | Other |
| PH53.00 | Congenital leukonychia | Yes | Other |
| PH54.11 | Enlarged nails | Yes | Other |
| PH63.00 | Accessory nipple | Yes | Other |
| PH65.00 | Supernumerary nipple | Yes | Other |
| PHz..11 | Congenital ectodermal defect | Yes | Other |
| PHz0.00 | Unspecified congenital anomalies of skin | Yes | Other |
| PHz0.11 | Congenital dermal defect | Yes | Other |
| 7C03111 | Excision of aberrant testis | Yes | Other |
| PC5..00 | Undescended testicle | Yes | Other |
| PC50.00 | Cryptorchidism | Yes | Other |
| PC50000 | Cryptorchidism, unilateral | Yes | Other |
| PC50100 | Cryptorchidism, bilateral | Yes | Other |
| PC50z00 | Cryptorchidism NOS | Yes | Other |
| PC51.00 | Ectopic testis | Yes | Other |
| PC5z.00 | Undescended testicle NOS | Yes | Other |
| PC5z.12 | Maldescent of testicle | Yes | Other |
| PC5z000 | Undescended testis, unilateral | Yes | Other |
| PC5z011 | Maldescent of testis, unilateral | Yes | Other |
| PC5z100 | Undescended testis, bilateral | Yes | Other |
| PC5z111 | Maldescent of testis, bilateral | Yes | Other |
| 7A61000 | Excision of congenital arteriovenous malformation | | Other |
| 7A61200 | Embolisation of arteriovenous abnormality | | Other |
| 7A61300 | Ligation of congenital arteriovenous malformation | | Other |
| 7A61500 | Percutan transluminal embolis arteriovenous malformation NEC | | Other |
| 7A61600 | Percut translumin venous embolisat arteriovenous malform | | Other |
| 7A61700 | Perc translum arterial venous embolis arteriovenous malform | | Other |
| 7A61800 | Embolisation of arteriovenous abnormality NEC | | Other |
| P357.00 | Posterior chamber vascular anomalies | | Other |
| P357100 | Congenital arteriovenous malformation of retina | | Other |
| P357z00 | Posterior chamber vascular anomalies NOS | | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P7...00 | Other congenital circulatory system anomalies | | Other |
| P753.00 | Two umbilical vessels | | Other |
| P76..00 | Other peripheral vascular system anomalies | | Other |
| P76..11 | Other congenital anomalies of peripheral arteries | | Other |
| P76..12 | Other congenital anomalies of peripheral veins | | Other |
| P760.00 | Absence of artery NEC | | Other |
| P761.00 | Anomaly of artery NEC | | Other |
| P762.00 | Atresia of artery NEC | | Other |
| P763.00 | Absence of vein NEC | | Other |
| P764.00 | Anomaly of vein NEC | | Other |
| P766.00 | Peripheral arterio-venous aneurysm | | Other |
| P766.11 | Peripheral arterio-venous malformation | | Other |
| P767.00 | Congenital peripheral aneurysm | | Other |
| P767.11 | Cirsoid aneurysm | | Other |
| P768.00 | Congenital phlebectasia | | Other |
| P769.00 | Congenital arterial stricture | | Other |
| P769000 | Renal artery stenosis | | Other |
| P76A.00 | Congenital varix | | Other |
| P76B.00 | Multiple renal arteries | | Other |
| P76B.11 | Accessory renal artery | | Other |
| P76C.00 | Anomalies of renal artery NEC | | Other |
| P76C000 | Aberrant main renal artery | | Other |
| P76Cz00 | Anomaly of renal artery NEC NOS | | Other |
| P76D.00 | Arteriovenous malformation | | Other |
| P76E.00 | Aber retro-oesophag subclavian artery causing dysphag lusori | | Other |
| P76y.00 | Congenital anomaly of peripheral vascular system OS | | Other |
| P76y100 | Four vessels in umbilical cord | | Other |
| P76yz00 | Other congenital anomaly of peripheral vascular system NOS | | Other |
| P76z.00 | Peripheral vascular system anomaly NOS | | Other |
| P77..00 | Arteriovenous malformation of precerebral vessels | | Other |
| P7W..00 | Congenital malformation of circulatory system, unspecif | | Other |
| P7X..00 | Congenital malformation of great arteries, unspecified | | Other |
| P7y..00 | Other specified circulatory system anomalies | | Other |
| P7y0.00 | Cerebrovascular system anomalies | | Other |
| P7y0000 | Congenital anomaly of cerebral vessel, unspecified | | Other |
| P7y0100 | Congenital cerebral arteriovenous aneurysm | | Other |
| P7y0111 | Congenital arteriovenous fistula of brain | | Other |
| P7y0112 | Congenital cerebral arteriovenous malformation | | Other |
| P7y0200 | Congenital brain aneurysm NEC | | Other |
| P7y0400 | Vein of Galen malformation | | Other |
| P7y0y00 | Other specified cerebrovascular anomaly | | Other |
| P7y0z00 | Cerebrovascular system anomaly NOS | | Other |
| P7yz.00 | Other cardiovascular system anomaly NOS | | Other |
| P7yz000 | Congenital aneurysm NEC | | Other |
| P7yzz00 | Other cardiovascular system anomaly NOS | | Other |
| P7z..00 | Circulatory system anomaly NOS | | Other |
| PKyG.00 | Men ret congen heart dis blepharophim blepharop hypopl teeth | | Other |
| Pyu2.00 | [X]Congenital malformations of the circulatory system | | Other |
| Pyu2B00 | [X]Oth specified cong malform of peripheral vascular system | | Other |
| Pyu2D00 | [X]Other malformations of cerebral vessels | | Other |
| Pyu2E00 | [X]Other specified cong malformations of circulatory system | | Other |
| Pyu2K00 | [X]Congenital malformation of circulatory system, unspecif | | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PB6yw11 | Liver hamartoma | | Other |
| PKz0.00 | Anomalies of umbilicus | | Other |
| pd73.00 | Persistent umbilical sinus | | Other |
| 14H..00 | H/O: congenital anomaly | | Other |
| 14HZ.00 | H/O: congenital anomaly NOS | | Other |
| P....00 | Congenital anomalies | | Other |
| PE8..00 | Other specified nonteratogenic anomalies | | Other |
| PE8y.00 | Other nonteratogenic anomalies OS | | Other |
| PE8yz00 | Other nonteratogenic anomaly NOS | | Other |
| PE8z.00 | Nonteratogenic anomalies NOS | | Other |
| PK...00 | Other and unspecified congenital anomalies | | Other |
| PK7..00 | Multiple congenital anomalies NOS | | Other |
| PK7z.00 | Multiple congenital anomalies NOS | | Other |
| PKy0.00 | Multiple system congenital anomalies NEC | | Other |
| PKyz.00 | Other specified anomalies NOS | | Other |
| PKz..00 | Other anomalies NOS | | Other |
| Py...00 | Other specified congenital anomaly | | Other |
| Pyu..00 | [X]Additional congenital disease classification terms | | Other |
| Pyu9.00 | [X]Other congenital malformations | | Other |
| ZV13600 | [V]Personal history of congenital malformations | | Other |
| P82..00 | Congenital web of larynx | | Other |
| P820.00 | Congenital web of larynx, unspecified | | Other |
| P821.00 | Congenital glottic web of larynx | | Other |
| P822.00 | Congenital subglottic web of larynx | | Other |
| P82z.00 | Congenital web of larynx nos | | Other |
| P831000 | Anomaly of cricoid cartilage | | Other |
| P831100 | Anomaly of epiglottis | | Other |
| P831200 | Anomaly of thyroid cartilage | | Other |
| P831500 | Laryngeal hypoplasia | | Other |
| P832000 | Atresia of epiglottis | | Other |
| P832100 | Atresia of glottis | | Other |
| P833000 | Congenital stenosis of larynx | | Other |
| P833300 | Congenital subglottic stenosis | | Other |
| P833400 | Congenital supraglottic stenosis | | Other |
| P83y300 | Congenital laryngocele | | Other |
| P83y600 | Congenital fissure of epiglottis | | Other |
| P83y700 | Congenital cleft of posterior cricoid cartilage | | Other |
| P83yX00 | Congenital malformation of larynx, unspecified | | Other |
| P83yw00 | Other anomaly of larynx | | Other |
| 7L0N100 | Cranio-orbital remodelling for trigonocephaly | | Other |
| J34..12 | Parasternal hernia | | Other |
| J34..13 | Retrosternal hernia | | Other |
| PG0..12 | Skull and face bone anomalies | | Other |
| PG00.00 | Congenital absence of skull bones | | Other |
| PG01.00 | Acrocephaly | | Other |
| PG02.00 | Congenital forehead deformity | | Other |
| PG03.00 | Craniosynostosis | | Other |
| PG03.11 | Scaphocephaly | | Other |
| PG03100 | Lambdoid synostosis | | Other |
| PG06.00 | Imperfect fusion of skull | | Other |
| PG07.00 | Oxycephaly | | Other |
| PG08.00 | Platybasia | | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PG09.00 | Premature cranial suture closure | | Other |
| PG0B.00 | Trigonocephaly | | Other |
| PG0G.00 | Localised skull defects | | Other |
| PG0G.11 | Craniolacunia | | Other |
| PG0G.12 | Lacunar skull | | Other |
| PG0y.00 | Other specified skull or face bone anomaly | | Other |
| PG0y.11 | Defect of skull ossification | | Other |
| PG0yz00 | Other anomaly of skull or face bone nos | | Other |
| PG0z.00 | Skull or face bone anomaly nos | | Other |
| PG13000 | Congenital absence of cervical vertebra | | Other |
| PG1u.00 | Congenital anomalies of cervical vertebrae nec | | Other |
| PG1uz00 | Congenital anomaly of cervical vertebrae nec nos | | Other |
| PG3..00 | Other rib and sternum anomalies | | Other |
| PG31.00 | Congenital absence of sternum | | Other |
| PG32.00 | Congenital fissure of sternum | | Other |
| PG35.00 | Mis-shapen ribs | | Other |
| PG3x.00 | Other congenital anomalies of ribs | | Other |
| PG3y.00 | Other congenital anomalies of sternum | | Other |
| PG3z.00 | Other rib or sternum anomaly nos | | Other |
| PG3z.11 | Anomalies of thoracic cage unspecified | | Other |
| PG42.00 | Multiple enchondromata | | Other |
| PG42.11 | Enchondromatosis | | Other |
| PG42.12 | Ollier's disease | | Other |
| PG42.18 | Dyschondroplasia | | Other |
| PG42000 | Multiple enchondromata with haemangioma | | Other |
| PG42011 | Kast's syndrome | | Other |
| PG42012 | Maffuci's syndrome | | Other |
| PG42z00 | Dyschondroplasia nos | | Other |
| PG49.00 | Dysplasia epiphysealis hemimelica | | Other |
| PG5..00 | Osteodysplasia | | Other |
| PG5..11 | Osteodystrophy | | Other |
| PG50.00 | Osteodysplasia, unspecified | | Other |
| PG54.00 | Polyostotic fibrous dysplasia | | Other |
| PG5y.00 | Other specified osteodysplasia | | Other |
| PG5y000 | Albright-sternberg syndrome | | Other |
| PG5y011 | Albright-mccune-sternberg syndrome | | Other |
| PG5y012 | Albright's polyostotic dysplasia | | Other |
| PG5yz00 | Other osteodysplasia nos | | Other |
| PG5z.00 | Osteodysplasia nos | | Other |
| PG5z.11 | Osteochondrodysplasia | | Other |
| PG6..00 | Anomalies of diaphragm | | Other |
| PG61.11 | Congenital defect of diaphragmatic nec | | Other |
| PG62.00 | Congenital foramen morgagni hernia | | Other |
| PG63.00 | Eventration of diaphragm | | Other |
| PG6y.00 | Other specified anomalies of diaphragm | | Other |
| PG6z.00 | Diaphragm anomalies nos | | Other |
| PGX..00 | Congenital malformation of bony thorax, unspecified | | Other |
| PGy..00 | Other specified muscle, tendon and fascia anomaly | | Other |
| PGy0.00 | Congenital absence of muscle and tendon | | Other |
| PGy0000 | Absent tendon | | Other |
| PGy0200 | Other absent muscle | | Other |
| PGy0211 | Muscle agenesis | | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PGy0212 | Orbinsky syndrome | | Other |
| PGy0z00 | Absent muscle or tendon nos | | Other |
| PGy1.00 | Accessory muscle | | Other |
| PGyy.00 | Other specified other anomalies of muscle, tendon and fascia | | Other |
| PGyy.11 | Ayala's disease | | Other |
| PGyy000 | Amyotrophica congenital | | Other |
| PGyy200 | Hypoplasia of muscle | | Other |
| PGyy400 | Aplasia of muscle | | Other |
| PGyyz00 | Other anomaly of tendon, fascia or muscle nos | | Other |
| PGyz.00 | Other muscle, tendon or fascia anomalies nos | | Other |
| Pyu8D00 | [X]other specified congenit malformation skull & face bones | | Other |
| n384000 | Dysplastic spondylolisthesis | | Other |
| pe23.00 | Congenital scoliosis due to congenital bony malformation | | Other |
| pe8yb00 | Discoid meniscus – congenital | | Other |
| pez..00 | Congenital musculoskeletal deformity nos | | Other |
| pf59400 | Poland's syndrome | | Other |
| pg11.00 | Congenital lumbosacral spondylolysis | | Other |
| pg12.00 | Congenital spondylolisthesis | | Other |
| pg13.00 | Congenital absence of vertebra | | Other |
| pg13200 | Congenital absence of lumbar vertebra | | Other |
| pg13300 | Congenital absence of sacrum | | Other |
| pg13311 | Sacral agenesis | | Other |
| pg14.00 | Hemivertebra | | Other |
| pg14000 | Cervical hemivertebra | | Other |
| pg14100 | Thoracic hemivertebra | | Other |
| pg14200 | Lumbar hemivertebra | | Other |
| pg14800 | Lumbar hemivertebra - unbalanced | | Other |
| pg14z00 | Hemivertebra nos | | Other |
| pg15.00 | Congenital fusion of spine | | Other |
| pg15.11 | Congenital lumbosacral fusion | | Other |
| pg15000 | Congenital complete fusion of spine | | Other |
| pg15100 | Congenital partial fusion of spine - balanced | | Other |
| pg15200 | Congenital partial fusion of spine - unbalanced | | Other |
| pg16000 | Wilderwanck's syndrome | | Other |
| pg18.00 | Congenital kyphosis | | Other |
| pg18.11 | Congenital kyphoscoliosis | | Other |
| pg1u000 | Supernumerary cervical vertebra | | Other |
| pg1v.00 | Congenital anomalies of thoracic vertebrae nec | | Other |
| pg1vz00 | Congenital anomaly of thoracic vertebrae nec nos | | Other |
| pg1w.00 | Congenital anomalies of lumbar vertebrae nec | | Other |
| pg1w000 | Supernumerary lumbar vertebra | | Other |
| pg1wz00 | Congenital anomaly of lumbar vertebra nec nos | | Other |
| pg1x.00 | Congenital sacrococcygeal anomalies nec | | Other |
| pg1x000 | Congenital absence of coccyx | | Other |
| pg1x100 | Congenital absence of sacrum | | Other |
| pg1xz00 | Congenital sacrococcygeal anomaly nos | | Other |
| pg1y.11 | Congenital deformity of lumbosacral joint | | Other |
| pg1y.12 | Congenital deformity of lumbosacral region | | Other |
| pg1y000 | Platyspondylia | | Other |
| pg1y100 | Supernumerary vertebra | | Other |
| pg1y300 | Defect of vertebral segmentation | | Other |
| pg1y400 | Hypoplasia of spine | | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pgw..00 | Osteochondrodyspl with defct growth tub bone spine unspec | | Other |
| pgy0100 | Poland's syndrome | | Other |
| pgyy100 | Congenital shortening of tendon | | Other |
| pgz..00 | Congenital musculoskeletal anomalies nos | | Other |
| pgz..11 | Congenital deformity of musculoskeletal system nec | | Other |
| pgz0.00 | Unspecified anomaly of muscle | | Other |
| pgz1.00 | Unspecified anomaly of tendon | | Other |
| pgz2.00 | Unspecified anomaly of bones | | Other |
| pgz3.00 | Unspecified anomaly of cartilage | | Other |
| pgz4.00 | Unspecified anomaly of connective tissue | | Other |
| pyu8f00 | [X]other congenital malformations of ribs | | Other |
| pyu8p00 | [X]congenital malformation of bony thorax, unspecified | | Other |
| Pyu3000 | [X]Other congenital malformations of nose | | Other |
| p81..00 | Other anomalies of nose | | Other |
| p810.00 | Congenital nose deformity, unspecified | | Other |
| p811.00 | Absent nose | | Other |
| p811000 | Agenesis of nose | | Other |
| p812.00 | Accessory nose | | Other |
| p813.00 | Congenital cleft nose | | Other |
| p816.00 | Congenital perforation of the nasal sinus wall | | Other |
| p817.00 | Perforated nasal septum | | Other |
| p818.00 | Congenital fissure of nose | | Other |
| p819.00 | Congenital hypoplastic nose | | Other |
| p81z.00 | Other anomalies of nose nos | | Other |
| p81z.11 | Single nostril | | Other |
| 7525.00 | Correction of deformity of palate | | Other |
| 7525.11 | Repair of deformity of palate | | Other |
| 7525712 | Plastic repair palate mucosal graft | | Other |
| 7525y00 | Other specified correction of deformity of palate | | Other |
| 7525z00 | Correction of deformity of palate NOS | | Other |
| PA24.11 | Congenital pits of lip | | Other |
| PA27100 | Congenital pharyngeal polyp | | Other |
| PA2A000 | Congenital ectropion of lip | | Other |
| 7131900 | Excision of accessory breast tissue | | Other |
| PH...00 | Congenital integument anomalies | | Other |
| PH...11 | Congenital skin anomalies | | Other |
| PH00.00 | Congenital lymphoedema | | Other |
| PH3..00 | Other specified skin anomalies | | Other |
| PH31.00 | Vascular hamartomas | | Other |
| PH31z00 | Vascular hamartoma nos | | Other |
| PH32000 | Congenital poikiloderma | | Other |
| PH32100 | Urticaria pigmentosa | | Other |
| PH32111 | Mast cell disease | | Other |
| PH32112 | Mastocytosis | | Other |
| PH32z00 | Congenital pigmentary skin anomaly nos | | Other |
| PH33.00 | Specified syndromes NEC involving skin anomalies | | Other |
| PH33200 | Mibelli's disease | | Other |
| PH33z00 | Specified syndromes involving skin anomalies NEC NOS | | Other |
| PH3y100 | Congenital scar | | Other |
| PH3y213 | Bullous eruption of hand | | Other |
| PH3yz11 | Lichen spinulosus | | Other |
| PH4..00 | Specified hair anomalies | | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PH40.00 | Congenital alopecia | | Other |
| PH40.11 | Congenital atrichosis | | Other |
| PH40000 | Congenital alopecia, unspecified | | Other |
| PH40100 | Congenital localised alopecia | | Other |
| PH40200 | Congenital generalised alopecia | | Other |
| PH40211 | Atrichosis | | Other |
| PH40z00 | Congenital alopecia nos | | Other |
| PH42.00 | Congenital hypertrichosis | | Other |
| PH43.11 | Hypertrichosis lanuginose | | Other |
| PH44.00 | Twisted hair | | Other |
| PH44.11 | Pili torti | | Other |
| PH5..00 | Specified anomalies of nails | | Other |
| PH50.00 | Anonychia | | Other |
| PH50.11 | Congenital absence of nails | | Other |
| PH51.00 | Congenital clubnail | | Other |
| PH52.00 | Congenital koilonychias | | Other |
| PH54.00 | Congenital onychauxis | | Other |
| PH55.00 | Congenital pachyonychia | | Other |
| PH55.11 | Hypertrophic nails | | Other |
| PH5z.00 | Specified nail anomalies nos | | Other |
| PH6..00 | Specified anomalies of breast | | Other |
| PH60.00 | Absent breast | | Other |
| PH61.00 | Absent nipple | | Other |
| PH62.00 | Accessory breast | | Other |
| PH64.00 | Supernumerary breast | | Other |
| PH66.00 | Hypoplasia of breast | | Other |
| PH67.00 | Small nipple | | Other |
| PH67.11 | Hypoplasia of nipple | | Other |
| PH68.00 | Ectopic breast tissue | | Other |
| PH6X.00 | Congenital malformation of breast, unspecified | | Other |
| PH6z.00 | Specified breast anomalies nos | | Other |
| PH7..00 | Cutis marmorata telangiectasia congenita | | Other |
| PHy..00 | Other specified integument anomaly | | Other |
| PHz..00 | Integument anomalies nos | | Other |
| PHz1.00 | Unspecified congenital anomalies of hair | | Other |
| PHz2.00 | Unspecified congenital anomalies of nail | | Other |
| PHz2.11 | Congenital deformity of nail | | Other |
| PK0..00 | Anomalies of spleen | | Other |
| PK00.00 | Aberrant spleen | | Other |
| PK01.00 | Absent spleen | | Other |
| PK01.11 | Asplenia | | Other |
| PK02.00 | Accessory spleen | | Other |
| PK03.00 | Congenital splenomegaly | | Other |
| PK03.11 | Hyperplasia of spleen | | Other |
| PK04.00 | Ectopic spleen | | Other |
| PK06.00 | Hypoplasia of spleen | | Other |
| PK07.00 | Mis-shapen spleen | | Other |
| PK0y.00 | Other specified anomalies of spleen | | Other |
| PK0z.00 | Anomalies of spleen nos | | Other |
| PK1..00 | Anomalies of adrenal gland | | Other |
| PK10.00 | Aberrant adrenal gland | | Other |
| PK11.00 | Absent adrenal gland | | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PK12.00 | Accessory adrenal gland | | Other |
| PK13.00 | Hypoplasia of adrenal gland | | Other |
| PK14.00 | Ectopic adrenal gland | | Other |
| PK15.00 | Aplasia of adrenal gland | | Other |
| PK1y.00 | Other specified anomalies of adrenal gland | | Other |
| PK1y000 | Congenital cyst of adrenal gland | | Other |
| PK1yz00 | Other congenital anomaly of adrenal gland nos | | Other |
| PK1z.00 | Anomalies of adrenal gland nos | | Other |
| PK2..00 | Other endocrine gland anomalies | | Other |
| PK20.00 | Absent parathyroid gland | | Other |
| PK21.00 | Accessory thyroid gland | | Other |
| PK22.00 | Persistent thyroglossal duct | | Other |
| PK23.00 | Thyroglossal duct cyst | | Other |
| PK24.00 | Anomalies of pituitary gland | | Other |
| PK24000 | Aberrant pituitary gland | | Other |
| PK24100 | Congenital absence of pituitary gland | | Other |
| PK24z00 | Anomaly of pituitary gland nos | | Other |
| PK25.00 | Anomalies of thyroid gland nec | | Other |
| PK25000 | Aberrant thyroid gland | | Other |
| PK25011 | Retrosternal thyroid gland | | Other |
| PK25100 | Congenital absence of thyroid gland | | Other |
| PK25z00 | Anomaly of thyroid gland nec nos | | Other |
| PK26.00 | Anomalies of thyroglossal duct nec | | Other |
| PK27.00 | Anomalies of parathyroid gland nec | | Other |
| PK27z00 | Anomaly of parathyroid gland nec nos | | Other |
| PK28.00 | Anomalies of thymus | | Other |
| PK28000 | Aberrant thymus gland | | Other |
| PK28100 | Congenital absence of thymus | | Other |
| PK28z00 | Anomaly of thymus gland nos | | Other |
| PK2y.00 | Other specified endocrine gland anomaly | | Other |
| PK2z.00 | Endocrine gland anomaly nos | | Other |
| PK3..00 | Situs inversus | | Other |
| PK30.00 | Situs inversus, unspecified | | Other |
| PK30.11 | Transposition of viscera unspecified | | Other |
| PK31.00 | Situs inversus abdominalis | | Other |
| PK31.11 | Transposition of abdominal viscera | | Other |
| PK32.00 | Situs inversus thoracis | | Other |
| PK33.00 | Complete situs inversus with dextrocardia | | Other |
| PK34.00 | Situs inversus with levocardia | | Other |
| PK3z.00 | Situs inversus nos | | Other |
| PK4..00 | Conjoined twins | | Other |
| PK40.00 | Craniopagus | | Other |
| PK40100 | Craniopagus occipitalis | | Other |
| PK40300 | Craniopagus parasiticus | | Other |
| PK42.11 | Buttock-joined twins | | Other |
| PK44.00 | Xiphopagus | | Other |
| PK44.11 | Xiphoid- and pelvis-joined twins | | Other |
| PK45.00 | Diaxial (double) monster | | Other |
| PK4z.00 | Conjoined twins nos | | Other |
| PK6..00 | Other hamartoses nec | | Other |
| PK61.00 | Sturge-weber syndrome | | Other |
| PK61.11 | Kalischer's disease | | Other |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| PK61.12 | Encephalocutaneous angiomatosis | | Other |
| PK64.00 | Proteus syndrome | | Other |
| PK6y.00 | Other specified hamartoses nec | | Other |
| PK6z.00 | Hamartoses nos | | Other |
| PK70.00 | Monster NOS | | Other |
| PKy..00 | Other specified anomalies | | Other |
| PKy0400 | Marshall-Smith syndrome | | Other |
| PKy3.00 | Single monster, specified type | | Other |
| PKy7700 | Caudal dysplasia sequence | | Other |
| PKyH.00 | Moulded baby syndrome | | Other |
| PKyz.12 | Local gigantism NEC | | Other |
| PKyz100 | Acardia | | Other |
| PKyz600 | Congenital hemihypertrophy | | Other |
| PKzz.00 | Congenital anomaly nos | | Other |
| Pyu9200 | [X]other specified congenital malformations of skin | | Other |
| Pyu9300 | [X]other congenital malformations of breast | | Other |
| Pyu9B00 | [X]other specified congenital malformations | | Other |
| Pyu9C00 | [X]congenital malformation of breast, unspecified | | Other |
| Pz...00 | Congenital anomaly nos | | Other |
| PB5z.12 | Short bowel syndrome | | Other |
| p110.11 | Split notochord syndrome | | Other |
| P7yz100 | Congenital chylothorax | | Other |
| PB58.12 | Anal and urogenital canal fusion | | Other |
| P831400 | Tracheomalacia | Yes | Respiratory |
| P86y100 | Azygos lobe of lung | Yes | Respiratory |
| P86y200 | Accessory lobe of lung | Yes | Respiratory |
| 7406200 | Correction of congenital atresia of choana | | Respiratory |
| 7448100 | Excision of cyst of bronchus | | Respiratory |
| P8...00 | Respiratory system congenital anomalies | | Respiratory |
| P80..00 | Choanal atresia | | Respiratory |
| P800.00 | Choanal atresia, unspecified | | Respiratory |
| P802.00 | Atresia of the posterior nares | | Respiratory |
| P803.00 | Congenital stenosis of the anterior nares | | Respiratory |
| P804.00 | Congenital stenosis of the posterior nares | | Respiratory |
| P80z.00 | Choanal atresia nos | | Respiratory |
| P83..00 | Other anomalies of larynx, trachea and bronchus | | Respiratory |
| P830200 | Agenesis of trachea | | Respiratory |
| P831.00 | Anomaly of laryngeal and tracheal cartilage | | Respiratory |
| P831300 | Anomaly of tracheal cartilage | | Respiratory |
| P831z00 | Anomaly of laryngeal or tracheal cartilage nos | | Respiratory |
| P832.00 | Atresia of larynx and trachea | | Respiratory |
| P832300 | Atresia of trachea | | Respiratory |
| P833.00 | Congenital stenosis of larynx, trachea and bronchus | | Respiratory |
| P833100 | Congenital stenosis of trachea | | Respiratory |
| P833200 | Congenital stenosis of bronchus | | Respiratory |
| P83y.00 | Other anomaly of larynx, trachea and bronchus | | Respiratory |
| P83y100 | Congenital dilatation of trachea | | Respiratory |
| P83y500 | Congenital diverticulum of trachea | | Respiratory |
| P83y800 | Rudimentary tracheal bronchus | | Respiratory |
| P83yB00 | Congenital bronchomalacia | | Respiratory |
| P83yx00 | Other anomaly of trachea | | Respiratory |
| P83yy00 | Other anomaly of bronchus | | Respiratory |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| P83yz00 | Other anomaly of larynx, trachea or bronchus nos | | Respiratory |
| P83z.00 | Other anomalies of larynx, trachea or bronchus nos | | Respiratory |
| P84..00 | Congenital cystic lung | | Respiratory |
| P840.00 | Congenital cystic lung disease, unspecified | | Respiratory |
| P841.00 | Congenital polycystic lung | | Respiratory |
| P841.11 | Multiple lung cysts | | Respiratory |
| P841.12 | Multiple congenital bronchogenic cysts | | Respiratory |
| P842.00 | Congenital honeycomb lung | | Respiratory |
| P843.00 | Single lung cyst | | Respiratory |
| P843.11 | Lung cyst | | Respiratory |
| P843.12 | Congenital bronchogenic cyst | | Respiratory |
| P844.00 | Congenital cystic adenomatoid malformation of the lung | | Respiratory |
| P84y.00 | Other specified congenital cystic lung | | Respiratory |
| P84z.00 | Congenital cystic lung nos | | Respiratory |
| P85..00 | Lung agenesis, hypoplasia and dysplasia | | Respiratory |
| P850.00 | Aplasia of lung | | Respiratory |
| P851.00 | Hypoplasia of lung | | Respiratory |
| P852.00 | Sequestration of lung | | Respiratory |
| P853.00 | Agenesis of lung | | Respiratory |
| P853.11 | Congenital absence of lung | | Respiratory |
| P853000 | Congenital absence of lung fissures | | Respiratory |
| P853100 | Congenital absence of lobe of lung | | Respiratory |
| P853z00 | Agenesis of lung nos | | Respiratory |
| P85y.00 | Other specified lung agenesis, hypoplasia or dysplasia | | Respiratory |
| P85y000 | Fusion of lobes of lung | | Respiratory |
| P85yz00 | Other lung agenesis, hypoplasia or dysplasia nos | | Respiratory |
| P85z.00 | Lung agenesis, hypoplasia or dysplasia nos | | Respiratory |
| P86..00 | Other lung anomalies | | Respiratory |
| P860.00 | Anomaly of lung, unspecified | | Respiratory |
| P861.00 | Congenital bronchiectasis | | Respiratory |
| P86y.00 | Other lung anomaly | | Respiratory |
| P86yz00 | Other lung anomaly nos | | Respiratory |
| P86z.00 | Lung anomaly nos | | Respiratory |
| P8y..00 | Other specified respiratory system anomalies | | Respiratory |
| P8y1.00 | Anomaly, pleural folds | | Respiratory |
| P8y2.00 | Atresia of nasopharynx | | Respiratory |
| P8y3.00 | Congenital cyst of mediastinum | | Respiratory |
| P8y4.00 | Congenital pulmonary lymphangiectasis | | Respiratory |
| P8yz.00 | Other specified respiratory system anomaly nos | | Respiratory |
| P8z..00 | Respiratory system anomaly nos | | Respiratory |
| Pyu3.00 | [X]congenital malformations of the respiratory system | | Respiratory |
| Pyu3300 | [X]other congenital malformations of bronchus | | Respiratory |
| Pyu3400 | [X]other congenital malformations of lung | | Respiratory |
| Pyu3500 | [X]other specified congen malformation respiratory system | | Respiratory |
| pd10.00 | Congenital renal cyst, single | Yes | Urinary |
| pd37.00 | Giant kidney | Yes | Urinary |
| pd47.00 | Congenital vesico-uretero-renal reflux | Yes | Urinary |
| 14h4.00 | H/o: urinary anomaly | | Urinary |
| 7B41200 | Closure of urethral fistula | | Urinary |
| 7B41211 | Excision of urethral fistula | | Urinary |
| 7b01300 | Heminephrectomy for horseshoe kidney | | Urinary |
| 7b01311 | Excision of half of horseshoe kidney | | Urinary |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| 7b02000 | Heminephrectomy for duplex kidney | | Urinary |
| 7b02100 | Division of isthmus of horseshoe kidney | | Urinary |
| 7b10400 | Excision of duplex ureter | | Urinary |
| 7b12.00 | Reimplantation of ureter | | Urinary |
| 7b12000 | Unspecified bilateral reimplantation of ureter | | Urinary |
| 7b12100 | Unspecified unilateral reimplantation of ureter | | Urinary |
| 7b12500 | Extravesical bilateral reimplantation of ureters | | Urinary |
| 7b12511 | Leadbetter bilateral reimplantation of ureters | | Urinary |
| 7b12512 | Politano bilateral reimplantation of ureters | | Urinary |
| 7b12611 | Cohen unilateral reimplantation of ureter | | Urinary |
| 7b12800 | Extravesical unilateral reimplantation of ureter | | Urinary |
| 7b12811 | Leadbetter unilateral reimplantation of ureter | | Urinary |
| 7b12812 | Politano unilateral reimplantation of ureter | | Urinary |
| 7b12y00 | Other specified reimplantation of ureter | | Urinary |
| 7b12z00 | Reimplantation of ureter nos | | Urinary |
| 7b16000 | Open excision of ureterocele | | Urinary |
| 7b17400 | Percut nephroscopic balloon dilatation of ureter | | Urinary |
| 7b17411 | Percut antegrade balloon dilatation of ureter | | Urinary |
| 7b18500 | Ureteroscopic endoluminal balloon rupture of stenosis ureter | | Urinary |
| 7b1a300 | Endoscopic dilatation of ureter | | Urinary |
| 7b1d300 | Endoscopic incision of ureterocele | | Urinary |
| 7b1d400 | Endoscopic dilatation of ureteric orifice | | Urinary |
| 7b1d600 | Endoscopic incision of ureterocele | | Urinary |
| 7b23400 | Closure of exstrophy of bladder | | Urinary |
| 7b41100 | Epispadias repair | | Urinary |
| 7b41112 | Denis-browne epispadias repair | | Urinary |
| 7b41113 | Young-dees epispadias repair | | Urinary |
| 7b43500 | Endoscopic destruction of posterior urethral valve | | Urinary |
| 7b43a00 | Endoscopic destruction of urethral valves | | Urinary |
| 7b45600 | Hook ablation of posterior urethral valve | | Urinary |
| PD8..00 | Congenital abnormality of the kidney | | Urinary |
| PD80.00 | Duplex kidney | | Urinary |
| PE02.00 | Potter's facies | | Urinary |
| PG72.00 | Prune belly syndrome | | Urinary |
| PKyA.00 | Cloacal exstrophy | | Urinary |
| Pyu7200 | [X]Other congenital malformations of ureter | | Urinary |
| k09..00 | Small kidney of unknown cause | | Urinary |
| k090.00 | Unilateral small kidney | | Urinary |
| k090100 | Unilateral small kidney with contralateral hypertrophy | | Urinary |
| k091.00 | Bilateral small kidneys | | Urinary |
| k09z.00 | Small kidneys unspecified | | Urinary |
| k11..00 | Hydronephrosis | | Urinary |
| k111.00 | Hydroureteronephrosis | | Urinary |
| k113.00 | Hydronephrosis with ureteropelvic junction obstruction | | Urinary |
| k113.11 | Hydronephrosis with pelviureteric junction obstruction | | Urinary |
| k11x.00 | Hydronephrosis with ureteral stricture nec | | Urinary |
| k11z.00 | Hydronephrosis nos | | Urinary |
| k133.00 | Stricture of ureter | | Urinary |
| k133100 | Stricture of pelviureteric junction | | Urinary |
| k133z00 | Stricture of ureter nos | | Urinary |
| k13b.00 | Calyceal diverticulum | | Urinary |
| k140000 | Calculus in diverticulum of bladder | | Urinary |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| k163.00 | Diverticulum of bladder | | Urinary |
| k191100 | Urethrorectal fistula | | Urinary |
| kyu1100 | [X]other and unspecified hydronephrosis | | Urinary |
| kyu1f00 | [X]hydronephrosis with ureteral stricture nec | | Urinary |
| pc61.00 | Epispadias | | Urinary |
| pd...00 | Urinary system congenital anomalies | | Urinary |
| pd0..00 | Renal agenesis and dysgenesis | | Urinary |
| pd00.00 | Renal agenesis, unspecified | | Urinary |
| pd00000 | Bilateral renal agenesis | | Urinary |
| pd00100 | Unilateral renal agenesis | | Urinary |
| pd00z00 | Renal agenesis, unspecified nos | | Urinary |
| pd01.00 | Congenital renal atrophy | | Urinary |
| pd02.00 | Congenital absence of kidney | | Urinary |
| pd02000 | Bilateral congenital absence of kidneys | | Urinary |
| pd02100 | Unilateral congenital absence of kidney | | Urinary |
| pd02z00 | Congenital absence of kidney nos | | Urinary |
| pd03.00 | Hypoplasia of kidney | | Urinary |
| pd03000 | Bilateral renal hypoplasia | | Urinary |
| pd03011 | Potter's syndrome | | Urinary |
| pd03100 | Unilateral renal hypoplasia | | Urinary |
| pd04.00 | Dysplasia of kidney | | Urinary |
| pd04000 | Bilateral renal dysplasia | | Urinary |
| pd04011 | Bilateral renal dysgenesis | | Urinary |
| pd04100 | Unilateral renal dysplasia | | Urinary |
| pd04111 | Unilateral renal dysgenesis | | Urinary |
| pd04200 | Renal dysplasia and retinal aplasia | | Urinary |
| pd04z00 | Dysplasia of kidney nos | | Urinary |
| pd0z.00 | Renal agenesis or dysgenesis nos | | Urinary |
| pd1..00 | Congenital cystic kidney disease | | Urinary |
| pd1..11 | Congenital cystic renal disease | | Urinary |
| pd13.00 | Multicystic renal dysplasia | | Urinary |
| pd1y.00 | Other specified congenital cystic kidney disease | | Urinary |
| pd1yz00 | Other congenital cystic kidney disease nos | | Urinary |
| pd1z.00 | Congenital cystic kidney disease nos | | Urinary |
| pd2..00 | Renal pelvis and ureter obstructive defects | | Urinary |
| pd20.00 | Atresia of ureter | | Urinary |
| pd21.00 | Occlusion of ureter | | Urinary |
| pd21.11 | Congenital ureteric valves | | Urinary |
| pd22.00 | Congenital stricture of ureter | | Urinary |
| pd22.11 | Congenital stenosis of ureter | | Urinary |
| pd22000 | Congenital stricture of ureter, unspecified | | Urinary |
| pd22100 | Congenital stricture of ureteropelvic junction | | Urinary |
| pd22200 | Congenital stricture of ureterovesical orifice | | Urinary |
| pd22z00 | Congenital stricture of ureter nos | | Urinary |
| pd23.00 | Congenital hydronephrosis | | Urinary |
| pd23.11 | Congenital dilated renal pelvis | | Urinary |
| pd24.00 | Congenital dilatation of ureter | | Urinary |
| pd25.00 | Hydroureter – congenital | | Urinary |
| pd26.00 | Megaloureter – congenital | | Urinary |
| pd27.00 | Ureterocele – congenital | | Urinary |
| pd2y.00 | Other specified obstructive defect of renal pelvis or ureter | | Urinary |
| pd2z.00 | Obstructive defect of renal pelvis or ureter nos | | Urinary |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pd3..00 | Other specified renal anomaly | | Urinary |
| pd30.00 | Accessory kidney | | Urinary |
| pd30.11 | Duplication of kidney | | Urinary |
| pd30.12 | Renal duplication nec | | Urinary |
| pd30.13 | Supernumerary kidney | | Urinary |
| pd31.00 | Congenital calculus of kidney | | Urinary |
| pd32.00 | Congenital displaced kidney | | Urinary |
| pd33.00 | Discoid kidney | | Urinary |
| pd34.00 | Double kidney with double pelvis | | Urinary |
| pd34.11 | Duplex kidneys | | Urinary |
| pd34.12 | Pyelon duplex | | Urinary |
| pd35.00 | Ectopic kidney | | Urinary |
| pd35.11 | Pelvic kidney | | Urinary |
| pd36.00 | Fusion of kidneys | | Urinary |
| pd38.00 | Horseshoe kidney | | Urinary |
| pd39.00 | Hyperplasia of kidney | | Urinary |
| pd3a.00 | Lobulation of kidney | | Urinary |
| pd3b.00 | Malrotation of kidney | | Urinary |
| pd3c.00 | Triple kidney with triple pelvis | | Urinary |
| pd3c.12 | Pyelon triplex | | Urinary |
| pd3d.00 | Enlarged kidney | | Urinary |
| pd3e.00 | Cake kidney | | Urinary |
| pd3f.00 | Bifid kidney | | Urinary |
| pd3z.00 | Other specified renal anomaly nos | | Urinary |
| pd4..00 | Other specified ureter anomalies | | Urinary |
| pd40.00 | Absent ureter | | Urinary |
| pd41.00 | Accessory ureter | | Urinary |
| pd42.00 | Deviation of ureter | | Urinary |
| pd43.00 | Displaced ureteric orifice | | Urinary |
| pd44.00 | Double ureter | | Urinary |
| pd44.11 | Duplication of ureter | | Urinary |
| pd45.00 | Ectopic ureter | | Urinary |
| pd45.12 | Ectopic insertion of ureter | | Urinary |
| pd46.00 | Anomalous ureter implantation | | Urinary |
| pd4z.00 | Other specified ureter anomaly nos | | Urinary |
| pd5..00 | Exstrophy of urinary bladder | | Urinary |
| pd5..11 | Ectopia vesicae | | Urinary |
| pd5..12 | Ectopic bladder | | Urinary |
| pd50.00 | Ectopic bladder | | Urinary |
| pd50.11 | Ectopia vesicae | | Urinary |
| pd5z.00 | Exstrophy of urinary bladder nos | | Urinary |
| pd6..00 | Urethra and bladder neck atresia and stenosis | | Urinary |
| pd60.00 | Congenital bladder neck obstruction | | Urinary |
| pd60000 | Atresia of bladder neck | | Urinary |
| pd60100 | Stenosis of bladder neck | | Urinary |
| pd60z00 | Congenital bladder neck obstruction nos | | Urinary |
| pd61.00 | Congenital obstruction of urethra | | Urinary |
| pd61000 | Atresia of anterior urethra | | Urinary |
| pd61100 | Stenosis of anterior urethra | | Urinary |
| pd61z00 | Congenital obstruction of urethra nos | | Urinary |
| pd62.00 | Congenital urethral valvular stricture | | Urinary |
| pd62.11 | Congenital posterior urethral valves | | Urinary |

| Read Code | Read term | Minor malformation? | Subgroup |
|---|---|---|---|
| pd63.00 | Congenital urinary meatus stricture | | Urinary |
| pd63.11 | Congenital urinary meatus obstruction | | Urinary |
| pd63.12 | Congenital pinhole urinary meatus | | Urinary |
| pd63100 | Stenosis of urinary meatus | | Urinary |
| pd63z00 | Congenital urinary meatus stricture nos | | Urinary |
| pd64.00 | Congenital vesicourethral orifice stricture | | Urinary |
| pd65.00 | Imperforate urinary meatus | | Urinary |
| pd66.00 | Impervious urethra | | Urinary |
| pd67.00 | Congenital posterior urethral valves | | Urinary |
| pd6y.00 | Other specified urethra or bladder neck atresia or stenosis | | Urinary |
| pd6z.00 | Urethra or bladder neck atresia or stenosis nos | | Urinary |
| pd7..00 | Anomalies of urachus | | Urinary |
| pd70.00 | Cyst of urachus | | Urinary |
| pd71.00 | Fistula of urachus | | Urinary |
| pd72.00 | Patent urachus | | Urinary |
| pd72.11 | Persistent urachus | | Urinary |
| pd7y.00 | Other specified anomalies of urachus | | Urinary |
| pd7z.00 | Anomalies of urachus nos | | Urinary |
| pdy..00 | Other specified bladder and urethral anomalies | | Urinary |
| pdy0.00 | Congenital absence of bladder | | Urinary |
| pdy2.00 | Accessory bladder | | Urinary |
| pdy3.00 | Accessory urethra | | Urinary |
| pdy4.00 | Congenital bladder diverticulum | | Urinary |
| pdy5.00 | Congenital bladder hernia | | Urinary |
| pdy6.00 | Congenital urethrorectal fistula | | Urinary |
| pdy7.00 | Congenital prolapse of bladder mucosa | | Urinary |
| pdy8.00 | Congenital prolapse of urethra | | Urinary |
| pdy9.00 | Double urethra | | Urinary |
| pdya.00 | Double urinary meatus | | Urinary |
| pdyz.00 | Other bladder or urethral anomaly nos | | Urinary |
| pdyz000 | Epispadias, female | | Urinary |
| pdz..00 | Urinary system anomalies nos | | Urinary |
| pdz0.00 | Unspecified anomaly of kidney | | Urinary |
| pdz1.00 | Unspecified anomaly of ureter | | Urinary |
| pdz2.00 | Unspecified anomaly of bladder | | Urinary |
| pdz3.00 | Unspecified anomaly of urethra | | Urinary |
| pky5e00 | Branchio-otorenal dysplasia | | Urinary |
| pyu7.00 | [X]congenital malformations of the urinary system | | Urinary |
| pyu7000 | [X]other cystic kidney diseases | | Urinary |
| pyu7100 | [X]other obstructive defects of renal pelvis and ureter | | Urinary |
| pyu7300 | [X]other specified congenital malformations of kidney | | Urinary |
| pyu7500 | [X]other congenital malformations of bladder and urethra | | Urinary |

## ICD-10 codes

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q79.2 | Exomphalos | | Abdominal Wall |
| Q79.3 | Gastroschisis | | Abdominal Wall |
| Q79.5 | Other congenital malformations of abdominal wall | | Abdominal Wall |
| Q25.0 | Patent ductus arteriosus | If gest. age <37 weeks | Heart |
| Q25.6 | Stenosis of pulmonary artery | If gest. age <37 weeks | Heart |
| Q26.1 | Persistent left superior vena cava | Yes | Heart |
| Q20 | Congenital malformations of cardiac chambers and connections | | Heart |
| Q20.0 | Common arterial trunk | | Heart |
| Q20.1 | Double outlet right ventricle | | Heart |
| Q20.2 | Double outlet left ventricle | | Heart |
| Q20.3 | Discordant ventriculoarterial connection | | Heart |
| Q20.4 | Double inlet ventricle | | Heart |
| Q20.5 | Discordant atrioventricular connection | | Heart |
| Q20.6 | Isomerism of atrial appendages | | Heart |
| Q20.8 | Other cong malforms of cardiac chambers and connections | | Heart |
| Q20.9 | Cong malforms of cardiac chambers and connections unspec | | Heart |
| Q21 | Congenital malformations of cardiac septa | | Heart |
| Q21.0 | Ventricular septal defect | | Heart |
| Q21.1 | Atrial septal defect | | Heart |
| Q21.2 | Atrioventricular septal defect | | Heart |
| Q21.3 | Tetralogy of Fallot | | Heart |
| Q21.4 | Aortopulmonary septal defect | | Heart |
| Q21.8 | Other congenital malformations of cardiac septa | | Heart |
| Q21.9 | Congenital malformation of cardiac septum, unspecified | | Heart |
| Q22 | Congenital malformations of pulmonary and tricuspid valves | | Heart |
| Q22.0 | Pulmonary valve atresia | | Heart |
| Q22.1 | Congenital pulmonary valve stenosis | | Heart |
| Q22.2 | Congenital pulmonary valve insufficiency | | Heart |
| Q22.3 | Other congenital malformations of pulmonary valve | | Heart |
| Q22.4 | Congenital tricuspid stenosis | | Heart |
| Q22.5 | Ebstein's anomaly | | Heart |
| Q22.6 | Hypoplastic right heart syndrome | | Heart |
| Q22.8 | Other congenital malformations of tricuspid valve | | Heart |
| Q22.9 | Congenital malformation of tricuspid valve, unspecified | | Heart |
| Q23 | Congenital malformations of aortic and mitral valves | | Heart |
| Q23.0 | Congenital stenosis of aortic valve | | Heart |
| Q23.1 | Congenital insufficiency of aortic valve | | Heart |
| Q23.2 | Congenital mitral stenosis | | Heart |
| Q23.3 | Congenital mitral insufficiency | | Heart |
| Q23.4 | Hypoplastic left heart syndrome | | Heart |
| Q23.8 | Other congenital malformations of aortic and mitral valves | | Heart |
| Q23.9 | Congenital malformation of aortic and mitral valves unspec | | Heart |
| Q24 | Other congenital malformations of heart | | Heart |
| Q24.0 | Dextrocardia | | Heart |
| Q24.1 | Laevocardia | | Heart |
| Q24.2 | Cor triatriatum | | Heart |
| Q24.3 | Pulmonary infundibular stenosis | | Heart |
| Q24.4 | Congenital subaortic stenosis | | Heart |
| Q24.5 | Malformation of coronary vessels | | Heart |
| Q24.6 | Congenital heart block | | Heart |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q24.8 | Other specified congenital malformations of heart | | Heart |
| Q24.9 | Congenital malformation of heart, unspecified | | Heart |
| Q25 | Congenital malformations of great arteries | | Heart |
| Q25.1 | Coarctation of aorta | | Heart |
| Q25.2 | Atresia of aorta | | Heart |
| Q25.3 | Stenosis of aorta | | Heart |
| Q25.4 | Other congenital malformations of aorta | | Heart |
| Q25.5 | Atresia of pulmonary artery | | Heart |
| Q25.7 | Other congenital malformations of pulmonary artery | | Heart |
| Q25.8 | Other congenital malformations of great arteries | | Heart |
| Q25.9 | Congenital malformation of great arteries, unspecified | | Heart |
| Q26 | Congenital malformations of great veins | | Heart |
| Q26.0 | Congenital stenosis of vena cava | | Heart |
| Q26.2 | Total anomalous pulmonary venous connection | | Heart |
| Q26.3 | Partial anomalous pulmonary venous connection | | Heart |
| Q26.4 | Anomalous pulmonary venous connection, unspecified | | Heart |
| Q26.5 | Anomalous portal venous connection | | Heart |
| Q26.6 | Portal vein-hepatic artery fistula | | Heart |
| Q26.8 | Other congenital malformations of great veins | | Heart |
| Q26.9 | Congenital malformation of great vein, unspecified | | Heart |
| Q38.1 | Ankyloglossia | Yes | Digestive |
| Q38.2 | Macroglossia | Yes | Digestive |
| Q40.0 | Congenital hypertrophic pyloric stenosis | Yes | Digestive |
| Q40.1 | Congenital hiatus hernia | Yes | Digestive |
| Q43.0 | Meckel's diverticulum | Yes | Digestive |
| Q44.4 | Choledochal cyst | | Digestive |
| Q38 | Other congenital malformations of tongue, mouth and pharynx | | Digestive |
| Q38.0 | Congenital malformations of lips, not elsewhere classified | | Digestive |
| Q38.3 | Other congenital malformations of tongue | | Digestive |
| Q38.4 | Congenital malformations of salivary glands and ducts | | Digestive |
| Q38.5 | Congenital malformations of palate, not elsewhere classified | | Digestive |
| Q38.6 | Other congenital malformations of mouth | | Digestive |
| Q38.7 | Pharyngeal pouch | | Digestive |
| Q38.8 | Other congenital malformations of pharynx | | Digestive |
| Q39 | Congenital malformations of oesophagus | | Digestive |
| Q39.0 | Atresia of oesophagus without fistula | | Digestive |
| Q39.1 | Atresia of oesophagus with tracheo-oesophageal fistula | | Digestive |
| Q39.2 | Congenital tracheo-oesophageal fistula without atresia | | Digestive |
| Q39.3 | Congenital stenosis and stricture of oesophagus | | Digestive |
| Q39.4 | Oesophageal web | | Digestive |
| Q39.5 | Congenital dilatation of oesophagus | | Digestive |
| Q39.6 | Diverticulum of oesophagus | | Digestive |
| Q39.8 | Other congenital malformations of oesophagus | | Digestive |
| Q39.9 | Congenital malformation of oesophagus, unspecified | | Digestive |
| Q40 | Other congenital malformations of upper alimentary tract | | Digestive |
| Q40.2 | Other specified congenital malformations of stomach | | Digestive |
| Q40.3 | Congenital malformation of stomach, unspecified | | Digestive |
| Q40.8 | Other spec congenital malforms of upper alimentary tract | | Digestive |
| Q40.9 | Congenital malformation of upper alimentary tract | | Digestive |
| Q41 | Congenital absence, atresia and stenosis of small intestine | | Digestive |
| Q41.0 | Congenital absence, atresia and stenosis of duodenum | | Digestive |
| Q41.1 | Congenital absence, atresia and stenosis of jejunum | | Digestive |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q41.2 | Congenital absence, atresia and stenosis of ileum | | Digestive |
| Q41.8 | Congen absence atresia stenosis oth spec parts small intest | | Digestive |
| Q41.9 | Cong absce atresia and stenosis small intestine part unspec | | Digestive |
| Q42 | Congenital absence, atresia and stenosis of large intestine | | Digestive |
| Q42.0 | Cong absence atresia and stenosis of rectum with fistula | | Digestive |
| Q42.1 | Cong absence atresia and stenosis rectum without fistula | | Digestive |
| Q42.2 | Cong absence atresia and stenosis anus with fistula | | Digestive |
| Q42.3 | Cong absence atresia and stenosis anus without fistula | | Digestive |
| Q42.8 | Congen absence atresia and sten oth parts of large intest | | Digestive |
| Q42.9 | Cong absce atresia and sten of large intest part unspec | | Digestive |
| Q43 | Other congenital malformations of intestine | | Digestive |
| Q43.1 | Hirschsprung's disease | | Digestive |
| Q43.2 | Other congenital functional disorders of colon | | Digestive |
| Q43.3 | Congenital malformations of intestinal fixation | | Digestive |
| Q43.4 | Duplication of intestine | | Digestive |
| Q43.5 | Ectopic anus | | Digestive |
| Q43.6 | Congenital fistula of rectum and anus | | Digestive |
| Q43.7 | Persistent cloaca | | Digestive |
| Q43.8 | Other specified congenital malformations of intestine | | Digestive |
| Q43.9 | Congenital malformation of intestine, unspecified | | Digestive |
| Q44 | Congenital malformations of gallbladder, bile ducts & liver | | Digestive |
| Q44.0 | Agenesis, aplasia and hypoplasia of gallbladder | | Digestive |
| Q44.1 | Other congenital malformations of gallbladder | | Digestive |
| Q44.2 | Atresia of bile ducts | | Digestive |
| Q44.3 | Congenital stenosis and stricture of bile ducts | | Digestive |
| Q44.5 | Other congenital malformations of bile ducts | | Digestive |
| Q44.6 | Cystic disease of liver | | Digestive |
| Q44.7 | Other congenital malformations of liver | | Digestive |
| Q45 | Other congenital malformations of digestive system | | Digestive |
| Q45.0 | Agenesis, aplasia and hypoplasia of pancreas | | Digestive |
| Q45.1 | Annular pancreas | | Digestive |
| Q45.2 | Congenital pancreatic cyst | | Digestive |
| Q45.3 | Other cong malformations of pancreas and pancreatic duct | | Digestive |
| Q45.8 | Other specified congenital malformations of digestive system | | Digestive |
| Q45.9 | Congenital malformation of digestive system, unspecified | | Digestive |
| Q79.0 | Congenital diaphragmatic hernia | | Digestive |
| Q17.0 | Accessory auricle | Yes | Ear, Face & Neck |
| Q17.1 | Macrotia | Yes | Ear, Face & Neck |
| Q17.2 | Microtia | Yes | Ear, Face & Neck |
| Q17.3 | Other misshapen ear | Yes | Ear, Face & Neck |
| Q17.4 | Misplaced ear | Yes | Ear, Face & Neck |
| Q17.5 | Prominent ear | Yes | Ear, Face & Neck |
| Q18.0 | Sinus, fistula and cyst of branchial cleft | Yes | Ear, Face & Neck |
| Q18.1 | Preauricular sinus and cyst | Yes | Ear, Face & Neck |
| Q18.2 | Other branchial cleft malformations | Yes | Ear, Face & Neck |
| Q18.4 | Macrostomia | Yes | Ear, Face & Neck |
| Q18.5 | Microstomia | Yes | Ear, Face & Neck |
| Q18.6 | Macrocheilia | Yes | Ear, Face & Neck |
| Q18.7 | Microcheilia | Yes | Ear, Face & Neck |
| Q16 | Congenital malforms of ear causing impairment of hearing | | Ear, Face & Neck |
| Q16.0 | Congenital absence of (ear) auricle | | Ear, Face & Neck |
| Q16.1 | Cong absence atresia & stricture auditory canal (external) | | Ear, Face & Neck |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q16.2 | Absence of eustachian tube | | Ear, Face & Neck |
| Q16.3 | Congenital malformation of ear ossicles | | Ear, Face & Neck |
| Q16.4 | Other congenital malformations of middle ear | | Ear, Face & Neck |
| Q16.5 | Congenital malformation of inner ear | | Ear, Face & Neck |
| Q16.9 | Cong malform of ear causing impairment of hearing unspec | | Ear, Face & Neck |
| Q17 | Other congenital malformations of ear | | Ear, Face & Neck |
| Q17.8 | Other specified congenital malformations of ear | | Ear, Face & Neck |
| Q17.9 | Congenital malformation of ear, unspecified | | Ear, Face & Neck |
| Q18 | Other congenital malformations of face and neck | | Ear, Face & Neck |
| Q18.3 | Webbing of neck | | Ear, Face & Neck |
| Q18.8 | Other specified congenital malformations of face and neck | | Ear, Face & Neck |
| Q18.9 | Congenital malformation of face and neck, unspecified | | Ear, Face & Neck |
| Q10.1 | Congenital ectropion | Yes | Eye |
| Q10.2 | Congenital entropion | Yes | Eye |
| Q10.3 | Other congenital malformations of eyelid | Yes | Eye |
| Q10.5 | Congenital stenosis and stricture of lacrimal duct | Yes | Eye |
| Q10 | Congen malformations of eyelid lacrimal apparatus & orbit | | Eye |
| Q10.0 | Congenital ptosis | | Eye |
| Q10.4 | Absence and agenesis of lacrimal apparatus | | Eye |
| Q10.6 | Other congenital malformations of lacrimal apparatus | | Eye |
| Q10.7 | Congenital malformation of orbit | | Eye |
| Q11 | Anophthalmos, microphthalmos and macrophthalmos | | Eye |
| Q11.0 | Cystic eyeball | | Eye |
| Q11.1 | Other anophthalmos | | Eye |
| Q11.2 | Microphthalmos | | Eye |
| Q11.3 | Macrophthalmos | | Eye |
| Q12 | Congenital lens malformations | | Eye |
| Q12.0 | Congenital cataract | | Eye |
| Q12.1 | Congenital displaced lens | | Eye |
| Q12.2 | Coloboma of lens | | Eye |
| Q12.3 | Congenital aphakia | | Eye |
| Q12.8 | Other congenital lens malformations | | Eye |
| Q12.9 | Congenital lens malformation, unspecified | | Eye |
| Q13 | Congenital malformations of anterior segment of eye | | Eye |
| Q13.0 | Coloboma of iris | | Eye |
| Q13.2 | Other congenital malformations of iris | | Eye |
| Q13.3 | Congenital corneal opacity | | Eye |
| Q13.4 | Other congenital corneal malformations | | Eye |
| Q13.8 | Other congenital malformations of anterior segment of eye | | Eye |
| Q13.9 | Congenital malformation of anterior segment of eye unspec | | Eye |
| Q14 | Congenital malformations of posterior segment of eye | | Eye |
| Q14.0 | Congenital malformation of vitreous humour | | Eye |
| Q14.1 | Congenital malformation of retina | | Eye |
| Q14.2 | Congenital malformation of optic disc | | Eye |
| Q14.3 | Congenital malformation of choroid | | Eye |
| Q14.8 | Other congenital malformations of posterior segment of eye | | Eye |
| Q14.9 | Congenital malformation of posterior segment of eye unspec | | Eye |
| Q15 | Other congenital malformations of eye | | Eye |
| Q15.0 | Congenital glaucoma | | Eye |
| Q15.8 | Other specified congenital malformations of eye | | Eye |
| Q15.9 | Congenital malformation of eye, unspecified | | Eye |
| Q50.1 | Developmental ovarian cyst | Yes | Genital |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q52.3 | Imperforate hymen | Yes | Genital |
| Q52.5 | Fusion of labia | Yes | Genital |
| Q50 | Cong malforms ovaries fallopian tubes and broad ligaments | | Genital |
| Q50.0 | Congenital absence of ovary | | Genital |
| Q50.2 | Congenital torsion of ovary | | Genital |
| Q50.3 | Other congenital malformations of ovary | | Genital |
| Q50.4 | Embryonic cyst of fallopian tube | | Genital |
| Q50.5 | Embryonic cyst of broad ligament | | Genital |
| Q50.6 | Other cong malformations of fallop tube and broad ligament | | Genital |
| Q51 | Congenital malformations of uterus and cervix | | Genital |
| Q51.0 | Agenesis and aplasia of uterus | | Genital |
| Q51.1 | Doubling of uterus with doubling of cervix and vagina | | Genital |
| Q51.2 | Other doubling of uterus | | Genital |
| Q51.3 | Bicornate uterus | | Genital |
| Q51.4 | Unicornate uterus | | Genital |
| Q51.5 | Agenesis and aplasia of cervix | | Genital |
| Q51.6 | Embryonic cyst of cervix | | Genital |
| Q51.7 | Cong fistulae btwn uterus and digestive and urinary tracts | | Genital |
| Q51.8 | Other congenital malformations of uterus and cervix | | Genital |
| Q51.9 | Congenital malformation of uterus and cervix, unspecified | | Genital |
| Q52 | Other congenital malformations of female genitalia | | Genital |
| Q52.0 | Congenital absence of vagina | | Genital |
| Q52.1 | Doubling of vagina | | Genital |
| Q52.2 | Congenital rectovaginal fistula | | Genital |
| Q52.4 | Other congenital malformations of vagina | | Genital |
| Q52.6 | Congenital malformation of clitoris | | Genital |
| Q52.7 | Other congenital malformations of vulva | | Genital |
| Q52.8 | Other specified congenital malformations of female genitalia | | Genital |
| Q52.9 | Congenital malformation of female genitalia, unspecified | | Genital |
| Q54 | Hypospadias | | Genital |
| Q54.0 | Hypospadias, balanic | | Genital |
| Q54.1 | Hypospadias, penile | | Genital |
| Q54.2 | Hypospadias, penoscrotal | | Genital |
| Q54.3 | Hypospadias, perineal | | Genital |
| Q54.4 | Congenital chordee | | Genital |
| Q54.8 | Other hypospadias | | Genital |
| Q54.9 | Hypospadias, unspecified | | Genital |
| Q55 | Other congenital malformations of male genital organs | | Genital |
| Q55.0 | Absence and aplasia of testis | | Genital |
| Q55.1 | Hypoplasia of testis and scrotum | | Genital |
| Q55.2 | Other congenital malformations of testis and scrotum | | Genital |
| Q55.3 | Atresia of vas deferens | | Genital |
| Q55.4 | Oth cong malform vas def epidid sem vesicle and prostate | | Genital |
| Q55.5 | Congenital absence and aplasia of penis | | Genital |
| Q55.6 | Other congenital malformations of penis | | Genital |
| Q55.8 | Other specified congen malformations of male genital organs | | Genital |
| Q55.9 | Congenital malformation of male genital organ, unspecified | | Genital |
| Q56 | Indeterminate sex and pseudohermaphroditism | | Genital |
| Q56.0 | Hermaphroditism, not elsewhere classified | | Genital |
| Q56.1 | Male pseudohermaphroditism, not elsewhere classified | | Genital |
| Q56.2 | Female pseudohermaphroditism, not elsewhere classified | | Genital |
| Q56.3 | Pseudohermaphroditism, unspecified | | Genital |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q56.4 | Indeterminate sex, unspecified | | Genital |
| Q65.3 | Congenital subluxation of hip, unilateral | Yes | Limb |
| Q65.4 | Congenital subluxation of hip, bilateral | Yes | Limb |
| Q65.5 | Congenital subluxation of hip, unspecified | Yes | Limb |
| Q65.6 | Unstable hip | Yes | Limb |
| Q66.2 | Metatarsus varus | Yes | Limb |
| Q66.4 | Talipes calcaneovalgus | Yes | Limb |
| Q66.5 | Congenital pes planus | Yes | Limb |
| Q66.6 | Other congenital valgus deformities of feet | Yes | Limb |
| Q66.7 | Pes cavus | Yes | Limb |
| Q67.0 | Facial asymmetry | Yes | Limb |
| Q67.1 | Compression facies | Yes | Limb |
| Q67.2 | Dolichocephaly | Yes | Limb |
| Q67.3 | Plagiocephaly | Yes | Limb |
| Q67.6 | Pectus excavatum | Yes | Limb |
| Q67.7 | Pectus carinatum | Yes | Limb |
| Q67.8 | Other congenital deformities of chest | Yes | Limb |
| Q68.0 | Congenital deformity of sternocleidomastoid muscle | Yes | Limb |
| Q68.3 | Congenital bowing of femur | Yes | Limb |
| Q68.4 | Congenital bowing of tibia and fibula | Yes | Limb |
| Q68.5 | Congenital bowing of long bones of leg, unspecified | Yes | Limb |
| Q65 | Congenital deformities of hip | | Limb |
| Q65.0 | Congenital dislocation of hip, unilateral | | Limb |
| Q65.1 | Congenital dislocation of hip, bilateral | | Limb |
| Q65.2 | Congenital dislocation of hip, unspecified | | Limb |
| Q65.8 | Other congenital deformities of hip | | Limb |
| Q65.9 | Congenital deformity of hip, unspecified | | Limb |
| Q66 | Congenital deformities of feet | | Limb |
| Q66.0 | Talipes equinovarus | | Limb |
| Q66.1 | Talipes calcaneovarus | | Limb |
| Q66.3 | Other congenital varus deformities of feet | | Limb |
| Q66.8 | Other congenital deformities of feet | | Limb |
| Q66.9 | Congenital deformity of feet, unspecified | | Limb |
| Q67 | Cong musculoskel deformities of head face spine and chest | | Limb |
| Q67.4 | Other congenital deformities of skull, face and jaw | | Limb |
| Q67.5 | Congenital deformity of spine | | Limb |
| Q68 | Other congenital musculoskeletal deformities | | Limb |
| Q68.1 | Congenital deformity of hand | | Limb |
| Q68.2 | Congenital deformity of knee | | Limb |
| Q68.8 | Other specified congenital musculoskeletal deformities | | Limb |
| Q69 | Polydactyly | | Limb |
| Q69.0 | Accessory finger(s) | | Limb |
| Q69.1 | Accessory thumb(s) | | Limb |
| Q69.2 | Accessory toe(s) | | Limb |
| Q69.9 | Polydactyly, unspecified | | Limb |
| Q70 | Syndactyly | | Limb |
| Q70.0 | Fused fingers | | Limb |
| Q70.1 | Webbed fingers | | Limb |
| Q70.2 | Fused toes | | Limb |
| Q70.3 | Webbed toes | | Limb |
| Q70.4 | Polysyndactyly | | Limb |
| Q70.9 | Syndactyly, unspecified | | Limb |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q71 | Reduction defects of upper limb | | Limb |
| Q71.0 | Congenital complete absence of upper limb(s) | | Limb |
| Q71.1 | Cong absence of upper arm and forearm with hand present | | Limb |
| Q71.2 | Congenital absence of both forearm and hand | | Limb |
| Q71.3 | Congenital absence of hand and finger(s) | | Limb |
| Q71.4 | Longitudinal reduction defect of radius | | Limb |
| Q71.5 | Longitudinal reduction defect of ulna | | Limb |
| Q71.8 | Other reduction defects of upper limb(s) | | Limb |
| Q71.9 | Reduction defect of upper limb, unspecified | | Limb |
| Q72 | Reduction defects of lower limb | | Limb |
| Q72.0 | Congenital complete absence of lower limb(s) | | Limb |
| Q72.1 | Congenital absence of thigh and lower leg with foot present | | Limb |
| Q72.2 | Congenital absence of both lower leg and foot | | Limb |
| Q72.3 | Congenital absence of foot and toe(s) | | Limb |
| Q72.4 | Longitudinal reduction defect of femur | | Limb |
| Q72.5 | Longitudinal reduction defect of tibia | | Limb |
| Q72.6 | Longitudinal reduction defect of fibula | | Limb |
| Q72.8 | Other reduction defects of lower limb(s) | | Limb |
| Q72.9 | Reduction defect of lower limb, unspecified | | Limb |
| Q73 | Reduction defects of unspecified limb | | Limb |
| Q73.0 | Congenital absence of unspecified limb(s) | | Limb |
| Q73.1 | Phocomelia, unspecified limb(s) | | Limb |
| Q73.8 | Other reduction defects of unspecified limb(s) | | Limb |
| Q74 | Other congenital malformations of limb(s) | | Limb |
| Q74.0 | Oth cong malformation of upper limb(s) inc shoulder girdle | | Limb |
| Q74.1 | Congenital malformation of knee | | Limb |
| Q74.2 | Other cong malformation of lower limb(s) incl pelvic girdle | | Limb |
| Q74.3 | Arthrogryposis multiplex congenita | | Limb |
| Q74.8 | Other specified congenital malformations of limb(s) | | Limb |
| Q74.9 | Unspecified congenital malformation of limb(s) | | Limb |
| Q04.6 | Congenital cerebral cysts | | Nervous System |
| Q00 | Anencephaly and similar malformations | | Nervous System |
| Q00.0 | Anencephaly | | Nervous System |
| Q00.1 | Craniorachischisis | | Nervous System |
| Q00.2 | Iniencephaly | | Nervous System |
| Q01 | Encephalocele | | Nervous System |
| Q01.0 | Frontal encephalocele | | Nervous System |
| Q01.1 | Nasofrontal encephalocele | | Nervous System |
| Q01.2 | Occipital encephalocele | | Nervous System |
| Q01.8 | Encephalocele of other sites | | Nervous System |
| Q01.9 | Encephalocele, unspecified | | Nervous System |
| Q02 | Microcephaly | | Nervous System |
| Q03 | Congenital hydrocephalus | | Nervous System |
| Q03.0 | Malformations of aqueduct of Sylvius | | Nervous System |
| Q03.1 | Atresia of foramina of Magendie and Luschka | | Nervous System |
| Q03.8 | Other congenital hydrocephalus | | Nervous System |
| Q03.9 | Congenital hydrocephalus, unspecified | | Nervous System |
| Q04 | Other congenital malformations of brain | | Nervous System |
| Q04.0 | Congenital malformations of corpus callosum | | Nervous System |
| Q04.1 | Arhinencephaly | | Nervous System |
| Q04.2 | Holoprosencephaly | | Nervous System |
| Q04.3 | Other reduction deformities of brain | | Nervous System |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q04.4 | Septo-optic dysplasia | | Nervous System |
| Q04.5 | Megalencephaly | | Nervous System |
| Q04.8 | Other specified congenital malformations of brain | | Nervous System |
| Q04.9 | Congenital malformation of brain, unspecified | | Nervous System |
| Q05 | Spina bifida | | Nervous System |
| Q05.0 | Cervical spina bifida with hydrocephalus | | Nervous System |
| Q05.1 | Thoracic spina bifida with hydrocephalus | | Nervous System |
| Q05.2 | Lumbar spina bifida with hydrocephalus | | Nervous System |
| Q05.3 | Sacral spina bifida with hydrocephalus | | Nervous System |
| Q05.4 | Unspecified spina bifida with hydrocephalus | | Nervous System |
| Q05.5 | Cervical spina bifida without hydrocephalus | | Nervous System |
| Q05.6 | Thoracic spina bifida without hydrocephalus | | Nervous System |
| Q05.7 | Lumbar spina bifida without hydrocephalus | | Nervous System |
| Q05.8 | Sacral spina bifida without hydrocephalus | | Nervous System |
| Q05.9 | Spina bifida, unspecified | | Nervous System |
| Q06 | Other congenital malformations of spinal cord | | Nervous System |
| Q06.0 | Amyelia | | Nervous System |
| Q06.1 | Hypoplasia and dysplasia of spinal cord | | Nervous System |
| Q06.2 | Diastematomyelia | | Nervous System |
| Q06.3 | Other congenital cauda equina malformations | | Nervous System |
| Q06.4 | Hydromyelia | | Nervous System |
| Q06.8 | Other specified congenital malformations of spinal cord | | Nervous System |
| Q06.9 | Congenital malformation of spinal cord, unspecified | | Nervous System |
| Q07 | Other congenital malformations of nervous system | | Nervous System |
| Q07.0 | Arnold-Chiari syndrome | | Nervous System |
| Q07.8 | Other specified congenital malformations of nervous system | | Nervous System |
| Q07.9 | Congenital malformation of nervous system, unspecified | | Nervous System |
| Q35 | Cleft palate | | Orofacial Clefts |
| Q35.1 | Cleft hard palate | | Orofacial Clefts |
| Q35.3 | Cleft soft palate | | Orofacial Clefts |
| Q35.5 | Cleft hard palate with cleft soft palate | | Orofacial Clefts |
| Q35.6 | Cleft palate, medial | | Orofacial Clefts |
| Q35.7 | Cleft uvula | | Orofacial Clefts |
| Q35.9 | Cleft palate, unspecified | | Orofacial Clefts |
| Q36 | Cleft lip | | Orofacial Clefts |
| Q36.0 | Cleft lip, bilateral | | Orofacial Clefts |
| Q36.1 | Cleft lip, medial | | Orofacial Clefts |
| Q36.9 | Cleft lip, unilateral | | Orofacial Clefts |
| Q37 | Cleft palate with cleft lip | | Orofacial Clefts |
| Q37.0 | Cleft hard palate with bilateral cleft lip | | Orofacial Clefts |
| Q37.1 | Cleft hard palate with unilateral cleft lip | | Orofacial Clefts |
| Q37.2 | Cleft soft palate with bilateral cleft lip | | Orofacial Clefts |
| Q37.3 | Cleft soft palate with unilateral cleft lip | | Orofacial Clefts |
| Q37.4 | Cleft hard and soft palate with bilateral cleft lip | | Orofacial Clefts |
| Q37.5 | Cleft hard and soft palate with unilateral cleft lip | | Orofacial Clefts |
| Q37.8 | Unspecified cleft palate with bilateral cleft lip | | Orofacial Clefts |
| Q37.9 | Unspecified cleft palate with unilateral cleft lip | | Orofacial Clefts |
| Q27.0 | Congenital absence and hypoplasia of umbilical artery | Yes | Other |
| Q31.4 | Congenital laryngeal stridor | Yes | Other |
| Q75.2 | Hypertelorism | Yes | Other |
| Q75.3 | Macrocephaly | Yes | Other |
| Q76.5 | Cervical rib | Yes | Other |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q53 | Undescended testicle | Yes | Other |
| Q53.0 | Ectopic testis | Yes | Other |
| Q53.1 | Undescended testicle, unilateral | Yes | Other |
| Q53.2 | Undescended testicle, bilateral | Yes | Other |
| Q53.9 | Undescended testicle, unspecified | Yes | Other |
| Q27 | Other congenital malformations of peripheral vascular system | | Other |
| Q27.1 | Congenital renal artery stenosis | | Other |
| Q27.2 | Other congenital malformations of renal artery | | Other |
| Q27.3 | Peripheral arteriovenous malformation | | Other |
| Q27.4 | Congenital phlebectasia | | Other |
| Q27.8 | Other spec cong malformations of peripheral vasc system | | Other |
| Q27.9 | Cong malformation of peripheral vascular system unspecified | | Other |
| Q28 | Other congenital malformations of circulatory system | | Other |
| Q28.0 | Arteriovenous malformation of precerebral vessels | | Other |
| Q28.1 | Other malformations of precerebral vessels | | Other |
| Q28.2 | Arteriovenous malformation of cerebral vessels | | Other |
| Q28.3 | Other malformations of cerebral vessels | | Other |
| Q28.8 | Other spec congenital malformations of circulatory system | | Other |
| Q28.9 | Congenital malformation of circulatory system, unspecified | | Other |
| Q31 | Congenital malformations of larynx | | Other |
| Q31.0 | Web of larynx | | Other |
| Q31.1 | Congenital subglottic stenosis | | Other |
| Q31.2 | Laryngeal hypoplasia | | Other |
| Q31.3 | Laryngocele | | Other |
| Q31.8 | Other congenital malformations of larynx | | Other |
| Q31.9 | Congenital malformation of larynx, unspecified | | Other |
| Q75 | Other congenital malformations of skull and face bones | | Other |
| Q75.0 | Craniosynostosis | | Other |
| Q75.8 | Other spec congenital malformations of skull and face bones | | Other |
| Q75.9 | Congenital malformation of skull and face bones, unspecified | | Other |
| Q76 | Congenital malformations of spine and bony thorax | | Other |
| Q76.0 | Spina bifida occulta | | Other |
| Q76.2 | Congenital spondylolisthesis | | Other |
| Q76.3 | Congenital scoliosis due to congenital bony malformation | | Other |
| Q76.4 | Oth cong malformation of spine not associated with scoliosis | | Other |
| Q76.6 | Other congenital malformations of ribs | | Other |
| Q76.7 | Congenital malformation of sternum | | Other |
| Q76.8 | Other congenital malformations of bony thorax | | Other |
| Q76.9 | Congenital malformation of bony thorax, unspecified | | Other |
| Q77 | Osteochondrodysplasia with defect growth tub bones spine | | Other |
| Q77.8 | Oth osteochondrodysplas with defect growth tub bone spine | | Other |
| Q77.9 | Osteochondrodyspl with defct growth tub bone spine unspec | | Other |
| Q78 | Other osteochondrodysplasias | | Other |
| Q78.1 | Polyostotic fibrous dysplasia | | Other |
| Q78.4 | Enchondromatosis | | Other |
| Q78.8 | Other specified osteochondrodysplasias | | Other |
| Q78.9 | Osteochondrodysplasia, unspecified | | Other |
| Q79 | Congenital malformations of the musculoskel system NEC | | Other |
| Q79.1 | Other congenital malformations of diaphragm | | Other |
| Q79.8 | Other congenital malformations of musculoskeletal system | | Other |
| Q79.9 | Congenital malformation of musculoskeletal system unspecf | | Other |
| Q30 | Congenital malformations of nose | | Other |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q30.1 | Agenesis and underdevelopment of nose | | Other |
| Q30.2 | Fissured, notched and cleft nose | | Other |
| Q30.3 | Congenital perforated nasal septum | | Other |
| Q30.8 | Other congenital malformations of nose | | Other |
| Q30.9 | Congenital malformation of nose, unspecified | | Other |
| Q82 | Other congenital malformations of skin | | Other |
| Q82.2 | Mastocytosis | | Other |
| Q82.5 | Congenital non-neopastic naevus | | Other |
| Q82.8 | Other specified congenital malformations of skin | | Other |
| Q82.9 | Congenital malformation of skin, unspecified | | Other |
| Q83 | Congenital malformations of breast | | Other |
| Q83.0 | Congenital absence of breast with absent nipple | | Other |
| Q83.1 | Accessory breast | | Other |
| Q83.2 | Absent nipple | | Other |
| Q83.3 | Accessory nipple | | Other |
| Q83.8 | Other congenital malformations of breast | | Other |
| Q83.9 | Congenital malformation of breast, unspecified | | Other |
| Q84 | Other congenital malformations of integument | | Other |
| Q84.0 | Congenital alopecia | | Other |
| Q84.1 | Congenital morphological disturbances of hair NEC | | Other |
| Q84.2 | Other congenital malformations of hair | | Other |
| Q84.3 | Anonychia | | Other |
| Q84.4 | Congenital leukonychia | | Other |
| Q84.5 | Enlarged and hypertrophic nails | | Other |
| Q84.6 | Other congenital malformations of nails | | Other |
| Q84.8 | Other specified congenital malformations of integument | | Other |
| Q84.9 | Congenital malformation of integument, unspecified | | Other |
| Q89 | Other congenital malformations, not elsewhere classified | | Other |
| Q89.0 | Congenital malformations of spleen | | Other |
| Q89.1 | Congenital malformations of adrenal gland | | Other |
| Q89.2 | Congenital malformations of other endocrine glands | | Other |
| Q89.3 | Situs inversus | | Other |
| Q89.4 | Conjoined twins | | Other |
| Q89.7 | Multiple congenital malformations, not elsewhere classified | | Other |
| Q89.8 | Other specified congenital malformations | | Other |
| Q89.9 | Congenital malformation, unspecified | | Other |
| Q32.0 | Congenital tracheomalacia | Yes | Respiratory |
| Q33.1 | Accessory lobe of lung | Yes | Respiratory |
| Q30.0 | Choanal atresia | | Respiratory |
| Q32 | Congenital malformations of trachea and bronchus | | Respiratory |
| Q32.1 | Other congenital malformations of trachea | | Respiratory |
| Q32.2 | Congenital bronchomalacia | | Respiratory |
| Q32.3 | Congenital stenosis of bronchus | | Respiratory |
| Q32.4 | Other congenital malformations of bronchus | | Respiratory |
| Q33 | Congenital malformations of lung | | Respiratory |
| Q33.0 | Congenital cystic lung | | Respiratory |
| Q33.2 | Sequestration of lung | | Respiratory |
| Q33.3 | Agenesis of lung | | Respiratory |
| Q33.4 | Congenital bronchiectasis | | Respiratory |
| Q33.5 | Ectopic tissue in lung | | Respiratory |
| Q33.6 | Hypoplasia and dysplasia of lung | | Respiratory |
| Q33.8 | Other congenital malformations of lung | | Respiratory |

| ICD-10 Code | Description | Minor malformation? | Subgroup |
|---|---|---|---|
| Q33.9 | Congenital malformation of lung, unspecified | | Respiratory |
| Q34 | Other congenital malformations of respiratory system | | Respiratory |
| Q34.0 | Anomaly of pleura | | Respiratory |
| Q34.1 | Congenital cyst of mediastinum | | Respiratory |
| Q34.8 | Other spec congenital malformations of respiratory system | | Respiratory |
| Q34.9 | Congenital malformation of respiratory system, unspecified | | Respiratory |
| Q61.0 | Congenital single renal cyst | Yes | Urinary |
| Q62.7 | Congenital vesico-uretero-renal reflux | Yes | Urinary |
| Q63.3 | Hyperplastic and giant kidney | Yes | Urinary |
| Q60 | Renal agenesis and other reduction defects of kidney | | Urinary |
| Q60.0 | Renal agenesis, unilateral | | Urinary |
| Q60.1 | Renal agenesis, bilateral | | Urinary |
| Q60.2 | Renal agenesis, unspecified | | Urinary |
| Q60.3 | Renal hypoplasia, unilateral | | Urinary |
| Q60.4 | Renal hypoplasia, bilateral | | Urinary |
| Q60.5 | Renal hypoplasia, unspecified | | Urinary |
| Q60.6 | Potter's syndrome | | Urinary |
| Q61 | Cystic kidney disease | | Urinary |
| Q61.4 | Renal dysplasia | | Urinary |
| Q61.8 | Other cystic kidney diseases | | Urinary |
| Q61.9 | Cystic kidney disease, unspecified | | Urinary |
| Q62 | Cong obstructive defect renal pelvis and cong malform ureter | | Urinary |
| Q62.0 | Congenital hydronephrosis | | Urinary |
| Q62.1 | Atresia and stenosis of ureter | | Urinary |
| Q62.2 | Congenital megaloureter | | Urinary |
| Q62.3 | Other obstructive defects of renal pelvis and ureter | | Urinary |
| Q62.4 | Agenesis of ureter | | Urinary |
| Q62.5 | Duplication of ureter | | Urinary |
| Q62.6 | Malposition of ureter | | Urinary |
| Q62.8 | Other congenital malformations of ureter | | Urinary |
| Q63 | Other congenital malformations of kidney | | Urinary |
| Q63.0 | Accessory kidney | | Urinary |
| Q63.1 | Lobulated, fused and horseshoe kidney | | Urinary |
| Q63.2 | Ectopic kidney | | Urinary |
| Q63.8 | Other specified congenital malformations of kidney | | Urinary |
| Q63.9 | Congenital malformation of kidney, unspecified | | Urinary |
| Q64 | Other congenital malformations of urinary system | | Urinary |
| Q64.0 | Epispadias | | Urinary |
| Q64.1 | Exstrophy of urinary bladder | | Urinary |
| Q64.2 | Congenital posterior urethral valves | | Urinary |
| Q64.3 | Other atresia and stenosis of urethra and bladder neck | | Urinary |
| Q64.4 | Malformation of urachus | | Urinary |
| Q64.5 | Congenital absence of bladder and urethra | | Urinary |
| Q64.6 | Congenital diverticulum of bladder | | Urinary |
| Q64.7 | Other congenital malformations of bladder and urethra | | Urinary |
| Q64.8 | Other specified congenital malformations of urinary system | | Urinary |
| Q64.9 | Congenital malformation of urinary system, unspecified | | Urinary |
| Q79.4 | Prune belly syndrome | | Urinary |

## OPCS-4 codes

| OPCS-4 Code | General description | Minor malformation? | Subgroup |
|---|---|---|---|
| T281 | Other repair of anterior abdominal wall | | Abdominal Wall |
| K196 | Creation of other cardiac conduit | | Heart |
| L021 | Open correction of patent ductus arteriosus | | Heart |
| L022 | Open correction of patent ductus arteriosus | | Heart |
| L023 | Open correction of patent ductus arteriosus | | Heart |
| L024 | Open correction of patent ductus arteriosus | | Heart |
| L028 | Open correction of patent ductus arteriosus | | Heart |
| L029 | Open correction of patent ductus arteriosus | | Heart |
| L031 | Transluminal operations on abnormality of great vessel | | Heart |
| K041 | Repair of tetralogy of fallot | | Heart |
| K042 | Repair of tetralogy of fallot | | Heart |
| K043 | Repair of tetralogy of fallot | | Heart |
| K044 | Repair of tetralogy of fallot | | Heart |
| K045 | Repair of tetralogy of fallot | | Heart |
| K046 | Repair of tetralogy of fallot | | Heart |
| K048 | Repair of tetralogy of fallot | | Heart |
| K049 | Repair of tetralogy of fallot | | Heart |
| K051 | Atrial inversion operations/transposition/great arterie | | Heart |
| K052 | Atrial inversion operations/transposition/great arterie | | Heart |
| K058 | Atrial inversion operations/transposition/great arterie | | Heart |
| K059 | Atrial inversion operations/transposition/great arterie | | Heart |
| K061 | Other repair of transposition of great arteries | | Heart |
| K062 | Other repair of transposition of great arteries | | Heart |
| K063 | Other repair of transposition of great arteries | | Heart |
| K064 | Other repair of transposition of great arteries | | Heart |
| K068 | Other repair of transposition of great arteries | | Heart |
| K069 | Other repair of transposition of great arteries | | Heart |
| K071 | Correction/total anomalous pulmonary venous connection | | Heart |
| K072 | Correction/total anomalous pulmonary venous connection | | Heart |
| K073 | Correction/total anomalous pulmonary venous connection | | Heart |
| K078 | Correction/total anomalous pulmonary venous connection | | Heart |
| K079 | Correction/total anomalous pulmonary venous connection | | Heart |
| K081 | Repair of double outlet ventricle | | Heart |
| K082 | Repair of double outlet ventricle | | Heart |
| K083 | Repair of double outlet ventricle | | Heart |
| K084 | Repair of double outlet ventricle | | Heart |
| K088 | Repair of double outlet ventricle | | Heart |
| K089 | Repair of double outlet ventricle | | Heart |
| K091 | Repair of defect of atrioventricular septum | | Heart |
| K092 | Repair of defect of atrioventricular septum | | Heart |
| K093 | Repair of defect of atrioventricular septum | | Heart |
| K094 | Repair of defect of atrioventricular septum | | Heart |
| K095 | Repair of defect of atrioventricular septum | | Heart |
| K096 | Repair of defect of atrioventricular septum | | Heart |
| K098 | Repair of defect of atrioventricular septum | | Heart |
| K099 | Repair of defect of atrioventricular septum | | Heart |
| K101 | Repair of defect of interatrial septum | | Heart |
| K102 | Repair of defect of interatrial septum | | Heart |
| K103 | Repair of defect of interatrial septum | | Heart |
| K104 | Repair of defect of interatrial septum | | Heart |

| OPCS-4 Code | General description | Minor malformation? | Subgroup |
|---|---|---|---|
| K105 | Repair of defect of interatrial septum | | Heart |
| K108 | Repair of defect of interatrial septum | | Heart |
| K109 | Repair of defect of interatrial septum | | Heart |
| K111 | Repair of defect of interventricular septum | | Heart |
| K112 | Repair of defect of interventricular septum | | Heart |
| K113 | Repair of defect of interventricular septum | | Heart |
| K114 | Repair of defect of interventricular septum | | Heart |
| K115 | Repair of defect of interventricular septum | | Heart |
| K116 | Repair of defect of interventricular septum | | Heart |
| K117 | Repair of defect of interventricular septum | | Heart |
| K118 | Repair of defect of interventricular septum | | Heart |
| K119 | Repair of defect of interventricular septum | | Heart |
| K121 | Repair of defect of unspecified septum of heart | | Heart |
| K122 | Repair of defect of unspecified septum of heart | | Heart |
| K123 | Repair of defect of unspecified septum of heart | | Heart |
| K124 | Repair of defect of unspecified septum of heart | | Heart |
| K125 | Repair of defect of unspecified septum of heart | | Heart |
| K128 | Repair of defect of unspecified septum of heart | | Heart |
| K129 | Repair of defect of unspecified septum of heart | | Heart |
| K131 | Transluminal repair of defect of septum | | Heart |
| K132 | Transluminal repair of defect of septum | | Heart |
| K133 | Transluminal repair of defect of septum | | Heart |
| K134 | Transluminal repair of defect of septum | | Heart |
| K135 | Transluminal repair of defect of septum | | Heart |
| K138 | Transluminal repair of defect of septum | | Heart |
| K139 | Transluminal repair of defect of septum | | Heart |
| K141 | Other open operations on septum of heart | | Heart |
| K142 | Other open operations on septum of heart | | Heart |
| K143 | Other open operations on septum of heart | | Heart |
| K144 | Other open operations on septum of heart | | Heart |
| K145 | Other open operations on septum of heart | | Heart |
| K148 | Other open operations on septum of heart | | Heart |
| K149 | Other open operations on septum of heart | | Heart |
| K151 | Closed operations on septum of heart | | Heart |
| K152 | Closed operations on septum of heart | | Heart |
| K158 | Closed operations on septum of heart | | Heart |
| K159 | Closed operations on septum of heart | | Heart |
| K161 | Other therapeutic transluminal operations on septum of | | Heart |
| K162 | Other therapeutic transluminal operations on septum of | | Heart |
| K163 | Other therapeutic transluminal operations on septum of | | Heart |
| K164 | Other therapeutic transluminal operations on septum of | | Heart |
| K165 | Other therapeutic transluminal operations on septum of | | Heart |
| K166 | Other therapeutic transluminal operations on septum of | | Heart |
| K168 | Other therapeutic transluminal operations on septum of | | Heart |
| K169 | Other therapeutic transluminal operations on septum of | | Heart |
| K171 | Repair of univentricular heart | | Heart |
| K172 | Repair of univentricular heart | | Heart |
| K173 | Repair of univentricular heart | | Heart |
| K174 | Repair of univentricular heart | | Heart |
| K175 | Repair of univentricular heart | | Heart |
| K176 | Repair of univentricular heart | | Heart |
| K177 | Repair of univentricular heart | | Heart |

| OPCS-4 Code | General description | Minor malformation? | Subgroup |
|---|---|---|---|
| K178 | Repair of univentricular heart | | Heart |
| K179 | Repair of univentricular heart | | Heart |
| K181 | Creation of valved cardiac conduit | | Heart |
| K182 | Creation of valved cardiac conduit | | Heart |
| K183 | Creation of valved cardiac conduit | | Heart |
| K184 | Creation of valved cardiac conduit | | Heart |
| K185 | Creation of valved cardiac conduit | | Heart |
| K186 | Creation of valved cardiac conduit | | Heart |
| K187 | Creation of valved cardiac conduit | | Heart |
| K188 | Creation of valved cardiac conduit | | Heart |
| K189 | Creation of valved cardiac conduit | | Heart |
| K191 | Creation of other cardiac conduit | | Heart |
| K192 | Creation of other cardiac conduit | | Heart |
| K193 | Creation of other cardiac conduit | | Heart |
| K194 | Creation of other cardiac conduit | | Heart |
| K195 | Creation of other cardiac conduit | | Heart |
| K198 | Creation of other cardiac conduit | | Heart |
| K199 | Creation of other cardiac conduit | | Heart |
| K201 | Refashioning of atrium | | Heart |
| K202 | Refashioning of atrium | | Heart |
| K203 | Refashioning of atrium | | Heart |
| K204 | Refashioning of atrium | | Heart |
| K208 | Refashioning of atrium | | Heart |
| K209 | Refashioning of atrium | | Heart |
| K222 | Other operations on wall of atrium | | Heart |
| K241 | Other operations on ventricles of heart | | Heart |
| K242 | Other operations on ventricles of heart | | Heart |
| K245 | Other operations on ventricles of heart | | Heart |
| K246 | Other operations on ventricles of heart | | Heart |
| K247 | Other operations on ventricles of heart | | Heart |
| K251 | Plastic repair of mitral valve | | Heart |
| K252 | Plastic repair of mitral valve | | Heart |
| K253 | Plastic repair of mitral valve | | Heart |
| K254 | Plastic repair of mitral valve | | Heart |
| K255 | Plastic repair of mitral valve | | Heart |
| K258 | Plastic repair of mitral valve | | Heart |
| K259 | Plastic repair of mitral valve | | Heart |
| K261 | Plastic repair of aortic valve | | Heart |
| K262 | Plastic repair of aortic valve | | Heart |
| K263 | Plastic repair of aortic valve | | Heart |
| K264 | Plastic repair of aortic valve | | Heart |
| K265 | Plastic repair of aortic valve | | Heart |
| K268 | Plastic repair of aortic valve | | Heart |
| K269 | Plastic repair of aortic valve | | Heart |
| K271 | Plastic repair of tricuspid valve | | Heart |
| K272 | Plastic repair of tricuspid valve | | Heart |
| K273 | Plastic repair of tricuspid valve | | Heart |
| K274 | Plastic repair of tricuspid valve | | Heart |
| K275 | Plastic repair of tricuspid valve | | Heart |
| K276 | Plastic repair of tricuspid valve | | Heart |
| K278 | Plastic repair of tricuspid valve | | Heart |
| K279 | Plastic repair of tricuspid valve | | Heart |

| OPCS-4 Code | General description | Minor malformation? | Subgroup |
|---|---|---|---|
| K281 | Plastic repair of pulmonary valve | | Heart |
| K282 | Plastic repair of pulmonary valve | | Heart |
| K283 | Plastic repair of pulmonary valve | | Heart |
| K284 | Plastic repair of pulmonary valve | | Heart |
| K285 | Plastic repair of pulmonary valve | | Heart |
| K288 | Plastic repair of pulmonary valve | | Heart |
| K289 | Plastic repair of pulmonary valve | | Heart |
| K291 | Plastic repair of unspecified valve of heart | | Heart |
| K292 | Plastic repair of unspecified valve of heart | | Heart |
| K293 | Plastic repair of unspecified valve of heart | | Heart |
| K294 | Plastic repair of unspecified valve of heart | | Heart |
| K295 | Plastic repair of unspecified valve of heart | | Heart |
| K296 | Plastic repair of unspecified valve of heart | | Heart |
| K297 | Plastic repair of unspecified valve of heart | | Heart |
| K298 | Plastic repair of unspecified valve of heart | | Heart |
| K299 | Plastic repair of unspecified valve of heart | | Heart |
| K301 | Revision of plastic repair of valve of heart | | Heart |
| K302 | Revision of plastic repair of valve of heart | | Heart |
| K303 | Revision of plastic repair of valve of heart | | Heart |
| K304 | Revision of plastic repair of valve of heart | | Heart |
| K305 | Revision of plastic repair of valve of heart | | Heart |
| K308 | Revision of plastic repair of valve of heart | | Heart |
| K309 | Revision of plastic repair of valve of heart | | Heart |
| K311 | Open incision of valve of heart | | Heart |
| K312 | Open incision of valve of heart | | Heart |
| K313 | Open incision of valve of heart | | Heart |
| K314 | Open incision of valve of heart | | Heart |
| K315 | Open incision of valve of heart | | Heart |
| K318 | Open incision of valve of heart | | Heart |
| K319 | Open incision of valve of heart | | Heart |
| K321 | Closed incision of valve of heart | | Heart |
| K322 | Closed incision of valve of heart | | Heart |
| K323 | Closed incision of valve of heart | | Heart |
| K324 | Closed incision of valve of heart | | Heart |
| K328 | Closed incision of valve of heart | | Heart |
| K329 | Closed incision of valve of heart | | Heart |
| K331 | Operations on aortic root | | Heart |
| K332 | Operations on aortic root | | Heart |
| K333 | Operations on aortic root | | Heart |
| K334 | Operations on aortic root | | Heart |
| K335 | Operations on aortic root | | Heart |
| K336 | Operations on aortic root | | Heart |
| K338 | Operations on aortic root | | Heart |
| K339 | Operations on aortic root | | Heart |
| K341 | Other open operations on valve of heart | | Heart |
| K342 | Other open operations on valve of heart | | Heart |
| K343 | Other open operations on valve of heart | | Heart |
| K344 | Other open operations on valve of heart | | Heart |
| K345 | Other open operations on valve of heart | | Heart |
| K346 | Other open operations on valve of heart | | Heart |
| K348 | Other open operations on valve of heart | | Heart |
| K349 | Other open operations on valve of heart | | Heart |

| OPCS-4 Code | General description | Minor malformation? | Subgroup |
|---|---|---|---|
| K351 | Therapeutic transluminal operations on valve of heart | | Heart |
| K352 | Therapeutic transluminal operations on valve of heart | | Heart |
| K353 | Therapeutic transluminal operations on valve of heart | | Heart |
| K354 | Therapeutic transluminal operations on valve of heart | | Heart |
| K355 | Therapeutic transluminal operations on valve of heart | | Heart |
| K356 | Therapeutic transluminal operations on valve of heart | | Heart |
| K357 | Therapeutic transluminal operations on valve of heart | | Heart |
| K358 | Therapeutic transluminal operations on valve of heart | | Heart |
| K359 | Therapeutic transluminal operations on valve of heart | | Heart |
| K361 | Excision of valve of heart | | Heart |
| K362 | Excision of valve of heart | | Heart |
| K368 | Excision of valve of heart | | Heart |
| K369 | Excision of valve of heart | | Heart |
| K371 | Removal/obstruction from structure adjacent/valve heart | | Heart |
| K372 | Removal/obstruction from structure adjacent/valve heart | | Heart |
| K373 | Removal/obstruction from structure adjacent/valve heart | | Heart |
| K374 | Removal/obstruction from structure adjacent/valve heart | | Heart |
| K375 | Removal/obstruction from structure adjacent/valve heart | | Heart |
| K376 | Removal/obstruction from structure adjacent/valve heart | | Heart |
| K378 | Removal/obstruction from structure adjacent/valve heart | | Heart |
| K379 | Removal/obstruction from structure adjacent/valve heart | | Heart |
| K381 | Other operations on structure adjacent to valve of hear | | Heart |
| K382 | Other operations on structure adjacent to valve of hear | | Heart |
| K383 | Other operations on structure adjacent to valve of hear | | Heart |
| K384 | Other operations on structure adjacent to valve of hear | | Heart |
| K385 | Other operations on structure adjacent to valve of hear | | Heart |
| K386 | Other operations on structure adjacent to valve of hear | | Heart |
| K388 | Other operations on structure adjacent to valve of hear | | Heart |
| K389 | Other operations on structure adjacent to valve of hear | | Heart |
| L011 | Open operations for combined abnormality of great vesse | | Heart |
| L012 | Open operations for combined abnormality of great vesse | | Heart |
| L013 | Open operations for combined abnormality of great vesse | | Heart |
| L014 | Open operations for combined abnormality of great vesse | | Heart |
| L018 | Open operations for combined abnormality of great vesse | | Heart |
| L019 | Open operations for combined abnormality of great vesse | | Heart |
| L032 | Transluminal operations on abnormality of great vessel | | Heart |
| L038 | Transluminal operations on abnormality of great vessel | | Heart |
| L039 | Transluminal operations on abnormality of great vessel | | Heart |
| G401 | Incision of pylorus | Yes | Digestive |
| G701 | Open extirpation of lesion of ileum | Yes | Digestive |
| G073 | Repair of oesophagus | | Digestive |
| G231 | Repair of diaphragmatic hernia | | Digestive |
| G232 | Repair of diaphragmatic hernia | | Digestive |
| G233 | Repair of diaphragmatic hernia | | Digestive |
| G234 | Repair of diaphragmatic hernia | | Digestive |
| G238 | Repair of diaphragmatic hernia | | Digestive |
| G239 | Repair of diaphragmatic hernia | | Digestive |
| G402 | Incision of pylorus | | Digestive |
| T164 | Other repair of diaphragm | | Digestive |
| T803 | Release of contracture of muscle | | Ear, Face & Neck |
| M731 | Repair of urethra | | Genital |
| N285 | Plastic operations on penis | | Genital |

| OPCS-4 Code | General description | Minor malformation? | Subgroup |
|---|---|---|---|
| X272 | Correction of minor congenital deformity of foot | Yes | Limb |
| X273 | Correction of minor congenital deformity of foot | Yes | Limb |
| X274 | Correction of minor congenital deformity of foot | Yes | Limb |
| X275 | Correction of minor congenital deformity of foot | Yes | Limb |
| T021 | Reconstruction of chest wall | | Limb |
| T022 | Reconstruction of chest wall | | Limb |
| X191 | Correction of congenital deformity of shoulder or upper | | Limb |
| X198 | Correction of congenital deformity of shoulder or upper | | Limb |
| X199 | Correction of congenital deformity of shoulder or upper | | Limb |
| X201 | Correction of congenital deformity of forearm | | Limb |
| X202 | Correction of congenital deformity of forearm | | Limb |
| X203 | Correction of congenital deformity of forearm | | Limb |
| X204 | Correction of congenital deformity of forearm | | Limb |
| X205 | Correction of congenital deformity of forearm | | Limb |
| X208 | Correction of congenital deformity of forearm | | Limb |
| X209 | Correction of congenital deformity of forearm | | Limb |
| X211 | Correction of congenital deformity of hand | | Limb |
| X212 | Correction of congenital deformity of hand | | Limb |
| X213 | Correction of congenital deformity of hand | | Limb |
| X214 | Correction of congenital deformity of hand | | Limb |
| X215 | Correction of congenital deformity of hand | | Limb |
| X216 | Correction of congenital deformity of hand | | Limb |
| X217 | Correction of congenital deformity of hand | | Limb |
| X218 | Correction of congenital deformity of hand | | Limb |
| X219 | Correction of congenital deformity of hand | | Limb |
| X221 | Correction of congenital deformity of hip | | Limb |
| X222 | Correction of congenital deformity of hip | | Limb |
| X223 | Correction of congenital deformity of hip | | Limb |
| X224 | Correction of congenital deformity of hip | | Limb |
| X225 | Correction of congenital deformity of hip | | Limb |
| X228 | Correction of congenital deformity of hip | | Limb |
| X229 | Correction of congenital deformity of hip | | Limb |
| X231 | Correction of congenital deformity of leg | | Limb |
| X232 | Correction of congenital deformity of leg | | Limb |
| X233 | Correction of congenital deformity of leg | | Limb |
| X234 | Correction of congenital deformity of leg | | Limb |
| X235 | Correction of congenital deformity of leg | | Limb |
| X236 | Correction of congenital deformity of leg | | Limb |
| X238 | Correction of congenital deformity of leg | | Limb |
| X239 | Correction of congenital deformity of leg | | Limb |
| X241 | Primary correction of congenital deformity of foot | | Limb |
| X242 | Primary correction of congenital deformity of foot | | Limb |
| X243 | Primary correction of congenital deformity of foot | | Limb |
| X244 | Primary correction of congenital deformity of foot | | Limb |
| X248 | Primary correction of congenital deformity of foot | | Limb |
| X249 | Primary correction of congenital deformity of foot | | Limb |
| X251 | Other correction of congenital deformity of foot | | Limb |
| X252 | Other correction of congenital deformity of foot | | Limb |
| X253 | Other correction of congenital deformity of foot | | Limb |
| X254 | Other correction of congenital deformity of foot | | Limb |
| X258 | Other correction of congenital deformity of foot | | Limb |
| X259 | Other correction of congenital deformity of foot | | Limb |

| OPCS-4 Code | General description | Minor malformation? | Subgroup |
|---|---|---|---|
| X271 | Correction of minor congenital deformity of foot | | Limb |
| X278 | Correction of minor congenital deformity of foot | | Limb |
| X279 | Correction of minor congenital deformity of foot | | Limb |
| A391 | Repair of dura | | Nervous System |
| A491 | Repair of spina bifida | | Nervous System |
| A492 | Repair of spina bifida | | Nervous System |
| A493 | Repair of spina bifida | | Nervous System |
| A494 | Repair of spina bifida | | Nervous System |
| A498 | Repair of spina bifida | | Nervous System |
| A499 | Repair of spina bifida | | Nervous System |
| F031 | Correction of deformity of lip | | Orofacial Clefts |
| F032 | Correction of deformity of lip | | Orofacial Clefts |
| F291 | Correction of deformity of palate | | Orofacial Clefts |
| F292 | Correction of deformity of palate | | Orofacial Clefts |
| F298 | Correction of deformity of palate | | Orofacial Clefts |
| F299 | Correction of deformity of palate | | Orofacial Clefts |
| T191 | Simple excision of inguinal hernial sac | Yes | Other |
| T192 | Simple excision of inguinal hernial sac | Yes | Other |
| T193 | Simple excision of inguinal hernial sac | Yes | Other |
| T198 | Simple excision of inguinal hernial sac | Yes | Other |
| T199 | Simple excision of inguinal hernial sac | Yes | Other |
| T201 | Primary repair of inguinal hernia | Yes | Other |
| T202 | Primary repair of inguinal hernia | Yes | Other |
| T203 | Primary repair of inguinal hernia | Yes | Other |
| T204 | Primary repair of inguinal hernia | Yes | Other |
| T208 | Primary repair of inguinal hernia | Yes | Other |
| T209 | Primary repair of inguinal hernia | Yes | Other |
| T211 | Repair of recurrent inguinal hernia | Yes | Other |
| T212 | Repair of recurrent inguinal hernia | Yes | Other |
| T213 | Repair of recurrent inguinal hernia | Yes | Other |
| T214 | Repair of recurrent inguinal hernia | Yes | Other |
| T218 | Repair of recurrent inguinal hernia | Yes | Other |
| T219 | Repair of recurrent inguinal hernia | Yes | Other |
| L751 | Other arteriovenous operations | | Other |
| E083 | Other operations on internal nose | | Respiratory |
| M024 | Total excision of kidney | | Urinary |
| M031 | Partial excision of kidney | | Urinary |
| M032 | Partial excision of kidney | | Urinary |
| M184 | Excision of ureter | | Urinary |
| M201 | Replantation of ureter | | Urinary |
| M202 | Replantation of ureter | | Urinary |
| M203 | Replantation of ureter | | Urinary |
| M208 | Replantation of ureter | | Urinary |
| M209 | Replantation of ureter | | Urinary |
| M211 | Other connection of ureter | | Urinary |
| M212 | Other connection of ureter | | Urinary |
| M213 | Other connection of ureter | | Urinary |
| M214 | Other connection of ureter | | Urinary |
| M215 | Other connection of ureter | | Urinary |
| M216 | Other connection of ureter | | Urinary |
| M218 | Other connection of ureter | | Urinary |
| M219 | Other connection of ureter | | Urinary |

| OPCS-4 Code | General description | Minor malformation? | Subgroup |
|---|---|---|---|
| M221 | Repair of ureter | | Urinary |
| M222 | Repair of ureter | | Urinary |
| M223 | Repair of ureter | | Urinary |
| M228 | Repair of ureter | | Urinary |
| M229 | Repair of ureter | | Urinary |
| M231 | Incision of ureter | | Urinary |
| M238 | Incision of ureter | | Urinary |
| M239 | Incision of ureter | | Urinary |
| M251 | Other open operations on ureter | | Urinary |
| M732 | Repair of urethra | | Urinary |

# Appendix 3 – Code lists for antenatal diagnoses of major congenital malformations

## Read codes for use in pregnant women

Specificity Level: 1 = Most specific; 2 = Moderately Specific; 3 = Least specific

| Read Code | Read Term | Specificity Level |
|---|---|---|
| L250100 | Fetus with central nervous system malformation - delivered | 1 |
| 7F1A300 | Drainage of hydrocephalus of fetus to facilitate delivery | 1 |
| L236.00 | Hydrocephalic disproportion | 1 |
| L250.00 | Fetus with central nervous system malformation | 1 |
| 7F03000 | Percutaneous insertion of fetal vesicoamniotic shunt | 1 |
| L250400 | Maternal care for CNS malformation in fetus | 1 |
| L250200 | Fetus with central nervous system malformation + a/n problem | 1 |
| L250000 | Fetus with central nervous system malformation unspecified | 1 |
| L250z00 | Fetus with central nervous system malformation NOS | 1 |
| L236100 | Hydrocephalic disproportion - delivered | 1 |
| L258.00 | Fetus with cardiovascular abnormality | 1 |
| L236z00 | Hydrocephalic disproportion NOS | 1 |
| 7F03400 | Percutaneous insertion of bladder drain to fetus | 1 |
| L236000 | Hydrocephalic disproportion unspecified | 1 |
| L236200 | Hydrocephalic disproportion with antenatal problem | 1 |
| L237.00 | Other fetal abnormality causing disproportion | 1 |
| L237100 | Other fetal abnormality causing disproportion - delivered | 1 |
| L237200 | Other fetal abnormality causing disproportion with a/n prob | 1 |
| 5847 | U-S scan - fetal abnormality | 1 |
| Lyu4500 | [X]Obstructed labour due to other abnormalities of fetus | 1 |
| L25z400 | Maternal care for fetal abnormality and damage | 1 |
| L250.13 | Suspect fetal spina bifida | 2 |
| L250.11 | Suspect fetal anencephaly | 2 |
| L250.12 | Suspect fetal hydrocephaly | 2 |
| L250300 | Maternal care for suspected CNS malformation in fetus | 2 |
| L25..00 | Known or suspected fetal abnormality | 2 |
| 62F9.00 | A/N amnio. for ? neural tube | 2 |
| Lyu3900 | [X]Maternal care/oth spcf known or suspected fetal problems | 2 |
| L51X.00 | Maternal care/known or suspected fetal problem | 2 |
| L51..00 | Maternal care for other known or suspected fetal problems | 2 |
| Lyu3A00 | [X]Maternal care/known or suspected fetal problem | 2 |
| L25z300 | Maternal care for suspect fetal abnormal and damage | 2 |
| 62G8.00 | A/N U/S scan abnormal | 3 |
| L2A..00 | Abnormal findings on antenatal screening of mother | 3 |
| 64B3.00 | Birth exam. abnormal -for obs. | 3 |
| 64D6.00 | 6 week exam.abnormal -referred | 3 |
| 64a6.00 | 8 week exam.abnormal -referred | 3 |

| Read Code | Read Term | Specificity Level |
|---|---|---|
| 64D5.00 | 6 week exam.abnormal -for obs. | 3 |
| 62G9.00 | A/N U/S scan for ? abnormality | 3 |
| L2A3.00 | Abnormal ultrasonic finding on antenatal screening of mother | 3 |
| 5843 | U-S obstetric scan abnormal | 3 |
| 68b3.00 | Antenatal screening shows significant disorder | 3 |
| 64B4.00 | Birth exam. abnormal -referred | 3 |
| 64B5.00 | Birth exam abn. - on treatment | 3 |
| 64a5.00 | 8 week exam.abnormal -for obs. | 3 |

## ICD-10 codes for use in pregnant women

Specificity Level: 1 = Most specific; 2 = Moderately Specific

| ICD-10 code | Description | Specificity Level |
|---|---|---|
| O33.6 | Maternal care for disproportion due to hydrocephalic fetus | 1 |
| O66.3 | Obstructed labour due to other abnormalities of fetus | 1 |
| O35.0 | Maternal care for (suspected) central nervous system malformation in fetus | 2 |
| O35.9 | Maternal care for (suspected) fetal abnormality and damage, unspecified | 2 |

# Appendix 4 – Code lists for malformations with known causes

## Read codes for antenatal diagnoses

| Read Code | Read Term |
|---|---|
| 62F7.00 | A/N amniocentesis - abnormal |
| L251.00 | Fetus with chromosomal abnormality |
| L251100 | Fetus with chromosomal abnormality - delivered |
| L251z00 | Fetus with chromosomal abnormality NOS |
| L251400 | Maternal care for chromosomal abnormality in fetus |
| L251000 | Fetus with chromosomal abnormality unspecified |
| L252000 | Fetus with hereditary disease unspecified |
| L251.11 | Suspect cystic fibrosis fetus |
| L252.00 | Fetus with hereditary disease |
| L252100 | Fetus with hereditary disease - delivered |
| L251.12 | Suspect mongol fetus |
| L252z00 | Fetus with hereditary disease NOS |
| L251300 | Maternal care for suspected chromosomal abnormality in fetus |

## Read codes for postnatal diagnoses

| Read Code | Read Term |
|---|---|
| PH3yA00 | Bloom syndrome |
| PH33600 | Siemen's syndrome |
| PH02.00 | Milroy's disease |
| PH33011 | Acropachyderma |
| PD12100 | Medullary cystic disease, adult type |
| PG4B200 | Fibrochondrogenesis |
| PG55.00 | Chondroectodermal dysplasia |
| PK82.00 | Dysmorphism due to warfarin |
| PJ50600 | Trisomy 12 |
| PG51400 | Osteogenesis imperfecta type II |
| PJ72.00 | Klinefelter's syndrome, male with 46XX karyotype |
| PG58.12 | Camurati-Engelmann disease |
| PJ22.00 | Trisomy 18, translocation |
| PG46100 | Spondyloepiphyseal dysplasia tarda |
| PE00100 | Asymmetrical crying face syndrome |
| PG51600 | Osteogenesis imperfecta type IV |
| PJ63300 | Turner's,karyotype 46X + abnorm. sex chromosome,not iso(Xq) |
| PH1z.12 | Alligator skin |
| PJ53300 | Individual with marker heterochromatin |
| PG51500 | Osteogenesis imperfecta type III |
| PJ53500 | Shwachman-Diamond syndrome |
| P22y200 | Gillespie syndrome |
| PG56.00 | Multiple epiphyseal dysplasia |

| Read Code | Read Term |
|---|---|
| PJ4..00 | Balanced autosomal translocation |
| PH02.11 | Meige's disease |
| PKyP.11 | Wolfram syndrome |
| PG5D.00 | Craniodiaphyseal dysplasia |
| PH33111 | Benign familial chronic pemphigus |
| PKyB.00 | CHARGE association |
| PD12y00 | Medullary cystic disease OS |
| PH3y411 | Darier's disease - keratosis follicularis |
| PJ01.00 | Trisomy 21, mosaicism |
| PJyz.00 | Sex chromosome anomaly NOS |
| PJ1z.00 | Patau's syndrome NOS |
| PF58.00 | Congenital cleft hand |
| PKy5400 | Waardenburg's syndrome |
| PF55.00 | Acrocephalosyndactyly |
| P336111 | Spherical lens |
| PF55000 | Acrocephalosyndactyly (Apert) |
| PJ36.00 | Whole chromosome monosomy, meiotic nondisjunction |
| PJ50w00 | Whole chromosome trisomy, meitotic nondisjunction |
| PKy9111 | Wiedemann - Beckwith syndrome |
| PKyP.00 | Diab insipidus,diab mell,optic atrophy and deafness |
| PD12011 | Nephronophthisis |
| PJ52400 | Polyploidy |
| PJ...00 | Chromosomal anomalies |
| PJ21.00 | Trisomy 18, mosaicism |
| PKy6600 | Dubowitz syndrome |
| PG4B100 | Hypochondrogenesis |
| 62Uz.00 | Downs screening blood test NOS |
| PG51300 | Osteogenesis imperfecta type I |
| PJ38.11 | Chromosome replaced with dicentric |
| PGy4.00 | Fibrodysplasia ossificans congenita |
| PJ63z11 | Bonnevie-Ullrich syndrome NOS |
| PKy6.00 | Congenital malformation syndromes with short stature |
| PD1y000 | Fibrocystic kidney disease |
| PJ50z00 | Whole chromosome trisomy syndrome NOS |
| PH03.00 | Congenital elephantiasis |
| PG4z.00 | Chondrodysplasia NOS |
| PG04.12 | Trigorhinophalangeal dysplasia |
| PKy7311 | Rubinstein-Taybi syndrome |
| PJzz.00 | Conditions due to anomaly of unspecified chromosome NOS |
| PJ74.00 | Klinefelter's syndrome, XY/XXY mosaic |
| PG4C.00 | Chondrodysplasia punctata |
| PJ0..11 | Mongolism |
| PK62.11 | Lindau's disease |
| PH3y611 | Tylosis palmaris et plantaris |
| PJ33212 | 18p- syndrome |

| Read Code | Read Term |
|---|---|
| p226000 | congenital bilateral perisylvian syndrome |
| PH33400 | Focal dermal hypoplasia |
| PA17.11 | Whiteman's syndrome |
| PJ3y011 | Velocardiofacial syndrome |
| PJz3.00 | Duplication of chromosome |
| PG4B.00 | lethal retarded ossification syndromes |
| PJ12.11 | Partial trisomy 13 in Patau's syndrome |
| PJ33000 | Deletion of long arm of chromosome 13 |
| PJ33400 | Jacobsen syndrome |
| PG52100 | Osteopetrosis - congenita type |
| PH10.00 | Congenital ichthyosis, unspecified |
| PG5y.11 | Dyschondrosteosis |
| PFy1.00 | Larsen's syndrome |
| PD11011 | Autosomal recessive polycystic kidney disease |
| PJ3y000 | Shprintzen syndrome |
| PF5r300 | Clinodactyly |
| PG5C.00 | Craniometaphyseal dysplasia |
| PF58.11 | Lobster-claw hand |
| PJ33500 | Greig cephalopolysyndactyly syndrome |
| PJ63600 | Turner's phenotype, other variant karyotypes |
| PJ31.11 | Deletion of short arm of chromosome 5 |
| PG5A.00 | Diaphyseal dysplasia |
| PyuAC00 | [X]Townes-Brocks syndrome |
| PG55.11 | Ellis - Van Creveld syndrome |
| PKy5200 | Cyclops |
| PG56000 | Chondrodysplasia calcificans congenita |
| PJy1100 | Mosaic XO/XX |
| PD11100 | Polycystic kidneys, adult type |
| PKyE.00 | Barber-Say syndrome |
| P345000 | Blue sclera |
| PG0z.11 | Dysmorphic features |
| PJ62.00 | Ovarian dysgenesis |
| PyuAB00 | [X]Pallister-Killian syndrome |
| PJy2.11 | Triple X female |
| P343.11 | Congenital absence of iris |
| PJ7..00 | Klinefelter's syndrome |
| PGy3.11 | Osteo-onychodysostosis |
| PJz3100 | MeCP2 duplication syndrome |
| PJ31.00 | Cri-du-chat syndrome |
| PH32300 | Incontinentia pigmenti |
| PyuA900 | [X]Other specified chromosome abnormalities |
| PJ52.00 | Trisomies of autosomes NEC |
| PJ51z00 | Partial trisomy syndrome NOS |
| PH3y400 | Congenital keratosis follicularis |
| PH1z.11 | Congenital ichthyosiform erythroderma |

| Read Code | Read Term |
|---|---|
| PG45.00 | Metaphyseal dysostosis |
| PG53.11 | Buschke-Ollendorff syndrome |
| PG44211 | Thanatophoric dysplasia |
| PKy7400 | Sirenomelia |
| PG44500 | Kniest dysplasia |
| P342200 | Rieger's anomaly |
| PG4A.00 | Metachondromatosis |
| PG5F.00 | Acrodysostosis |
| PyuA.00 | [X]Chromosomal abnormalities, not elswhere classified |
| PJ33800 | Chromosome 4q deletion syndrome |
| PKy5311 | Freeman Sheldon syndrome |
| C391100 | Di George syndrome |
| F4J7011 | stilling-turck-duane syndrome |
| P11z.13 | Billroth's disease |
| PKy6400 | Seckel syndrome |
| PGy3.12 | Onycho-osteodysplasia |
| PG44000 | Diastrophic dwarfism |
| PKy7.00 | Congenital malformation syndromes involving limbs |
| P313.00 | Lenz microphthalmia syndrome |
| P336000 | Microphakia |
| PG52200 | Osteopetrosis - tarda type |
| P342100 | Peter's anomaly |
| P342300 | Peters-plus syndrome |
| PH41.00 | Congenital monilethrix |
| PH3y200 | Epidermolysis bullosa |
| PG52.00 | Osteopetrosis |
| PH33311 | Atrophic heredofamilial dermatosis |
| PC4yF00 | Rokitansky sequence |
| PD1..14 | Sponge kidney |
| PJ33300 | Smith-Magenis syndrome |
| PD13.11 | Multicystic kidney |
| PGy2100 | Ehlers-Danlos syndrome type II |
| PKy8.00 | Congenital malformation syndromes with other skeletal change |
| PD11z11 | Cystic kidney disease NEC |
| PD12000 | Medullary cystic disease, juvenile type |
| PJ11.00 | Trisomy 13, mosaicism |
| PD12211 | Autosomal dominant medullary cystic disease |
| P22y100 | Familial aplasia of the vermis |
| PD12z00 | Medullary cystic disease NOS |
| PKy5z00 | Congenital malform syndrome affecting facial appearance NOS |
| PD1y100 | Cortical cystic disease |
| PJ51400 | Trisomy 9p syndrome |
| PGy3.00 | Nail-patella syndrome |
| PF55.11 | Apert's syndrome |
| P342000 | Axenfield's anomaly |

| Read Code | Read Term |
|---|---|
| PJ71.00 | Klinefelter's syndrome,male with more than two X chromosomes |
| PF5r800 | Camptodactyly-little finger |
| PG0G.13 | Parietal foramina |
| PKyC.00 | Pena-Shokeir syndrome type I |
| PJ54.00 | Ulnar mammary syndrome |
| PG45.13 | Craniometaphyseal dysostosis |
| PG0E.11 | Hallerman - Streif syndrome |
| P344.00 | Other iris and ciliary body anomalies |
| PG41.00 | Achondroplasia |
| PH33100 | Hailey-Hailey disease |
| PJ50.00 | Whole chromosome trisomy syndromes |
| PG47.00 | Congenital exostosis |
| PG4..00 | Chondrodysplasia |
| PH32311 | Bloch - Sulzberger syndrome |
| 62U8.00 | Downs screening - blood sent |
| P354.00 | Congenital macular changes |
| PKy9.00 | Congenital malformation syndromes with metabolic disturbance |
| PGy2300 | Ehlers-Danlos syndrome type IV |
| PJ12.00 | Trisomy 13, translocation |
| PKy0511 | Multiple hamartoma syndrome |
| PG4B300 | Short-rib/polydactyly syndrome |
| PH2..00 | Dermatoglyphic anomalies |
| PG51.12 | Eddowe's syndrome |
| 1JB0.00 | Suspected Downs syndrome |
| PH33711 | Zinsser-Cole-Engman syndrome |
| PKy5L00 | Cardio-facio-cutaneous syndrome |
| PJ33200 | Deletion of short arm of chromosome 18 |
| PG56z00 | Multiple epiphyseal dysplasia NOS |
| PJ1z.11 | Trisomy 13 NOS |
| PKy8000 | Noonan's syndrome |
| PJX..00 | Sex chromosome abnormality, male phenotype, unspecified |
| PH33312 | Thomson's disease |
| PKy7z00 | Congenital malformation syndrome involving limbs NOS |
| PJ52z00 | Trisomy of autosomes NEC NOS |
| PKy7600 | Aglossia - adactyly syndrome |
| PG41.11 | Dwarfism |
| PKyz.11 | Cockayne's syndrome |
| PJyyz00 | Other sex chromosome abnormality NOS |
| PKyz711 | Angelman syndrome |
| PG43.00 | Asphyxiating thoracic dysplasia |
| PG51.14 | Lobstein's syndrome |
| PJ37z00 | Whole chromosome monosomy, mosaicism NOS |
| PH33511 | Darier's disease - pseudoxanthoma elasticum |
| PGy2.00 | Ehlers-Danlos syndrome |
| Pyu9D00 | [X]Primary ciliary dyskinesia |

| Read Code | Read Term |
|---|---|
| PG41.13 | Achondroplastic dwarf |
| PK63.00 | Gardner's syndrome |
| PKy5600 | Marchesani syndrome |
| PyuA100 | [X]Other deletions of part of a chromosome |
| PKy1.11 | Biedl-Bardet syndrome |
| pg16.00 | klippel-feil syndrome |
| PKy5500 | Gorlin-Chaudhry-Moss syndrome |
| PKy0.12 | Prader-Willi syndrome |
| PKyz000 | Ullrich - Feichtiger syndrome, chimaera |
| PG57.00 | Infantile cortical hyperostosis |
| PG52000 | Osteopetrosis - unclassified |
| PK8..00 | Congenital malformation syndromes due to known exogen causes |
| PG56011 | Chondrodysplasia calcificans congenita |
| PJ00.00 | Trisomy 21, meiotic nondisjunction |
| PKy9600 | VATER association |
| PKy5B00 | Costello syndrome |
| PKyM.00 | Johanson-Blizzard syndrome |
| 44qH.00 | Downs screening test |
| PF67600 | Rocker bottom foot |
| PJ2..00 | Edward's syndrome - trisomy 18 |
| PKy5F00 | Coffin-Lowry syndrome |
| PH01.00 | Hereditary trophoedema |
| PJ70.00 | Klinefelter's phenotype, karyotype 47XXY |
| PKy9200 | Menke's syndrome |
| PKyF.00 | Alstrom syndrome |
| PG52.11 | Albers - Schonberg syndrome |
| PJy1.00 | Sex chromosome mosaicism |
| PKy9400 | Zellweger's syndrome |
| PJ3z.00 | Monosomies and deletions from the autosomes NOS |
| PKyD.00 | Nicolaides-Baraitser syndrome |
| PJ01.11 | Trisomy 21, mitotic nondisjunction |
| PJ52200 | Extra marker chromosomes |
| PJ1..00 | Patau's syndrome - trisomy 13 |
| PG04.11 | Crouzon's disease |
| PKy0000 | Bannayan-Riley-Ruvalcaba syndrome |
| PKy5.00 | Congen malformation syndromes affecting facial appearance |
| PJ51500 | 15q partial trisomy syndrome |
| PKy9100 | Beckwith's syndrome |
| PD11111 | Autosomal dominant polycystic kidney disease |
| PG43.11 | Jeune's syndrome |
| PJ63.00 | Turner's syndrome |
| PJ6..00 | Gonadal dysgenesis |
| PJ37.00 | Whole chromosome monosomy, mosaicism |
| PJ5y.00 | Other specified conditions due to autosomal anomalies |
| PG5y.12 | furst-ostrum syndrome |

| Read Code | Read Term |
|---|---|
| PJ53100 | Balanced autosomal rearrangement in abnormal individual |
| PGy2500 | Ehlers-Danlos syndrome type VI |
| PJ51411 | 9p duplication syndrome |
| PJyy400 | Fragile X syndrome |
| PKy5011 | Papillon-Leage-Psaume syndrome |
| PF5r900 | Camptodactyly-other or multiple |
| PH3y800 | Epidermolysis bullosa letalis |
| PJ0..00 | Down's syndrome - trisomy 21 |
| PKyB.11 | CHARGE syndrome |
| P322112 | Congenital macrocornea |
| PJ33900 | Langer-Giedion syndrome |
| PJ51100 | Minor partial trisomy |
| PJ50400 | Trisomy 10 |
| PJ33A00 | Kleefstra syndrome |
| pfy3.00 | distal arthrogryposis syndrome |
| PJ50200 | Trisomy 8 |
| PJ10.00 | Trisomy 13, meiotic nondisjunction |
| PJ5..00 | Other condition due to autosomal anomaly |
| PJ50311 | Trisomy 9 Mosaic Syndrome |
| PD12200 | Nephronophthisis - medullary cystic disease |
| P2x3.00 | Jaw-winking syndrome |
| PG44400 | Acromesomolic dysplasia |
| P2x5.00 | Riley - Day syndrome |
| PKy9211 | Kinky hair syndrome |
| PKy5J00 | Branchio-oculo-facial syndrome |
| PJ51.00 | Partial trisomy syndromes |
| PJ33113 | 18q deletion syndrome |
| PF55100 | Acrocephalosyndactyly (Pfeiffer) |
| PJ0..12 | Trisomy 21 |
| PG53.00 | Osteopoikilosis |
| PJ3..00 | Monosomies and deletions from the autosomes |
| F4J7000 | duane's syndrome |
| PKy5700 | Otopalatodigital syndrome |
| PJ63500 | Turner's,mosaic, 45X/other cell line with abn.sex chromosome |
| PJ30.11 | Deletion of long arm of chromosome 21 |
| PK35.00 | Kartagener's syndrome |
| PH3y212 | Koebner's disease |
| PG4D.00 | Metaphyseal chondrodysplasia |
| PJy..00 | Other sex chromosome anomaly |
| PKy5M00 | Oculofaciocardiodental syndrome |
| PH11.00 | Harlequin fetus |
| PJ32.00 | Deletion of short arm of chromosome 4 |
| PJyy200 | Fragile X chromosome |
| PJyy000 | Chimera 46XX/46XY |
| PJy3.00 | XXY syndrome |

| Read Code | Read Term |
|---|---|
| PF5rA00 | Clinodactyly with delta phalanx |
| PKy1.00 | Laurence-Moon-Biedl syndrome |
| PH1y000 | Netherton's syndrome |
| PJy2.12 | Karyotype 47, XXX |
| PG45.11 | Jansen's metaphyseal dysostosis |
| PKy5612 | Spherophakia-brachymorphia syndrome |
| PG46000 | Spondyloepiphyseal dysplasia congenita |
| PJy1000 | Mosaic XO/XY |
| PG44200 | Thanatophoric dwarfism |
| PG4F.00 | Lei-Weill dyschondrosteosis |
| PJ9..00 | Mowat-Wilson syndrome |
| PJ71.12 | Klinefelter's syndrome, XXXXY |
| PJ30.00 | Antimongolism syndrome |
| PK5..12 | Epiloia |
| PKyK.00 | Loeys-Dietz syndrome |
| PK83.00 | Fetus and newborn affected by maternal use of alcohol |
| PJ64.00 | Other gonadal dysgenesis phenotype |
| PJ63612 | Turner's phenotype, partial X deletion karyotype |
| PF29.11 | Ectrodactyly of finger |
| PK81.00 | Fetal hydantoin syndrome |
| PG0D.12 | Treacher - Collins syndrome |
| PJ8..00 | Balanced translocation and insertion in normal individual |
| PKy7500 | Arachnodactyly |
| PC03.00 | Streak ovary |
| PJ33100 | Deletion of long arm of chromosome 18 |
| PJy5.00 | Mosaicism, lines with various numbers of X chromosomes |
| 62UA.00 | Downs screen blood test abnormal |
| PKyz500 | Happy puppet syndrome |
| PKy5800 | Usher's syndrome |
| PG51.15 | Van der Hoeve's syndrome |
| PKy7300 | Rubenstein - Tayi syndrome |
| PJyy.00 | Other specified sex chromosome anomaly |
| PKy6z00 | Congenital malformation syndrome with short stature NOS |
| P344311 | Ectopic pupil |
| PJ50100 | Trisomy 7 |
| PJ51200 | 10q partial trisomy syndrome |
| PK5..00 | Tuberous sclerosis |
| PKy5900 | Oculo-palato-digital syndrome |
| PKy5D00 | Kabuki make-up syndrome |
| PJ64000 | XY, female phenotype |
| PH33300 | Rothmund-Thomson syndrome |
| PG40.00 | Chondrodysplasia, unspecified |
| PGy2600 | Ehlers-Danlos syndrome type VII |
| P228300 | Aicardi syndrome |
| PJ50x00 | Whole chromosome trisomy, mosaicism |

| Read Code | Read Term |
|---|---|
| PG4B000 | Achondrogenesis |
| PJ60.00 | Mixed gonadal dysgenesis |
| PJ0z.11 | Trisomy 21 NOS |
| PG51000 | Fragilitas ossium |
| PH2z.00 | Dermatoglyphic anomalies NOS |
| PJ51000 | Major partial trisomy |
| PH32113 | Nettleship's syndrome |
| PG0F.00 | Goldenhar's syndrome |
| PGy2000 | Ehlers-Danlos syndrome type I |
| PH1y.00 | Other specified ichthyosis congenita |
| PJ50300 | Trisomy 9 |
| Pyu9100 | [X]Other epidermolysis bullosa |
| PJ33111 | 18p- syndrome |
| PH0..00 | Hereditary oedema of legs |
| PKy0.13 | Noonan's syndrome |
| PH32200 | Xeroderma pigmentosum |
| PG51.13 | Adair-Dighton syndrome |
| PD11z00 | Polycystic kidney disease NOS |
| PKy5000 | Oral - facial - digital syndrome |
| PKy6100 | Cockayne syndrome |
| PKy0200 | Adams-Oliver syndrome |
| PG44300 | Mesomelic dysplasia |
| PG56012 | Conradi - Hunermann syndrome |
| PKy5K00 | Cohen syndrome |
| PJz3000 | Potocki-Lupski syndrome |
| PJ0z.00 | Down's syndrome NOS |
| PKyz700 | Angelman's syndrome |
| PH3y500 | Acanthosis nigricans, congenital |
| PH3y900 | Epidermolysis bullosa dystrophica |
| PJ02.11 | Partial trisomy 21 in Down's syndrome |
| pg16z00 | klippel - feil syndrome nos |
| PGy2700 | Ehlers-Danlos syndrome type VIII |
| PKy5300 | Whistling face syndrome |
| PJ50y00 | Other specified whole chromosome trisomy syndrome |
| PG58.11 | Engelmann's syndrome |
| PKy0300 | Weaver syndrome |
| PG52.12 | Marble bones |
| PG47.11 | Multiple congenital exostosis |
| PK60.00 | Peutz - Jegher's syndrome |
| PKy7000 | Carpenter's syndrome |
| PJy2.00 | XXX syndrome |
| PKy9300 | Prader - Willi syndrome |
| PJ33.00 | Other deletions of part of a chromosome |
| PD12012 | Autosomal recessive medullary cystic disease |
| PK80.00 | Fetal alcohol syndrome |

| Read Code | Read Term |
|---|---|
| PyuA500 | [X]Other variants of Turner's syndrome |
| PG44100 | Metatropic dwarfism |
| PJ3y.00 | Other deletions from the autosomes |
| PKy7900 | Popliteal pterygium syndrome |
| PG42.17 | Pseudochondroplasia |
| P322100 | Congenital megalocornea |
| PG51.16 | Brittle bone disease |
| PKy9000 | Alport's syndrome |
| PJ5z.11 | Aneuploidy NEC |
| PJy1300 | Mosaic including XXXXY |
| PJ38.00 | Chromosome replaced with ring or dicentric |
| PF58200 | Cleft hand with syndactyly |
| PKy7A00 | Congenital contractural arachnodactyly |
| PJ6z.00 | Gonadal dysgenesis NOS |
| PJ63611 | Turner's phenotype, ring chromosome karyotype |
| PJ7z.00 | Klinefelter's syndrome NOS |
| PF67500 | Lobster claw foot |
| PJ20.00 | Trisomy 18, meiotic nondisjunction |
| PG48.00 | Diaphyseal aclasis |
| PJ2z.11 | TRISOMY 18 NOS |
| PH15.00 | X-linked ichthyosis |
| PF5rB00 | Clinodactyly, no delta phalanx |
| PKy6900 | Borjeson-Forssman-Lehmann syndrome |
| PJy1200 | Mosaic XY/XXY |
| P336100 | Spherophakia |
| PJ22.11 | Partial trisomy 18 in Edward's syndrome |
| PKy7B00 | Stickler syndrome |
| P3y0.00 | Ocular albinism |
| PG44.00 | Other specified dwarfing syndromes |
| PKy5H00 | Simpson-Golabi-Behmel syndrome |
| PJz1.00 | Additional chromosome NOS |
| PJ53000 | Chromosome inversion in normal individual |
| PG0J.00 | Pierre Robin association |
| PJ37.12 | Autosomal deletion - mosaicism |
| PJyy300 | Karyotype 47,XYY |
| PG44011 | Diastrophic dysplasia |
| PG42.14 | Chondrodystrophy NEC |
| PJ38.12 | Chromosome replaced with ring |
| PH31300 | Angiomatosis |
| PKy7100 | Holt - Oram syndrome |
| PKy5611 | Weill-Marchesani syndrome |
| P322111 | Enlarged cornea |
| PyuAD00 | [X]Li-Fraumeni syndrome |
| PJ2z.00 | Edward's syndrome NOS |
| PJy4.00 | Female with more than three X chromosomes |

| Read Code | Read Term |
|---|---|
| PG03000 | Muenke syndrome |
| P2x2.00 | Familial dysautonomia |
| PKy7800 | Multiple pterygium syndrome |
| PG46.00 | Spondyloepiphyseal dysplasia |
| Pyu9000 | [X]Other congenital ichthyosis |
| PJ73.00 | Klinefelter's syndrome, XXYY |
| PJ53.11 | Balanced translocations |
| P343.00 | Aniridia |
| PH0z.00 | Hereditary oedema of legs NOS |
| PK84.00 | Fetal valproate syndrome |
| PD12111 | Medullary sponge kidney |
| PJ63z12 | Ovarian dwarfism NEC |
| P322000 | Congenital keratoglobus |
| 62U9.00 | Downs screen blood test normal |
| PG45.12 | Schmid's metaphyseal dysostosis |
| PH13.00 | Collodion baby |
| PJ52100 | Duplications with other complex rearrangements |
| PKy6000 | Amsterdam dwarf |
| PG41000 | Hypochondroplasia |
| PD1..13 | Polycystic kidney |
| PG51200 | Osteogenesis imperfecta - unclassifiable |
| PD1y011 | Fibrocystic renal degeneration |
| PJ52300 | Triploidy |
| PH33700 | Dyskeratosis congenita |
| PKy6500 | Aarskog syndrome |
| PH20.00 | Abnormal palmar creases |
| PKyJ.00 | Lujan-Fryns syndrome |
| PH3y700 | Epidermolysis bullosa simplex |
| PKy0.11 | Prader-Willi Syndrome |
| PG45.15 | Metaphyseal dysplasia |
| PJ33211 | 18q- syndrome |
| PJy6.00 | Male with structurally abnormal sex chromosome |
| P22y111 | Joubert syndrome |
| P302.00 | Cryptophthalmos syndrome |
| P2x4.00 | Marcus - Gunn syndrome |
| PG42.15 | Hypochondroplasia |
| PKy0100 | Currarino triad |
| PKy5A00 | Trichorhinophalangeal syndrome |
| 13L2.11 | Downs child in family |
| PH14.00 | Ichthyosis vulgaris |
| PKy6700 | Robinow syndrome |
| PJ32.11 | Wolff - Hirschorn syndrome |
| PE00000 | Hemifacial microsomia |
| PH30.00 | Congenital ectodermal dysplasia |
| PJ63200 | Turner's phenotype, karyotype 46X iso (Xq) |

| Read Code | Read Term |
|---|---|
| PJy0.00 | Additional sex chromosome |
| PKy5100 | Mohr's syndrome |
| PKy4.00 | William syndrome |
| PF55300 | Saethre-Chotzen syndrome |
| PD11000 | Polycystic kidneys, infantile type |
| PG58.00 | Progressive diaphyseal dysplasia |
| PK5..11 | Bourneville's disease |
| PKy8z00 | Congenital malformation syndrome+other skeletal changes NOS |
| PJ63000 | Turner's phenotype, karyotype normal |
| PG0D.00 | Mandibulofacial dysostosis |
| PJ51311 | 4p duplication syndrome |
| PJy1z00 | Sex chromosome mosaicism NOS |
| PKy6800 | Floating-Harbor syndrome |
| PG0C.00 | Pierre - Robin syndrome |
| PF58300 | Cleft hand with polydactyly |
| PG51.00 | Osteogenesis imperfecta |
| PH1..00 | Ichthyosis congenita |
| PJ52000 | Duplications seen only at prometaphase |
| PJyy.11 | Absence of sex chromosome |
| PJyy100 | 46XX true hermaphrodite |
| PKy6011 | Cornelia de Lange syndrome |
| P235.00 | X-linked hydrocephalus |
| PJ71.11 | Klinefelter's syndrome, XXXY |
| PH1z.00 | Ichthyosis congenita NOS |
| PF5r200 | Camptodactyly |
| PG0E.00 | Oculomandibular dysostosis |
| PJz0.00 | Mosaicism NOS |
| PKy7412 | Mermaid sirenomelia |
| PKyz511 | Angelman syndrome |
| PJ33z00 | Other deletion of part of a chromosome NOS |
| PG51100 | Osteopsathyrosis |
| PJ50800 | Trisomy 22 |
| 62U..00 | Downs screen - blood test |
| PJ63z00 | Turner's syndrome NOS |
| 8CEM.00 | Downs syndrome antenatal screening information leaflet given |
| PC73.00 | Pure gonadal dysgenesis |
| PG4B400 | Camptomelia dysplasia |
| PKy0600 | Feingold syndrome |
| PG44600 | Pseudoachondroplasia |
| PH33500 | Pseudoxanthoma elasticum |
| PG42.16 | Osteopathia striata |
| PH3y300 | Congenital keratoderma |
| PF3A.00 | Split foot |
| PH12.11 | Sjogren - Larsson syndrome |
| PE1..12 | Sternomastoid tumour |

| Read Code | Read Term |
|---|---|
| PKy7A11 | Beals syndrome |
| PKy6200 | Russell - Silver syndrome |
| PKy0500 | Cowden syndrome |
| PKy7200 | Klippel - Trenaunay - Weber syndrome |
| PD11.00 | Polycystic kidney disease |
| PK62.00 | Von Hippel-Lindau syndrome |
| PKy7611 | Hanhart syndrome |
| PJ53400 | Individual with autosomal fragile site |
| PG4E.00 | Spondylometaphyseal dysplasia |
| PJ63400 | Turner's phenotype, mosaicism 45X/46XX or 45X/46XY |
| PJ63100 | Turner's phenotype, karyotype 45X |
| PG57.11 | Caffey's syndrome |
| PJ33600 | Chromosome 22q11 deletion syndrome |
| PG42100 | Myotonic chondrodysplasia |
| PKy6300 | Smith - Lemli - Opitz syndrome |
| PJz2.00 | Deletion of chromosome NOS |
| PH12.00 | Ichthyosiform erythroderma |
| PD12.00 | Medullary cystic disease |
| PJ53.00 | Balanced rearrangements and structural markers NEC |
| PGy2200 | Ehlers-Danlos syndrome type III |
| PG5B.00 | Multiple synostosis syndrome |
| PG51z00 | Osteogenesis imperfecta NOS |
| PKy5C00 | Treacher Collins syndrome |
| PJ5z.00 | Unspecified conditions due to autosomal anomalies |
| PG51.11 | Vrolik's disease |
| PGyy300 | Popliteal web syndrome |
| PKyL.00 | FG syndrome |
| PJz..00 | Chromosomal anomalies NOS |
| PG44z00 | Other dwarfing syndromes NOS |
| PG04.00 | Craniofacial dysostosis |
| PB63500 | Alagille syndrome |
| PJ02.00 | Trisomy 21, translocation |
| PKyG.11 | Ohdo blepharophimosis syndrome |
| PKy2.00 | Marfan's syndrome |
| PD1..12 | Fibrocystic kidney |
| PH33000 | Brugsch's syndrome |

## ICD-10 codes for antenatal diagnoses

| ICD-10 Code | Description |
|---|---|
| O28.5 | Abnrm chromosom and genet find antenat screen of mother |
| O35.1 | Mat care for (suspected) chromosomal abnormality in fetus |
| O35.2 | Maternal care for (suspected) hereditary disease in fetus |

ICD-10 codes for postnatal diagnoses

| ICD-10 | Description |
|---|---|
| D18.1 | Lymphangioma, any site |
| D82.1 | Di George's syndrome |
| Q12.4 | Spherophakia |
| Q13.1 | Absence of iris |
| Q13.5 | Blue sclera |
| Q61.1 | Polycystic kidney, infantile type |
| Q61.2 | Polycystic kidney, adult type |
| Q61.3 | Polycystic kidney, unspecified |
| Q61.5 | Medullary cystic kidney |
| Q71.6 | Lobster-claw hand |
| Q72.7 | Split foot |
| Q75.1 | Craniofacial dysostosis |
| Q75.4 | Mandibulofacial dysostosis |
| Q75.5 | Oculomandibular dysostosis |
| Q76.1 | Klippel-Feil syndrome |
| Q77.0 | Achondrogenesis |
| Q77.1 | Thanatophoric short stature |
| Q77.2 | Short rib syndrome |
| Q77.3 | Chondrodysplasia punctata |
| Q77.4 | Achondroplasia |
| Q77.5 | Dystrophic dysplasia |
| Q77.6 | Chondroectodermal dysplasia |
| Q77.7 | Spondyloepiphyseal dysplasia |
| Q78.0 | Osteogenesis imperfecta |
| Q78.2 | Osteopetrosis |
| Q78.3 | Progressive diaphyseal dysplasia |
| Q78.5 | Metaphyseal dysplasia |
| Q78.6 | Multiple congenital exostoses |
| Q79.6 | Ehlers-Danlos syndrome |
| Q80 | Congenital ichthyosis |
| Q80.0 | Ichthyosis vulgaris |
| Q80.1 | X-linked ichthyosis |
| Q80.2 | Lamellar ichthyosis |
| Q80.3 | Congenital bullous ichthyosiform erythroderma |
| Q80.4 | Harlequin fetus |
| Q80.8 | Other congenital ichthyosis |
| Q80.9 | Congenital ichthyosis, unspecified |
| Q81 | Epidermolysis bullosa |
| Q81.0 | Epidermolysis bullosa simplex |
| Q81.1 | Epidermolysis bullosa letalis |
| Q81.2 | Epidermolysis bullosa dystrophica |
| Q81.8 | Other epidermolysis bullosa |

| ICD-10 | Description |
|---|---|
| Q81.9 | Epidermolysis bullosa, unspecified |
| Q82.0 | Hereditary lymphoedema |
| Q82.1 | Xeroderma pigmentosum |
| Q82.3 | Incontinentia pigmenti |
| Q82.4 | Ectodermal dysplasia (anhidrotic) |
| Q85 | Phakomatoses, not elsewhere classified |
| Q85.0 | Neurofibromatosis (nonmalignant) |
| Q85.1 | Tuberous sclerosis |
| Q85.8 | Other phakomatoses, not elsewhere classified |
| Q85.9 | Phakomatosis, unspecified |
| Q86 | Cong malformation syndromes due to known exogen causes NEC |
| Q86.0 | Fetal alcohol syndrome (dysmorphic) |
| Q86.1 | Fetal hydantoin syndrome |
| Q86.2 | Dysmorphism due to warfarin |
| Q86.8 | Oth cong malform syndromes due to known exogen causes |
| Q87 | Oth spec cong malform syndromes affecting multiple sys |
| Q87.0 | Cong malform syndromes predom affect facial appearance |
| Q87.1 | Cong malform syndromes predomin assoc with short stature |
| Q87.2 | Cong malformation syndromes predominantly involving limbs |
| Q87.3 | Congenital malformation syndromes involving early overgrowth |
| Q87.4 | Marfan's syndrome |
| Q87.5 | Other cong malform syndromes with other skeletal changes |
| Q87.8 | Other specified congenital malformation syndromes NEC |
| Q90 | Down's syndrome |
| Q90.0 | Trisomy 21, meiotic nondisjunction |
| Q90.1 | Trisomy 21, mosaicism (mitotic nondisjunction) |
| Q90.2 | Trisomy 21, translocation |
| Q90.9 | Down's syndrome, unspecified |
| Q91 | Edwards' syndrome and Patau's syndrome |
| Q91.0 | Trisomy 18, meiotic nondisjunction |
| Q91.1 | Trisomy 18, mosaicism (mitotic nondisjunction) |
| Q91.2 | Trisomy 18, translocation |
| Q91.3 | Edwards' syndrome, unspecified |
| Q91.4 | Trisomy 13, meiotic nondisjunction |
| Q91.5 | Trisomy 13, mosaicism (mitotic nondisjunction) |
| Q91.6 | Trisomy 13, translocation |
| Q91.7 | Patau's syndrome, unspecified |
| Q92 | Other trisomies and partial trisomies of the autosomes NEC |
| Q92.0 | Whole chromosome trisomy, meiotic nondisjunction |
| Q92.1 | Whole chromosome trisomy, mosaicism (mitotic nondisjunction) |
| Q92.2 | Major partial trisomy |
| Q92.3 | Minor partial trisomy |
| Q92.4 | Duplications seen only at prometaphase |
| Q92.5 | Duplications with other complex rearrangements |
| Q92.6 | Extra marker chromosomes |

| ICD-10 | Description |
|---|---|
| Q92.7 | Triploidy and polyploidy |
| Q92.8 | Other specified trisomies and partial trisomies of autosomes |
| Q92.9 | Trisomy and partial trisomy of autosomes, unspecified |
| Q93 | Monosomies and deletions from the autosomes NEC |
| Q93.0 | Whole chromosome monosomy, meiotic nondisjunction |
| Q93.1 | Whole chrom monosomy mosaicism (mitotic nondisjunction) |
| Q93.2 | Chromosome replaced with ring or dicentric |
| Q93.3 | Deletion of short arm of chromosome 4 |
| Q93.4 | Deletion of short arm of chromosome 5 |
| Q93.5 | Other deletions of part of a chromosome |
| Q93.6 | Deletions seen only at prometaphase |
| Q93.7 | Deletions with other complex rearrangements |
| Q93.8 | Other deletions from the autosomes |
| Q93.9 | Deletion from autosomes, unspecified |
| Q95 | Balanced rearrangements and structural markers NEC |
| Q95.0 | Balanced translocation and insertion in normal individual |
| Q95.1 | Chromosome inversion in normal individual |
| Q95.2 | Balanced autosomal rearrangement in abnormal individual |
| Q95.3 | Balanced sex/autosomal rearrangement in abnormal individual |
| Q95.4 | Individuals with marker heterochromatin |
| Q95.5 | Individuals with autosomal fragile site |
| Q95.8 | Other balanced rearrangements and structural markers |
| Q95.9 | Balanced rearrangement and structural marker, unspecified |
| Q96 | Turner's syndrome |
| Q96.0 | Karyotype 45,X |
| Q96.1 | Karyotype 46,X iso (Xq) |
| Q96.2 | Karyotype 46,X with abnormal sex chromosome, except iso (Xq) |
| Q96.3 | Mosaicism, 45,X/46,XX or XY |
| Q96.4 | Mosaicism 45X/oth cell line(s) with abnorm sex chromosome |
| Q96.8 | Other variants of Turner's syndrome |
| Q96.9 | Turner's syndrome, unspecified |
| Q97 | Other sex chromosome abnormalities, female phenotype NEC |
| Q97.0 | Karyotype 47,XXX |
| Q97.1 | Female with more than three X chromosomes |
| Q97.2 | Mosaicism, lines with various numbers of X chromosomes |
| Q97.3 | Female with 46,XY karyotype |
| Q97.8 | Oth spec sex chromosome abnormalities female phrenotype |
| Q97.9 | Sex chromosome abnormality, female phenotype, unspecified |
| Q98 | Other sex chromosome abnormalities, male phenotype NEC |
| Q98.0 | Klinefelter's syndrome karyotype 47,XXY |
| Q98.1 | Klinefelter's syn male with more than two X chromosomes |
| Q98.2 | Klinefelter's syndrome, male with 46,XX karyotype |
| Q98.3 | Other male with 46,XX karyotype |
| Q98.4 | Klinefelter's syndrome, unspecified |
| Q98.5 | Karyotype 47,XYY |

| ICD-10 | Description |
|---|---|
| Q98.6 | Male with structurally abnormal sex chromosome |
| Q98.7 | Male with sex chromosome mosaicism |
| Q98.8 | Other specified sex chromosome abnormalities, male phenotype |
| Q98.9 | Sex chromosome abnormality, male phenotype, unspecified |
| Q99 | Other chromosome abnormalities, not elsewhere classified |
| Q99.0 | Chimera 46,XX/46,XY |
| Q99.1 | 46,XX true hermaphrodite |
| Q99.2 | Fragile X chromosome |
| Q99.8 | Other specified chromosome abnormalities |
| Q99.9 | Chromosomal abnormality, unspecified |

# Appendix 5 – Code lists for congenital infections

## Read codes for use in pregnant women

| Read code | Read Term |
|---|---|
| 43C3.11 | HIV positive |
| A788200 | HIV infection with persistent generalised lymphadenopathy |
| A788U00 | HIV disease result/haematological+immunologic abnorms,NEC |
| A788W00 | HIV disease resulting in unspecified malignant neoplasm |
| A788X00 | HIV disease resulting/unspcf infectious+parasitic disease |
| A789000 | HIV disease resulting in mycobacterial infection |
| A789100 | HIV disease resulting in cytomegaloviral disease |
| A789200 | HIV disease resulting in candidiasis |
| A789300 | HIV disease resulting in Pneumocystis carinii pneumonia |
| A789311 | HIV disease resulting in Pneumocystis jirovecii pneumonia |
| A789400 | HIV disease resulting in multiple infections |
| A789500 | HIV disease resulting in Kaposi's sarcoma |
| A789511 | HIV disease resulting in Kaposi sarcoma |
| A789600 | HIV disease resulting in Burkitt's lymphoma |
| A789700 | HIV dis resulting oth types of non-Hodgkin's lymphoma |
| A789800 | HIV disease resulting in multiple malignant neoplasms |
| A789900 | HIV disease resulting in lymphoid interstitial pneumonitis |
| A789A00 | HIV disease resulting in wasting syndrome |
| A789X00 | HIV dis reslt/oth mal neopl/lymph,h'matopoetc+reltd tissu |
| AyuC100 | [X]HIV disease resulting in other viral infections |
| AyuC300 | [X]HIV disease resulting in multiple infections |
| AyuC400 | [X]HIV disease resulting/other infectious+parasitic diseases |
| AyuC600 | [X]HIV disease resulting in other non-Hodgkin's lymphoma |
| AyuCB00 | [X]HIV disease result/haematological+immunologic abnorms,NEC |
| AyuCC00 | [X]HIV disease resulting in other specified conditions |
| AyuCD00 | [X]Unspecified human immunodeficiency virus [HIV] disease |
| L179.00 | HIV disease complicating pregnancy childbirth puerperium |
| R109.00 | [D]Laboratory evidence of human immunodeficiency virus [HIV] |
| Eu02400 | [X]Dementia in human immunodef virus [HIV] disease |
| A788.11 | Human immunodeficiency virus infection |
| 65QA.00 | AIDS carrier |
| A788.00 | Acquired immune deficiency syndrome |
| ZV01A00 | [V]Asymptomatic human immunodeficency virus infection status |
| 4J34.00 | HIV viral load |
| 65VE.00 | Notification of AIDS |
| A788z00 | Acquired human immunodeficiency virus infection syndrome NOS |
| 43j7.00 | HIV 1 nucleic acid detection |
| A789.00 | Human immunodef virus resulting in other disease |
| A788400 | Human immunodeficiency virus with neurological disease |
| A788000 | Acute human immunodeficiency virus infection |
| A788100 | Asymptomatic human immunodeficiency virus infection |

| Read code | Read Term |
|---|---|
| AyuC.00 | [X]Human immunodeficiency virus disease |
| A788y00 | Human immunodeficiency virus with other clinical findings |
| A788500 | Human immunodeficiency virus with secondary infection |
| A788300 | Human immunodeficiency virus with constitutional disease |
| 43w3.00 | Human immunodeficiency virus RNA/DNA ratio |
| 4J3F.00 | Human immunodeficiency virus viral load by log rank |
| 66j0.00 | Human immunodeficiency virus annual review |
| A788600 | Human immunodeficiency virus with secondary cancers |
| 9kl..00 | HIV pos gen health check serv declind - enhanc service admin |
| 4J3N.00 | Human immunodeficiency virus drug resistance test |
| 4J3P.00 | Human immunodeficiency virus type 1 subtype identification |
| 43wC.00 | Detection of Varicella zoster virus using PCR technique |
| A52..00 | Chickenpox - varicella |
| A52..11 | Chickenpox |
| A520.00 | Postvaricella encephalitis |
| A521.00 | Varicella pneumonitis |
| A52x.00 | Varicella with other specified complications |
| A52y.00 | Varicella with unspecified complications NOS |
| A52z.00 | Varicella with no complication NOS |
| AyuA200 | [X]Varicella with other complications |
| AyuA300 | [X]Varicella without complications |
| F011700 | Varicella meningitis |
| F035000 | Encephalitis following chickenpox |
| F035011 | Encephalitis due to varicella |
| F037000 | Varicella transverse myelitis |
| H24y700 | Pneumonia with varicella |
| 43jF.00 | Varicella zoster nucleic acid detection |
| A570.00 | Erythema infectiosum - fifth disease |
| A570.11 | Fifth disease |
| A570.12 | Slapped cheek syndrome |
| A796.00 | Parvovirus infection |
| A7y0400 | Parvovirus as cause of diseases classified to oth chapters |
| AyuDD00 | [X]Parvovirus infection, unspecified |
| 43jB.00 | Parvovirus B19 nucleic acid detection |
| L175.00 | Maternal rubella in pregnancy, childbirth and the puerperium |
| L175.11 | Rubella contact in pregnancy |
| L175000 | Maternal rubella, unspecified whether pregnancy/puerperium |
| L175100 | Maternal rubella during pregnancy - baby delivered |
| L175300 | Maternal rubella during pregnancy - baby not yet delivered |
| L175z00 | Maternal rubella in pregnancy/childbirth/puerperium NOS |
| L253.11 | Fetus with suspected rubella damage via mother |
| L253300 | Maternal care for damage to fetus from maternal rubella |
| 43jm.00 | Rubella virus nucleic acid detection |
| 65VG.00 | Notification of rubella |
| A56..00 | Rubella |

| Read code | Read Term |
|---|---|
| A56..11 | German measles |
| A56xz00 | Rubella with other specified complication NOS |
| A56y.00 | Rubella with unspecified complication |
| A56z.00 | Rubella with no complication NOS |
| AyuA900 | [X]Rubella with other complications |
| AyuAA00 | [X]Rubella without complication |
| A56..12 | French measles |
| A56..13 | Liberty measles |
| L169.00 | Herpes gestationis |
| L169000 | Herpes gestationis unspecified |
| L169100 | Herpes gestationis - delivered |
| L169200 | Herpes gestationis - delivered with postnatal complication |
| L169300 | Herpes gestationis - not delivered |
| L169400 | Herpes gestationis with postnatal complication |
| L169z00 | Herpes gestationis NOS |
| 43j6.00 | Herpes simplex nucleic acid detection |
| 43jt.00 | Human herpes virus 6 nucleic acid detection |
| 43ju.00 | Human herpes virus 7 nucleic acid detection |
| 43jv.00 | Human herpes virus 8 nucleic acid detection |
| 43w5.00 | Herpes simplex virus type 2 nucleic acid detection |
| 4J3C.00 | Herpes simplex virus isolation |
| A54..00 | Herpes simplex |
| A54..11 | Herpes simplex viral infection |
| A546.00 | Herpes simplex whitlow |
| A54x.00 | Herpes simplex with other specified complication |
| A54x000 | Visceral herpes simplex |
| A54x300 | Herpesviral vesicular dermatitis |
| A54xz00 | Herpes simplex with other specified complication NOS |
| A54y.00 | Herpes simplex with unspecified complication |
| A54z.00 | Herpes simplex no complication NOS |
| A54z.11 | Herpes labialis |
| AyuA000 | [X]Other forms of herpesviral infections |
| AyuA100 | [X]Herpesviral infection, unspecified |
| 43w4.00 | Herpes simplex virus type 1 nucleic acid detection |
| L170.00 | Maternal syphilis in pregnancy/childbirth/puerperium |
| L170000 | Maternal syphilis, unspec whether in pregnancy or puerperium |
| L170100 | Maternal syphilis during pregnancy - baby delivered |
| L170200 | Maternal syphilis in puerperium - baby delivered |
| L170z00 | Maternal syphilis in pregnancy/childbirth/puerperium NOS |
| L254.12 | Suspect fetal damage from maternal toxoplasmosis |
| 43j0.00 | Cytomegalovirus nucleic acid detection |
| A751.00 | Cytomegaloviral mononucleosis |
| A785000 | Cytomegaloviral pneumonitis |
| A785100 | Cytomegaloviral pancreatitis |
| A785200 | Cytomegaloviral hepatitis |

| Read code | Read Term |
|---|---|
| A785X00 | Cytomegaloviral disease, unspecified |
| A799.00 | Cytomegalovirus infection |
| A799.11 | CMV - Cytomegalovirus infection |
| AyuD000 | [X]Other cytomegaloviral diseases |
| AyuD100 | [X]Cytomegaloviral disease, unspecified |

## Read codes for use in infants

| Read code | Read Term |
|---|---|
| Q400.00 | Congenital rubella |
| Q401.00 | Congenital cytomegalovirus infection |
| Q402000 | Congenital herpes simplex |
| Q402300 | Congenital toxoplasmosis |
| Q402311 | Congenital hydrocephalus due to toxoplasmosis |
| Q402312 | Lymphadenopathy due to congenital toxoplasmosis |
| A90..00 | Congenital syphilis |
| A900.00 | Early congenital syphilis with symptoms |
| A900.12 | Congenital syphilitic choroiditis |
| A900.13 | Congenital syphilitic chronic coryza |
| A900.14 | Congenital syphilitic epiphysitis |
| A900.16 | Congenital syphilitic osteochondritis |
| A901.00 | Early latent congenital syphilis |
| A902.00 | Early congenital syphilis NOS |
| A904200 | Congenital syphilitic meningitis |
| A905.00 | Other late congenital syphilis |
| A905000 | Congenital syphilitic gumma |
| A905300 | Late congenital syphilitic oculopathy |
| A906.00 | Latent late congenital syphilis |
| A907.00 | Unspecified late congenital syphilis |
| A90z.00 | Congenital syphilis NOS |
| Ayu4300 | [X]Congenital syphilis, unspecified |
| F007400 | Meningitis due to congenital syphilis |
| F033100 | Encephalitis due to congenital syphilis |

## ICD-10 codes for use in infants

| ICD-10 code | Description |
|---|---|
| A50 | congenital syphilis |
| A500 | early congenital syphilis, symptomatic |
| A501 | early congenital syphilis, latent |
| A502 | early congenital syphilis, unspecified |
| A503 | late congenital syphilitic oculopathy |
| A504 | late congenital neurosyphilis [juvenile neurosyphilis] |
| A505 | other late congenital syphilis, symptomatic |

| ICD-10 code | Description |
|---|---|
| A506 | late congenital syphilis, latent |
| A507 | late congenital syphilis, unspecified |
| A509 | congenital syphilis, unspecified |
| A51 | early syphilis |
| A513 | secondary syphilis of skin and mucous membranes |
| A514 | other secondary syphilis |
| A515 | early syphilis, latent |
| A519 | early syphilis, unspecified |
| A52 | late syphilis |
| A520 | cardiovascular syphilis |
| A521 | symptomatic neurosyphilis |
| A522 | asymptomatic neurosyphilis |
| A523 | neurosyphilis, unspecified |
| A527 | other symptomatic late syphilis |
| A528 | late syphilis, latent |
| A529 | late syphilis, unspecified |
| A53 | other and unspecified syphilis |
| A530 | latent syphilis, unspecified as early or late |
| A539 | syphilis, unspecified |
| I980 | cardiovascular syphilis |
| K672 | syphilitic peritonitis |
| M031 | postinfective arthropathy in syphilis |
| M731 | syphilitic bursitis |
| N290 | late syphilis of kidney |
| B20 | human immunodef virus dis result infectious parasitic dis |
| B200 | hiv disease resulting in mycobacterial infection |
| B201 | hiv disease resulting in other bacterial infections |
| B202 | hiv disease resulting in cytomegaloviral disease |
| B203 | hiv disease resulting in other viral infections |
| B204 | hiv disease resulting in candidiasis |
| B205 | hiv disease resulting in other mycoses |
| B206 | hiv disease resulting in pneumocystis carinii pneumonia |
| B207 | hiv disease resulting in multiple infections |
| B208 | hiv dis resulting in oth infectious and parasitic dis |
| B209 | hiv disease resulting in unspec infectious or parasitic dis |
| B21 | human immunodef virus dis resulting malignant neopl |
| B210 | hiv disease resulting in kaposi's sarcoma |
| B211 | hiv disease resulting in burkitt's lymphoma |
| B212 | hiv dis resulting oth types of non-hodgkin's lymphoma |
| B213 | hiv dis result oth mal neo lymphoid haematopoietic rel tis |
| B217 | hiv disease resulting in multiple malignant neoplasms |
| B218 | hiv disease resulting in other malignant neoplasms |
| B219 | hiv disease resulting in unspecified malignant neoplasm |
| B22 | human immunodef virus dis resulting in other spec dis |
| B220 | hiv disease resulting in encephalopathy |

| ICD-10 code | Description |
|---|---|
| B221 | hiv disease resulting in lymphoid interstitial pneumonitis |
| B222 | hiv disease resulting in wasting syndrome |
| B227 | hiv dis resulting in multiple diseases classif elsewhere |
| B23 | human immunodef virus dis resulting in other conditions |
| B230 | acute hiv infection syndrome |
| B231 | hiv dis result (persistent) generalized lymphadenopathy |
| B232 | hiv dis result haematologic / immunologic abnorm nec |
| B238 | hiv disease resulting in other specified conditions |
| B24 | unspecified human immunodefiency virus [hiv] disease |
| F024 | dementia in human immunodef virus [hiv] disease |
| R75 | laboratory evidence of human immunodefiency virus [hiv] |
| Z114 | spec screening exam for human immunodefiency virus [hiv] |
| Z206 | contact with and exposure to human immunodef virus [hiv] |
| Z21 | asymptomatic human immunodef virus [hiv] infect status |
| P350 | congenital rubella syndrome |
| P352 | congenital herpesviral [herpes simplex] infection |
| P351 | congenital cytomegalovirus infection |
| P371 | congenital toxoplasmosis |

# Appendix 6 – Code lists used for influenza vaccination

## Read codes

Where a code describes the "administration" of a vaccine, this does not mean the vaccine was given to the patient but rather that some administrative task relating to vaccination was carried out. This could include sending reminders to patients, for example. Such codes were classified as "advised".

| Read Code | Read Term | Seasonal vaccine | Pandemic vaccine | Unspecified flu vaccine | Received | Refused | Advised | Given Elsewhere | Not indicated | Adverse |
|---|---|---|---|---|---|---|---|---|---|---|
| 68NV000 | Consent given for seasonal influenza vaccination | 1 | | | 1 | | | | | |
| 65ED.00 | Seasonal influenza vaccination | 1 | | | 1 | | | | | |
| 9N4q100 | DNA first intranasal seasonal influenza vaccination | 1 | | | | 1 | | | | |
| 8I2F000 | Seasonal influenza vaccination contraindicated | 1 | | | | 1 | | | | |
| 9OX5600 | Second intranasal seasonal influenza vaccination declined | 1 | | | | 1 | | | | |
| 9OX5100 | Seasonal influenza vaccination declined | 1 | | | | 1 | | | | |
| 68NE000 | No consent for seasonal influenza vaccination | 1 | | | | 1 | | | | |
| 9OX5200 | First intranasal influenza vaccination declined | 1 | | | | 1 | | | | |
| 9OX5300 | Second intranasal influenza vaccination declined | 1 | | | | 1 | | | | |
| 9OX5400 | First intranasal seasonal influenza vaccination declined | 1 | | | | 1 | | | | |
| 65EE100 | Administration of second intranasal influenza vaccination | 1 | | | | | 1 | | | |
| 65EE.00 | Administration of intranasal influenza vaccination | 1 | | | | | 1 | | | |
| 65ED100 | Administration of first intranasal seasonal influenza vacc | 1 | | | | | 1 | | | |
| 65ED400 | Administration of first inactivated seasonal influenza vacc | 1 | | | | | 1 | | | |
| 65ED300 | Administration of second intranasal | 1 | | | | | 1 | | | |

| Read Code | Read Term | Seasonal vaccine | Pandemic vaccine | Unspecified flu vaccine | Received | Refused | Advised | Given Elsewhere | Not indicated | Adverse |
|---|---|---|---|---|---|---|---|---|---|---|
| | seasonal influenza vacc | | | | | | | | | |
| 65EE000 | Administration of first intranasal influenza vaccination | 1 | | | | | 1 | | | |
| 8BQ1.00 | Long term indication for seasonal influenza vaccination | 1 | | | | | 1 | | | |
| 65ED200 | Seasonal influenza vaccination given while hospital inpt | 1 | | | | | | 1 | | |
| 65E2000 | Seasonal influenza vaccin given by other healthcare provider | 1 | | | | | | 1 | | |
| 65E2100 | First intranasal seasonal flu vacc gvn by othr hlthcare prov | 1 | | | | | | 1 | | |
| 65E2400 | 1st intramuscular seasonal influenza vacc given by other HCP | 1 | | | | | | 1 | | |
| 65E2300 | 2nd intramuscular seasonal influenza vacc given by other HCP | 1 | | | | | | 1 | | |
| 65E2200 | Secnd intranasal seasonal flu vacc gvn by othr hlthcare prov | 1 | | | | | | 1 | | |
| 65ED000 | Seasonal influenza vaccination given by pharmacist | 1 | | | | | | 1 | | |
| 8I6D000 | Seasonal influenza vaccination not indicated | 1 | | | | | | | 1 | |
| 65E6.00 | CELVAPAN - second influenza A (H1N1v) 2009 vaccination given | | 1 | | 1 | | | | | |
| 65E0.00 | First pandemic influenza vaccination | | 1 | | 1 | | | | | |
| 65E1.00 | Second pandemic influenza vaccination | | 1 | | 1 | | | | | |
| 65E5.00 | CELVAPAN - first influenza A (H1N1v) 2009 vaccination given | | 1 | | 1 | | | | | |
| 65E9.00 | PANDEMRIX - first influenza A (H1N1v) 2009 vaccination given | | 1 | | 1 | | | | | |
| 65EA.00 | PANDEMRIX - second influenza A (H1N1v) 2009 vaccination give | | 1 | | 1 | | | | | |
| 68Nr.00 | Consent given for pandemic influenza vaccination | | 1 | | 1 | | | | | |

| Read Code | Read Term | Seasonal vaccine | Pandemic vaccine | Unspecified flu vaccine | Received | Refused | Advised | Given Elsewhere | Not indicated | Adverse |
|---|---|---|---|---|---|---|---|---|---|---|
| 68Nt.00 | Consent given for influenza A subtype H1N1 vaccination | | 1 | | 1 | | | | | |
| 68Ns.00 | No consent for influenza A (H1N1v) 2009 vaccination | | 1 | | | 1 | | | | |
| 8I2d.00 | Pandemic influenza vaccination contraindicated | | 1 | | | 1 | | | | |
| 8IAG.00 | Pandemic influenza vaccination declined | | 1 | | | 1 | | | | |
| 9OX5500 | First intranasal pandemic influenza vaccination declined | | 1 | | | 1 | | | | |
| 9OX5000 | Influenza A virus subtype H1N1 vaccination declined | | 1 | | | 1 | | | | |
| 9N4q000 | Did not attend influenza A virus subtype H1N1 vaccination | | 1 | | | 1 | | | | |
| 6.50E+01 | Administration of first intranasal pandemic influenza vacc | | 1 | | | | 1 | | | |
| 65E1000 | Administration of second intranasal pandemic influenza vacc | | 1 | | | | 1 | | | |
| 2J63.00 | High priority for influenza A subtype H1N1 vaccination | | 1 | | | | 1 | | | |
| 9OXC000 | Influenza A virus subtype H1N1 vac inv SMS text message sent | | 1 | | | | 1 | | | |
| 65E3.00 | 1st pandemic influenza vacc give by other healthcare providr | | 1 | | | | | 1 | | |
| 65E3000 | First intranasal pndmc influenza vcc gvn othr hlthcare prvdr | | 1 | | | | | 1 | | |
| 65EB.00 | PANDEMRIX - 1st flu A (H1N1v) 2009 vac by othr hlth provider | | 1 | | | | | 1 | | |
| 65EC.00 | PANDEMRIX - 2nd flu A (H1N1v) 2009 vac by othr hlth provider | | 1 | | | | | 1 | | |
| 65E7.00 | CELVAPAN - 1st flu A (H1N1v) 2009 vacc by othr hlth provider | | 1 | | | | | 1 | | |
| 65E4.00 | 2nd pandemic influenza vacc give by other healthcare providr | | 1 | | | | | 1 | | |
| 65E8.00 | CELVAPAN - 2nd flu A (H1N1v) 2009 vacc by othr hlth provider | | 1 | | | | | 1 | | |

| Read Code | Read Term | Seasonal vaccine | Pandemic vaccine | Unspecified flu vaccine | Received | Refused | Advised | Given Elsewhere | Not indicated | Adverse |
|---|---|---|---|---|---|---|---|---|---|---|
| 8I6g.00 | Pandemic influenza vaccination not indicated | | 1 | | | | | | 1 | |
| 68NV.00 | Influenza vacc consent given | | | 1 | 1 | | | | | |
| 65E..00 | Influenza vaccination | | | 1 | 1 | | | | | |
| ZV04811 | [V]Flu - influenza vaccination | | | 1 | 1 | | | | | |
| ZV04800 | [V]Influenza vaccination | | | 1 | 1 | | | | | |
| 68Nu.00 | No response to influenza vaccination invitation | | | 1 | | 1 | | | | |
| 8I2F.00 | Influenza vaccination contraindicated | | | 1 | | 1 | | | | |
| 9OX5.00 | Influenza vaccination declined | | | 1 | | 1 | | | | |
| 68NE.00 | No consent - influenza imm. | | | 1 | | 1 | | | | |
| 9N4q.00 | Did not attend flu vaccination appointment | | | 1 | | 1 | | | | |
| 9OX7200 | Influenza vaccination third telephone invitation | | | 1 | | | 1 | | | |
| 9OXD.00 | Influenza vaccination verbal invitation | | | 1 | | | 1 | | | |
| 9OXC200 | Influenza vaccination invitation 2nd SMS text message sent | | | 1 | | | 1 | | | |
| 9OXD000 | Influenza vaccination first verbal invitation | | | 1 | | | 1 | | | |
| 9OXC300 | Influenza vaccination invitation 3rd SMS text message sent | | | 1 | | | 1 | | | |
| 9OX4.00 | Needs influenza immunisation | | | 1 | | | 1 | | | |
| 9OXB.00 | Influenza vaccination invitation third letter sent | | | 1 | | | 1 | | | |
| 9k7..00 | Influenza immunisation - enhanced services administration | | | 1 | | | 1 | | | |
| 9OXE100 | Influenza vaccination invitation second email | | | 1 | | | 1 | | | |
| 9OXA.00 | Influenza vaccination invitation second letter sent | | | 1 | | | 1 | | | |

| Read Code | Read Term | Seasonal vaccine | Pandemic vaccine | Unspecified flu vaccine | Received | Refused | Advised | Given Elsewhere | Not indicated | Adverse |
|---|---|---|---|---|---|---|---|---|---|---|
| 9OX7000 | Influenza vaccination first telephone invitation | | | 1 | | | 1 | | | |
| 9OX..00 | Influenza vacc. administratn. | | | 1 | | | 1 | | | |
| 9OXC100 | Influenza vaccination invitation 1st SMS text message sent | | | 1 | | | 1 | | | |
| 9OXE.00 | Influenza vaccination invitation email | | | 1 | | | 1 | | | |
| 6797000 | Education about influenza vaccination | | | 1 | | | 1 | | | |
| 9OXE200 | Influenza vaccination invitation third email | | | 1 | | | 1 | | | |
| 9OXE000 | Influenza vaccination invitation first email | | | 1 | | | 1 | | | |
| 8ME..00 | Influenza vaccination requested | | | 1 | | | 1 | | | |
| 9OX7100 | Influenza vaccination second telephone invitation | | | 1 | | | 1 | | | |
| 9OXD200 | Influenza vaccination third verbal invitation | | | 1 | | | 1 | | | |
| 9OXD100 | Influenza vaccination second verbal invitation | | | 1 | | | 1 | | | |
| 9OX..11 | Flu vaccination administration | | | 1 | | | 1 | | | |
| 68NN.11 | Influenza immunization advised | | | 1 | | | 1 | | | |
| 68NO.00 | Influenza imm.advised at home | | | 1 | | | 1 | | | |
| 9OX9.00 | Influenza vaccination invitation first letter sent | | | 1 | | | 1 | | | |
| 9OX6.00 | Influenza vaccination invitation letter sent | | | 1 | | | 1 | | | |
| 9OXC.00 | Influenza vaccination invitation SMS text message sent | | | 1 | | | 1 | | | |
| 9OX7.00 | Influenza vaccination telephone invite | | | 1 | | | 1 | | | |
| 9OXZ.00 | Influenza vacc.administrat.NOS | | | 1 | | | 1 | | | |
| 9OX1.00 | Has 'flu vaccination at home | | | 1 | | | | 1 | | |
| 9OX3.00 | Has 'flu vaccination at hosp. | | | 1 | | | | 1 | | |

| Read Code | Read Term | Seasonal vaccine | Pandemic vaccine | Unspecified flu vaccine | Received | Refused | Advised | Given Elsewhere | Not indicated | Adverse |
|---|---|---|---|---|---|---|---|---|---|---|
| 65E2.00 | Influenza vaccination given by other healthcare provider | | | 1 | | | | 1 | | |
| 9OX8.00 | Has influenza vaccination at work | | | 1 | | | | 1 | | |
| 9OX2.00 | Has'flu vaccination at surgery | | | 1 | | | | 1 | | |
| 8I6D.00 | Influenza vaccination not indicated | | | 1 | | | | | 1 | |
| F034G00 | Post influenza vaccination encephalitis | | | 1 | | | | | | 1 |
| U60K400 | [X]Influenza vaccine causing adverse effects therapeutic use | | | 1 | | | | | | 1 |

## Immunisation codes

Immunisation codes cannot be categorized as indicating vaccine receipt, refusal or advice. Whether a vaccine is received, refused or advised is available under a different variable in the immunisation file and must be used in conjunction with the immunisation codes.

| Immunisation code | Immunisation type | Pandemic vaccine | Seasonal vaccine | Unspecified vaccine | Vaccine Given Elsewhere |
|---|---|---|---|---|---|
| 4 | FLU | | | 1 | |
| 71 | PFLUGEN | 1 | | | |
| 72 | PFLUGSK | 1 | | | |
| 73 | PFLUGSKO | 1 | | | 1 |
| 74 | PFLUGS | 1 | | | |
| 75 | PFLUBAXO | 1 | | | 1 |
| 76 | PFLUBAX | 1 | | | |
| 78 | PFLUGENO | 1 | | | 1 |
| 84 | FLUSOHP | | 1 | | 1 |
| 85 | FLUSPHARMA | | 1 | | 1 |
| 89 | FLUSIN | | 1 | | |
| 97 | FLUSINOHP | | 1 | | 1 |
| 100 | FLUSIMOHP | | 1 | | 1 |

## Product codes

Records in the therapy file are created when a prescription is generated. Therefore, all codes are thought to indicate that the vaccine has been received.

| Product code | Product name | Pandemic vaccine | Seasonal vaccine |
|---|---|---|---|
| 41150 | Pandemrix vaccine emulsion and suspension for emulsion for injection (GlaxoSmithKline UK Ltd) | 1 | |
| 41240 | Influenza H1N1 vaccine (whole virion, Vero cell derived, inactivated) suspension for injection | 1 | |
| 41168 | Influenza H1N1 vaccine (split virion, inactivated, adjuvanted) emulsion and suspension for emulsion for injection | 1 | |

| | | | |
|---|---|---|---|
| 41925 | Celvapan (H1N1) vaccine (whole virion, Vero cell derived, inactivated) suspension for injection (Baxter Healthcare Ltd) | 1 | |
| 44759 | INFLUENZA PRE-FILLED SYRINGE | | 1 |
| 9710 | Agrippal vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd) | | 1 |
| 43827 | Intanza 9microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd) | | 1 |
| 61792 | Fluenz Tetra vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd) | | 1 |
| 27407 | Imuvac vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd) | | 1 |
| 57401 | Influvac Desu vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd) | | 1 |
| 51289 | Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose | | 1 |
| 48085 | Influenza inactivated split virion Vaccination (Chiron UK Ltd) | | 1 |
| 16585 | Viroflu vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd) | | 1 |
| 48658 | Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd) | | 1 |
| 1329 | Fluvirin vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd) | | 1 |
| 48740 | Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes | | 1 |
| 54677 | Preflucel vaccine suspension for injection 0.5ml pre-filled syringes (Baxter Healthcare Ltd) | | 1 |
| 57140 | Influenza vaccine (live attenuated) nasal suspension 0.2ml unit dose | | 1 |
| 11824 | Enzira vaccine suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd) | | 1 |
| 834 | Begrivac vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd) | | 1 |
| 47932 | Fluenz vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd) | | 1 |
| 61580 | Influenza vaccine (split virion, inactivated) suspension for injection 0.25ml pre-filled syringes | | 1 |
| 30156 | Invivac vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd) | | 1 |
| 40876 | Influenza vaccine (split virion, inactivated) 9microgram strain suspension for injection 0.1ml pre-filled syringes | | 1 |
| 2552 | Influvac Sub-unit vaccine suspension for injection 0.5ml pre-filled syringes (Abbott Healthcare Products Ltd) | | 1 |
| 63690 | Inflexal V suspension for injection 0.5ml pre-filled syringes (sanofi pasteur MSD Ltd) | | 1 |
| 51087 | Optaflu vaccine suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd) | | 1 |
| 49716 | Influenza vaccine (surface antigen, inactivated, virosome) suspension for injection 0.5ml pre-filled syringes | | 1 |
| 398 | Influenza inactivated split virion Vaccination (Aventis Pasteur MSD) | | 1 |
| 7951 | FLUVIRIN AQUEOUS ML VAC | | 1 |
| 65205 | FluMist Quadrivalent vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd) | | 1 |
| 43825 | Intanza 15microgram strain vaccine suspension for injection 0.1ml pre-filled syringes (sanofi pasteur MSD Ltd) | | 1 |
| 57917 | Fluarix Tetra vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd) | | 1 |
| 18612 | Mastaflu vaccine suspension for injection 0.5ml pre-filled syringes (Masta Ltd) | | 1 |
| 2139 | Fluarix vaccine suspension for injection 0.5ml pre-filled syringes (GlaxoSmithKline UK Ltd) | | 1 |
| 45661 | Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (Pfizer Ltd) | | 1 |
| 32391 | Influenza vaccine (surface antigen, inactivated) suspension for injection 0.5ml pre-filled syringes (Novartis Vaccines and Diagnostics Ltd) | | 1 |

| | | | |
|---|---|---|---|
| 10030 | Inflexal V vaccine suspension for injection 0.5ml pre-filled syringes (Janssen-Cilag Ltd) | | 1 |
| 13595 | Fluzone Vaccination (Aventis Pasteur MSD) | | 1 |
| 639 | Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes | | 1 |
| 40760 | Influenza vaccine (split virion, inactivated) 15microgram strain suspension for injection 0.1ml pre-filled syringes | | 1 |
| 61898 | Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes (A A H Pharmaceuticals Ltd) | | 1 |
| 30198 | Influenza inactivated split virion Vaccination (sanofi pasteur MSD Ltd) | | 1 |
| 922 | Influenza inactivated surface antigen Vaccination | | 1 |
| 23251 | FLUVIRIN PRE-FILLED SYRINGE | | 1 |
| 2601 | Mfv-ject Vaccination (Aventis Pasteur MSD) | | 1 |
| 38421 | Influenza inactivated split virion Vaccination (Evans Vaccines Ltd) | | 1 |
| 57678 | Fluenz vaccine nasal suspension 0.2ml unit dose (AstraZeneca UK Ltd) | | 1 |

## Appendix 7 – Read codes used in the published THIN study

Read codes used in the published THIN study[195] to identify major congenital malformations but not used in the algorithm developed as part of this thesis.

| Read Code | Read Term |
|---|---|
| 7L0F000 | REDUCTION OF GIGANTISM OF HAND |
| 7L0K200 | REDUCTION OF GIGANTISM OF FOOT |
| 7L0G111 | ALBEE OSTEOTOMY OF PELVIS |
| 7L0G116 | PEMBERTON OSTEOTOMY OF ILIUM |
| 7L0G117 | SALTER OSTEOTOMY OF PELVIS |
| 7L0G118 | SHELF PROCEDURE FOR STABILISATION OF HIP JOINT |
| 7L0K000 | OSTEOTOMY OF BODY OF OS CALCIS |
| 7L0K012 | DWYER OSTEOTOMY OF BODY OF OS CALCIS |
| 7L0H112 | MCFARLAND BONE GRAFT PSEUDOARTHROSIS OF TIBIA |
| 7L0G115 | GILL OSTEOTOMY OF PELVIS |
| 7L0L311 | LAPIDUS TRANSPLANTATION OF TENDON OF FIFTH TOE |
| 7L0L000 | RELEASE OF STREETER(CONSTRICTION) BAND |
| 7L0K111 | ELMSLIE WEDGE TARSECTOMY |
| 7L0H600 | COVENTRY TIBIAL OSTEOTOMY |
| 7L0G211 | COLONNA ARTHROPLASTY OF HIP |
| 7L0F900 | RELEASE OF THUMB-IN-PALM DEFORMITY |
| 7L0K011 | BAKER OSTEOTOMY OF BODY OF OS CALCIS |
| 7L0H200 | EXCISION OF ANLAGE OF FIBULA |
| 7043000 | FREEING OF SPINAL TETHER |
| 7L0N400 | FRONTAL ADVANCEMENT - FIXED |
| 7L0G11A | SUTHERLAND OSTEOTOMY OF PELVIS |
| 7L0H700 | GRUCA TIBIAL BIFURCATION PROCEDURE |
| 7L0H511 | VAN NES ROTATIONPLASTY FOR CONGENITAL DEFORMITY |
| 7L0H500 | REVERSAL ROTATION PLASTY ANKLE CORRECT CONGENITAL DEFORM LEG |
| 7L0H100 | CORRECTION OF PSEUDARTHROSIS OF TIBIA |
| 7L0H300 | EXCISION OF ANLAGE OF TIBIA |