# An investigation of the utilisation and safety of influenza A(H1N1)pdm 2009 vaccines using the UK GPRD

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# An investigation of the utilisation and safety of influenza A(H1N1)pdm 2009 vaccines using the UK GPRD


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**Abstract**

**Background** Following the outbreak of the Influenza A(H1N1) pandemic, mass vaccination was recommended in the UK, Europe and many other countries throughout the world. Given the limited pre-marketing experience with these vaccines, national and international post-marketing surveillance was recommended.

**Aim** To contribute to the post-marketing surveillance of the influenza A(H1N1) pdm09 vaccine using the GPRD, to assess the performance of the GPRD as a vaccine surveillance tool and to assess the potential of the VAESCO collaborative working model.

**Methods** Several studies were carried out, both independently using UK GPRD data and in collaboration with VAESCO partners elsewhere in Europe. Cohort, case-control and self-controlled case series methodologies were used to estimate influenza A(H1N1) pdm09 vaccine uptake in high risk groups, provide background rates of events commonly reported following vaccination for use in passive surveillance and evaluate the risk of Guillain-Barré syndrome and foetal death following influenza A(H1N1) pdm09 vaccination.

**Results** Uptake of influenza A(H1N1) pdm09 vaccine in clinical risk groups (40.3%) and pregnant women (21.6%) was low. Background rates of facial nerve palsy varied by data source, age, calendar year and calendar month. The risk of Guillain-Barré syndrome was not significantly higher among vaccinated than unvaccinated individuals in the case control ($OR_{adj}$ 1.0, $CI_{95}$ 0.3 to 2.7) or self-controlled case series ($IRR_{adj}$ 1.3 $CI_{95}$ 0.6 to 2.7) studies while the risk of first ($HR_{unadj}$ 0.74, $CI_{95}$ 0.62 to 0.88), second ($HR_{unadj}$ 0.59, $CI_{95}$ 0.45 to 0.77) and third ($HR_{unadj}$ 0.70, $CI_{95}$ 0.47 to 1.03) trimester foetal death was not higher in vaccinated than unvaccinated individuals.

**Conclusion** The GPRD performed well as a vaccine surveillance tool, providing accurate data on influenza A(H1N1) pdm09 vaccination and disease incidence. While the VAESCO studies produced useful data in a number of European data sources, limitations encountered suggest modification of the working model would be needed for future collaboration.

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# List of abbreviations

General Practice Research Database (GPRD)
Chronic Obstructive Pulmonary Disease (COPD)
World Health Organisation (WHO)
Vaccine Adverse Event Surveillance and Communication (VAESCO)
Adverse Events of Special Interest (AESI)
European Centre for Disease prevention and Control (ECDC)
General Practitioner (GP)
Multi-Centre Ethics Committee (MREC)
Up-To-Standard (UTS)
Clinical Practice Research Datalink (CPRD)
Hospital Episode Statistics (HES)
Office of National Statistics (ONS)
Independent Scientific Advisory Committee (ISAC)
Guillain-Barré syndrome (GBS)
Periodic Safety Update Report (PSUR)
Indices of Multiple Deprivation (IMD)
Upper Respiratory Tract Infection (URTI)
Influenza-Like-Illness (ILI)
Pandemic Influenza Vaccine (PIV)
Seasonal Influenza Vaccine (SIV)
Incidence Rate Ratio (IRR)
95% Confidence Interval (CI95)
Body Mass Index (BMI)
Health Protection Agency (HPA)
Last Menstrual Period (LMP)
Indices of Multiple Deprivation (IMD)
Observed versus Expected (OE)
Structured Query Language (SQL)
Self-Controlled Case Series (SCCS)
Case Control (CC)
Facial Nerve Palsy (FNP)
Transient Ischemic attack (TIA)
Hazard Ratio (HR)
Odds Ratio (OR)

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*Buíochas a ghabháil leat go léir!*

# 1. Introduction

## 1.1 Vaccination

It has been noted since ancient times that exposure to an infectious disease can confer protection against future infection, and attempts at inducing such protection through controlled exposure to infectious agents, have been described since the 10th century [1]. Early attempts at immunisation generally amounted to exposing individuals to limited amounts of the causative infectious agent. While these techniques achieved varying levels of success the risk of developing severe infection was never adequately controlled. 'Modern immunisation' is therefore considered by many to have begun with the work of Edward Jenner in the late 18$^{th}$ century. Jenner described how infection of individuals with cowpox, a disease related to smallpox, but far less severe, could confer protection against smallpox [2]. Jenner's experiments were the first to garner widespread acceptance of the potential of immunisation and by the middle of the 19$^{th}$ century the benefits of smallpox immunisation were such that it was made compulsory in Britain. While Jenner's work was a vital step in the development of modern vaccines, smallpox was unique in that for most other infectious diseases there does not exist an obvious, naturally occurring, less severe form, such as cowpox. Therefore over the years that followed scientists sought to discover ways to safely induce immunity to other infectious diseases, culminating in the discovery of pathogen inactivation and the development of the first human rabies vaccine using an inactivated version of the rabies virus by Louis Pasteur and Emile Roux in 1885 [3]. This finding ushered in a new era of lab based vaccine development and vaccination has since become one of the most successful medical interventions in use today with effective vaccines now existing for a wide range of infectious diseases. Vaccination is credited with the eradication of smallpox, the near eradication of polio and measles and the prevention of more than 2 to 3 million deaths worldwide every year [4].

Despite these successes immunisation has always been controversial and a strong anti-vaccination movement has existed since before the times of Jenner and Pasteur. Early criticisms of vaccination questioned its effectiveness and the ethics of the compulsory vaccination programmes it had bred. The successes of vaccination and the move from compulsory to optional vaccination policies have largely overcome these criticisms with attention instead turning to the safety of the vaccines [5]. As with any medical intervention, vaccination is not 100% safe and vaccines are known to cause a number of adverse events. Examples of such events range from minor reactions such

as fever, malaise and pain/swelling at the injection site to more serious reactions such as anaphylaxis, seizures and thrombocytopenia [6]. These events can result from incorrect administration of the vaccine, contamination of the vaccine or as a biological consequence of the vaccine's mechanism of action. Any decision to grant marketing approval to a vaccine is not therefore based on benefit alone, but on a careful judgement of whether the potential benefits of vaccination outweigh any potential risks. In order to make this judgement, regulatory agencies must consider all available pre-clinical and clinical trial data.

Despite the careful assessment that is carried out by regulatory agencies, unsafe vaccines can slip through the regulatory net, damaging public confidence in the value of vaccination and vaccine uptake rates [2]. Notably a number of recent safety concerns raised by vaccine critics have been based on very little scientific evidence. These reports usually arise due to a coincidental association between the time of the purported adverse event and the time of vaccination [7]. Such unsubstantiated reports have severely damaged public confidence in vaccination campaigns in the past [8] resulting in increases in vaccine preventable morbidity and mortality. It is therefore important for public health authorities to study the validity of any associations identified in order to provide a scientific evidence base to support or oppose continued vaccination.

### 1.2 Seasonal influenza

Influenza is an acute viral infection that is capable of rapid human to human transmission. Infection with influenza can result in symptoms such as sore throat, cough, fever, muscle pain and headache; however more serious complications such as pneumonia and death may also occur [9]. Subgroups of the population believed to be at higher risk of suffering the more serious complications of influenza include all those aged >65 and those of any age in a clinical risk group (i.e. those suffering from asthma, chronic obstructive pulmonary disease (COPD), chronic heart disease, chronic kidney disease, diabetes, chronic liver disease, stroke/transient ischaemic attack, central nervous system degeneration and immunosuppression) [10]. The World Health Organisation (WHO) estimates that between 250,000 and 500,000 deaths are caused by influenza every year [11].

The pathogen responsible for influenza illness, the influenza virus, was first identified in 1933 [9]. In 1938 it was first noted that more than one subtype of influenza virus

existed and that one of the influenza subtypes, the influenza A virus, was capable of changing genetically in response to evolutionary pressure from the human immune system [12]. These genetic changes have since been found to occur through point mutations in the hemagglutinin and neuraminidase antigens; a process that has come to be known as 'antigenic drift' [13]. Antigenic drift prevents humans from developing long-term immunity to influenza following influenza infection, as the protective antibodies raised against antigens on one influenza strain often cannot recognise the mutated antigens on a 'drifted' strain [14].

### *1.3 Seasonal influenza vaccine*

At the time the influenza virus was identified, vaccine development was progressing rapidly with pertussis, Bacillus Calmette–Guérin, diphtheria and tetanus vaccines all having been developed in the 1920s. Work on developing an influenza vaccine therefore began immediately and within three years the first live and killed influenza vaccines had been developed [3]. Poor antigen purification and yield, as well as a lack of recognition of the importance of antigenic drift, limited the utility of these early influenza vaccines [3]. Since then however, advances in centrifugation, the development of techniques to disrupt viruses and purify their antigens and the use of high yield strains have all significantly improved the production and efficacy of influenza vaccines [3]. Recently, immunogenic material, known as an 'adjuvant', has also been added to influenza vaccines in order to illicit a greater immune response against the antigenic material contained in the vaccine [82]. Despite these advances, the problem remains that in order for an influenza vaccine to effectively prevent infection the antigens contained in the vaccine must match the antigens in the circulating influenza strains [15]. In an effort to address this, the WHO set up the Global Influenza Surveillance program which monitors antigenic drift through surveillance of circulating influenza strains. Based on the Global Influenza Surveillance program's recommendations, the strains contained in the influenza vaccine are changed annually in an effort to provide the best match for the circulating strains [12].

Prevention from infection therefore requires the costly process of annually manufacturing new vaccines containing the recommended strains and revaccinating the susceptible population with them. Despite the costs involved vaccination is now widely recognised as the gold standard intervention for the prevention of seasonal

influenza infection with seasonal influenza campaigns implemented annually in countries throughout the world [83, 84].

## 1.4 Pandemic influenza

In addition to antigenic drift, influenza viruses are capable of altering their antigenic make-up more substantially through a much rarer process known as 'antigenic shift' [13]. This situation most commonly arises when two or more influenza viruses co-infect an organism. Reassortment of the viruses, resulting in the creation of a virus possessing antigenic material from both strains, is known as antigenic shift. If antigenic shift creates a reassorted virus that is capable of rapid human to human transmission, and that contains antigenic material that a large proportion of the world's population are immunologically naïve to, a worldwide influenza outbreak known as an 'influenza pandemic' may occur [85].

Influenza pandemics have most likely occurred throughout history however there is little evidence to support or refute their occurrence before the 18$^{th}$ century [16]. Since the 18$^{th}$ century however, there is general agreement that several influenza pandemics have occurred. The most notable of these was the 1918 "Spanish" flu pandemic, which is estimated to have resulted in infection of one third of the world's population with mortality estimates ranging from 20-100 million deaths [16-19]. While exact details remain unclear, it is believed that the 1918 pandemic was caused by an antigenic shift that resulted in the adaption of an avian influenza strain to human transmission. Since 1918, antigenic shifts have resulted in two less severe pandemic outbreaks, one in 1957 and one in 1968. The strains responsible for these pandemics emerged through the reassortment of a drifted ancestor of the 1918 strain with genes from avian influenza strains. The 1957 and 1968 pandemics were far less severe than the 1918 outbreak, possibly due to pre-existing immunity to the drifted 1918 portion of the pandemic strain. The availability of antibiotics to treat secondary pneumonia may also have limited the severity of these more recent pandemics [20].

## 1.5 Pandemic influenza vaccines

Acknowledging the potential for further pandemics, over the past 20 years, national and international public health organisations have drawn up pandemic preparedness plans [86]. These plans set out the key activities to be undertaken in the event of a pandemic outbreak of influenza. The availability of a vaccine against the pandemic

influenza strain is a vital element of many of these plans. However, as the strains that will be involved in antigenic shifts cannot currently be predicted it is not possible to know in advance which antigens a pandemic-causing influenza virus will contain, therefore development of a pandemic vaccine in advance of a pandemic outbreak is not possible; vaccine development can only begin once an outbreak has already started. Under the normal vaccine approval process, marketing authorisation of a vaccine in the EU takes 18-24 months [21]. Given the typical duration of influenza pandemics, this would mean that if a pandemic vaccine were to undergo the normal authorisation procedures the most severe waves of a pandemic would be likely to have passed by the time a vaccine would be authorised. In 2005 the European Medicines Agency (EMA) approved the setup of a special approval process known as the 'mock up authorisation procedure' in an effort to prevent such a situation arising.

The mock-up authorisation procedure is made up of two distinct steps, the first of which involves vaccine manufacturers developing a 'mock up' vaccine in the pre- or inter- pandemic period. The mock-up vaccine is made using an influenza strain that the general population are immunologically naïve to, and which could therefore potentially cause a pandemic. The manufacturer performs all pre-clinical and clinical tests that a vaccine would undergo in the normal approval process and submits a 'core dossier' to the EMA detailing the results of these tests. Based on these data the EMA decide whether to grant the mock-up vaccine approval under 'exceptional circumstances' or not. At the beginning of the 2009 pandemic more than 20 mock up vaccines had received approval, most of them using H5N1 avian influenza as the mock up strain [22].

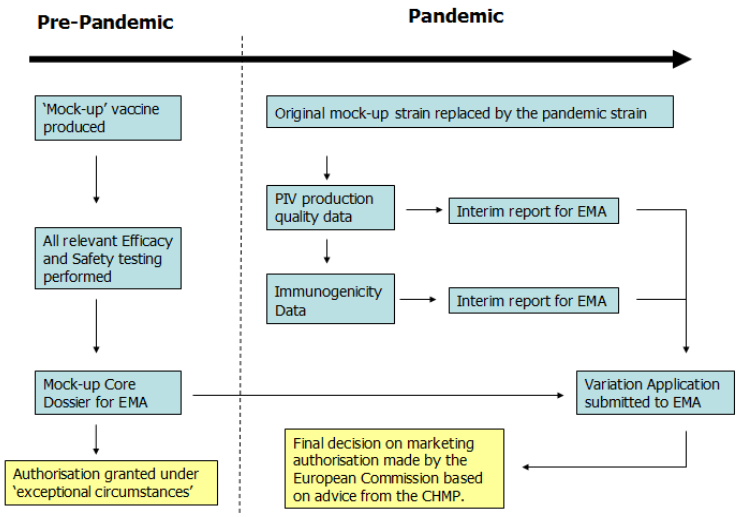


**Figure 1.1** EMA mock up authorisation procedure. Adapted from [21]

PIV; Pandemic Influenza Vaccine

The second part of the approval process occurs during the pandemic. Isolates from some of the earliest infected cases are sent to WHO contracted laboratories, each of which attempt to reassort the pandemic strain with a higher yielding strain in order to produce a seed strain that is more suitable for mass production. Once a high yielding seed strain has been identified it is sent to all companies that intend to develop a pandemic vaccine. The pandemic vaccine must then be produced in the same way the mock-up vaccine was, the only difference being that the H5N1 strain used for the mock-up is replaced with the pandemic seed strain. The only data that must then be submitted to the EMA in order to gain approval for a pandemic vaccine are quality data on the development and production of the pandemic vaccine and immunogenicity data for one batch of pandemic vaccine [22].

The principle of the mock up system is that changing only the seed strain used for the vaccine will not affect its characteristics greatly therefore many of the mock up results can be extrapolated to the pandemic vaccine. Regulatory authorities acknowledge that in order to speed up the approval process many of the usual premarketing safety and efficacy studies must be omitted meaning the pandemic vaccine will be introduced into the general population with limited efficacy and safety data [23]. In an effort to compensate for this, the post-marketing surveillance requirements for pandemic vaccines that undergo mock-up authorisation are much greater than normal.

## 1.6 Influenza A(H1N1)pdm09

On the 12$^{th}$ of April 2009 Mexican authorities informed the WHO of a local outbreak of respiratory disease occurring in La Gloria, Veracruz. This was closely followed by reports of increased numbers of severe cases of pneumonia arising in other regions of Mexico [24]. Concomitantly, on the 17$^{th}$ of April the Centre for Disease Prevention and control (CDC) confirmed that swine origin influenza A(H1N1)pdm09 was the causative agent in two cases of febrile respiratory disease arising in California [25]. Surveillance of respiratory disease was subsequently increased in both the USA and Mexico. Six days later the Public Health Agency of Canada identified swine influenza A(H1N1)pdm09 in samples from both Mexican and Canadian patients leading the WHO to declare on the 25$^{th}$ of April that the influenza outbreak had become ”a public health emergency of international concern” [26]. In response to this announcement, surveillance and containment measures were implemented in countries throughout the world. In the UK, containment involved active identification and antiviral treatment of potential cases, lab confirmation of illness and antiviral treatment of the close contacts

of any lab confirmed cases [48]. In addition schools in which cases were identified were closed for at least 7 days [48]. Despite this, over the next two months the outbreak progressed such that by the 11th of June 28,774 lab confirmed cases had been reported across 74 countries [27] leading the WHO to move their pandemic alert level to 6 (indicating that community level transmission of influenza occurring in multiple countries in one WHO region had spread to a second WHO region [88]) thereby officially declaring the outbreak of a pandemic [28].

The clinical characteristics of influenza A(H1N1)pdm09 infection became evident quite early in the outbreak the most frequently reported symptoms in all analyses were fever, cough and sore throat [29], all of which are classic symptoms of seasonal flu infection. However, a number of studies found a large proportion of patients also presented with diarrhoea, nausea or vomiting (24% of European cases [30], 38% of US patients [31]) none of which are frequently associated with seasonal flu infection. As with seasonal influenza, more serious outcomes such as respiratory failure and death were also reported [32-35], however measures of severity, such as case fatality ratios, varied widely making estimation of severity difficult [36].

The number of cases of influenza A(H1N1)pdm09 infection peaked in the northern hemisphere over the summer, in what is generally referred to as the "first wave" of the pandemic [87]. During this time epidemiological studies began to identify the risk factors associated with influenza A(H1N1)pdm09 infection. In contrast to seasonal influenza infection, the risk of influenza A(H1N1)pdm09 infection appeared to decrease with increasing age, with those aged >60 least likely to be infected [37-39]. A shift in the age groups susceptible to infection had been observed in the 1918 pandemic [19]. In 2009 this phenomenon was believed to result from pre-existing immunity among individuals exposed to pre-1957 influenza viruses and/or vaccines [40, 41]. With regard to risk factors for suffering severe symptoms following influenza A(H1N1)pdm09 infection, those individuals normally at higher risk of morbidity and mortality following seasonal influenza infection appeared to be at highest risk following influenza A(H1N1)pdm09infection [42]. Notably pregnant women appeared to be at a greater risk of serious illness than the general population [35, 43, 44].

By July 2009 the vast majority of countries throughout the world had followed the WHO recommendation to move from pandemic containment, or 'delaying', to mitigation [45, 46]. While vaccination represents the gold standard intervention for pandemic influenza mitigation, it was clear that even with the mock up system in place, vaccines against a pandemic strain would not be available until a potential

second wave [47]. In the UK, the mitigation, or treatment only phase, saw a move away from routine lab confirmation of cases, tracing of close contacts and school closures. Instead, antiviral treatment of clinically diagnosed cases was pursued with an emphasis on treatment of those in high risk groups [48].

The first wave of the pandemic illustrated that a large proportion of the world's population were immunologically naïve to the influenza A(H1N1)pdm09strain and that the strain was highly transmissible, however it also illustrated that the severity of the pandemic was much lower than feared at first. Acknowledging this, the UK government revised the case fatality and case hospitalisation ratios used in their worst case scenario estimates thereby revising estimates of the number of pandemic deaths from 65,000 to 19,000 [49]. Despite this, the authorities did not dismiss the threat of the pandemic completely as the experience of previous pandemics, particularly the 1918 pandemic, suggested that the second wave might prove to be considerably more severe than the first.

### 1.7 Influenza A(H1N1)pdm09 vaccines

With a second wave of uncertain severity expected, public attention began to turn to the impending availability of influenza A(H1N1)pdm09 vaccines. Vaccine production had been underway since the official announcement of the pandemic and the subsequent activation of the advance purchase agreements between vaccine manufacturers and national authorities [50]. Production was not going completely to plan however and despite the use of adjuvants in some vaccines it became clear that manufacturing delays would necessitate most countries to adopt a phased vaccination strategy [51].

In order to plan a phased vaccination strategy, national health authorities needed to split their population into sub-groups according to vaccination priority. As the major worldwide public health organisation, the WHO published recommendations on the composition of these sub-groups [51]. These recommendations emphasized the need to maintain healthcare capacity while protecting those at greatest risk from influenza A(H1N1)pdm09. The groups recommended for H1N1 vaccination in the UK (Table 1.1) [52] and most other countries European countries largely followed these WHO guidelines [53].

**Table 1.1** Priority groups for influenza A(H1N1)pdm09 vaccination in the UK.

| |
|---|
| Frontline healthcare workers |
| Individuals aged six months and up to 65 years in the current seasonal flu risk groups |
| All pregnant women |
| Household contacts of immunocompromised individuals |
| Individuals aged 65 and over in the 2009/10 seasonal flu vaccine clinical at-risk groups |
| All children aged between 6 months and 5 years old* |

*This group were only recommended as a priority group on the 19/11/2009, as safety data was deemed inadequate until this point [54].

Data from clinical trials using the mock-up (H5N1) vaccines suggested efficacy and safety was similar to that of seasonal influenza vaccines. Both vaccines that had been purchased by the UK, Pandemrix® and Celvapan®, met all other production quality and immunogenicity requirements set out by the regulatory authorities, receiving approval just over 100 days after the pandemic was declared (Table 1.2) [55, 56]. As the main aim of the mock up procedure was to expedite the approval process, in many respects it can be seen as a success; however, the problem remained that at the time of introduction into the population very little was known about the efficacy and safety of the specific vaccines that were being administered.

With both vaccines purchased by the UK having received marketing approval, a vaccination strategy in place and the first batches of vaccine delivered and ready for administration, the UK H1N1 vaccination campaign began on the 21 October 2009 [57].

**Table 1.2** Characteristics of the influenza A(H1N1)pdm09 vaccines used in the UK.

| **Vaccine name** | Pandemrix® | Celvapan® |
|---|---|---|
| **Marketing Authorisation Holder** | GlaxoSmithKline | Baxter |
| **Production** | Egg based | Cell based |
| **Type** | Split influenza virus, inactivated | Whole virion influenza, inactivated |
| **Antigen (mcg)** | 3.75 | 7.5 |
| **Adjuvanted** | Yes (AS03) | No |
| **Marketing approval date** | 24/09/2009 | 01/10/2009 |
| **Doses purchased (UK)** | 60 million | 30 million |

## 1.8 Post-marketing surveillance

Given the lack of safety and efficacy data available at the start of the vaccination campaign, The EMA, the European Centre for Disease Prevention and Control (ECDC) and the Head of Medicines Agencies set out a "European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring" [58]. This strategy described the safety, effectiveness and immunogenicity activities these bodies believed would be required to support the pandemic vaccination campaign. The safety section of this strategy contained several different components.

*Spontaneous reporting*

Spontaneous adverse event reports are routinely collected in many European countries for all newly marketed drugs [59] and vaccines [60]. The existing reporting systems could therefore be used to collect spontaneous event reports following exposure to influenza A(H1N1)pdm09 vaccines [58]. In the UK the existing reporting system was adapted somewhat, creating a specific online portal for reporting adverse events suspected to be associated with influenza anti-virals and influenza A(H1N1)pdm09 vaccines [61]. This portal allowed the collection of reports from both healthcare providers and their patients. Spontaneous reporting is primarily used for signal

detection. Data mining approaches, using measures such as the proportional reporting ratio, are used to detect whether an adverse event is reported a disproportionate number of times for a certain drug or vaccine [59, 60]. Where a signal is detected, causality assessments can be carried out using global introspection and causality algorithms [62]. The variability in the nature of the potential causal mechanisms under study limits these causality assessments, therefore in order to further assess a signal, classic epidemiological methods are also used [59]. The aim of these methods is to define the incidence of the adverse event among exposed individuals and to compare this to the known incidence of that event in the general population. Measures of exposure prevalence can be used as a denominator in the calculation of an approximate incidence rate of the adverse event among the exposed and measures of the incidence of the adverse event in the unexposed, or the background incidence rate, can be used for the comparison [59]. If this information is available, observed versus expected (OE) analyses can be conducted to obtain crude relative risk estimates. Notably all of these measures are limited by under- and selective reporting of events; however with careful consideration these analyses represent a cost effective way to rapidly assess postmarketing drug or vaccine safety [59, 60, 63, 64].

*Background incidence rates*

In order to be of the greatest use in OE analyses, background incidence rates need to be accurate, detailed and generalisable to the population in which the spontaneous reports arise [65]. At the beginning of the vaccination campaign, the background incidence rates of many potential adverse events had not been estimated and, where they had been, they often lacked the requisite level of accuracy, detail or generalisability. In the wake of the pandemic outbreak, and with the imminent vaccination of millions of people, the need for reliable background incidence rates became clear. In an effort to address this, the rates of a number of diseases in a number of countries were reported in advance of the influenza A(H1N1)pdm09 vaccination campaign [66]. Realising the utility of such rates, the ECDC sponsored the VAESCO (Vaccine Adverse Event Surveillance and COmmunication) consortium to carry out a similar study estimating the rates of 11 adverse events of special interest (AESI) (Table 1.3) in 8 different countries [58, 67]. The VAESCO consortium is a network of investigators from European member states exploring the feasibility and demonstrating the benefits of collaborative post-licensure epidemiological studies investigating the safety of human vaccines [68]. The consortium is composed of experts from a range of professional backgrounds including academia, patient care, public health and regulatory affairs.

**Table 1.3** Adverse events of special interest (AESI)

| |
|---|
| Anaphylaxis |
| Generalized convulsive seizure |
| Guillain-Barré syndrome |
| Thrombocytopenia |
| Vasculitis |
| Spontaneous abortion |
| Bell's Palsy (Facial Nerve Palsy) |
| Neuritis |
| Demyelinating disease |
| Optic neuritis |
| Encephalitis |

*Vaccine uptake*

Prior to the pandemic, many European countries monitored exposure to seasonal influenza vaccine using either immunisation registries or vaccine uptake surveys [69]. These systems give an estimate of the number of people in a known sampling fraction who have a record of vaccination, that is, they estimate the prevalence or incidence of vaccine exposure in the population. As with background incidence rates, if these measures of vaccine uptake are to be utilised in OE analyses they need to be accurate, detailed and generalisable to the population of interest. In addition, as exposure prevalence changes over time the uptake measures need to be regularly updated. The success of promotional campaigns supporting vaccination can be measured against uptake and sub-populations with low uptake can be identified and targeted for future promotional efforts [70].

*Industry responsibilities*

Manufacturers are normally obliged to submit Periodic Safety Update Reports (PSURs) on any newly authorised drugs to the EMA every 6 months [71]. These reports detail any emerging safety data the manufacturer has produced in that time period. In order to identify rapidly any safety concerns with a vaccine that had gone through the mock up approval process, the EMA required that during the first six months of the vaccination campaign simplified PSURs should be submitted to them on a monthly basis [72]. A further obligation of the mock up approval process was that every manufacturer had to consent to carrying out a prospective cohort study involving a minimum of 9,000 subjects followed for at least 6 months after the first or second dose [72].

*Safety in population sub-groups*

The safety of the vaccine among individuals in clinical risk groups must be considered separately from the general population as the conditions that render them more susceptible to severe influenza illness might also render them more susceptible to suffering vaccine associated adverse events. The rarity of many of the medical conditions defining risk group status makes it difficult to investigate safety for any specific condition in clinical trials. In addition, exclusion criteria for clinical trials can be prevalent among individuals with these conditions. Premarketing vaccine safety in clinical risk groups must therefore be extrapolated from the population used in clinical trials or from previous experience with seasonal influenza vaccine. As a result the vaccine benefit-risk plan stressed that once the vaccination campaign was underway, existing networks of specialists (eg. paediatricians, neurologists, and respiratory specialists) and registries (e.g. pregnancy registries) should be used to carry out observational studies providing additional safety information on these high risk groups [58]. A high risk sub -group of particular concern were pregnant women as the effects of an exposure on the developing foetus cannot be extrapolated from the general population [73]. While previous experience with seasonal influenza vaccination of pregnant women suggested there were no major safety concerns [74], evidence from active surveillance was needed to support this observation. In an effort to provide such evidence vaccine manufacturers were obligated to provide regulatory authorities with the results of a pregnancy registry study [72] however given the limitations of studies conducted in pregnancy registries [75] it was likely that studies using other data sources would also be needed [58].

*Active surveillance –Guillain-Barré syndrome*

While passive surveillance using spontaneous reports provides rapid information on the safety of a newly introduced vaccine, its limitations result in it being used primarily in hypothesis generation. Where a specific safety concern is suspected, more active surveillance may be required. The primary pre-existing safety concern regarding the influenza A(H1N1)pdm09 vaccine was the rare neurological condition Guillain-Barré syndrome (GBS). In 1976 a mass swine influenza campaign in the US was halted following a substantial increase in the number of GBS cases. Specifically it was found that those who received the 1976 swine influenza vaccine were 4-8 times more likely to develop GBS in the 6 weeks following vaccination than those who did not [76]. A number of studies have since been carried out to assess whether an association exists between seasonal influenza vaccines and GBS and while the majority of these have indicated there is no association [77-79], a slightly increased risk was found in the

1992-93 and 1993-94 seasons [80]. A number of theories have been put forward suggesting such an association is biologically plausible, the strongest of which hypothesises that antibodies raised against vaccine components may cross-react with gangliosides on peripheral nerves [81]. With a sample size of ~9,000 subjects per vaccine the manufacturer led cohort studies were not powerful enough to produce accurate risk estimates for the occurrence of rare events such as GBS (GBS incidence 1-2/100,000 person years) following vaccination. As a result, the post marketing surveillance plan highlighted the need for specific analyses evaluating the risk of GBS associated with influenza A(H1N1)pdm09 vaccines [58]. In an effort to address this, the ECDC again commissioned the VAESCO consortium to carry out a study, this time investigating the risk of GBS following influenza A(H1N1)pdm09 vaccination. The plan was to use two study designs, a case control and a self-controlled case series, in an effort to provide both rapid and unconfounded estimates of the risk of GBS following vaccination.

*Unexpected safety signals*

The plan acknowledged that any unexpected safety signals arising during the campaign would require rapid evaluation. Electronic healthcare databases and clinical specialist networks were identified as the most readily available and accessible data sources that could be used to evaluate such signals, while the possibility of performing large collaborative studies to investigate any association was also emphasised in the plan [58]. In addition vaccine manufacturers agreed to cooperate and independently investigate any unexpected safety signals.

[1] Gross CP, Sepkowitz KA. The myth of the medical breakthrough: Smallpox, vaccination, and Jenner reconsidered. International Journal of Infectious Diseases 2007;3(1):54-60.

[2] Link K. The vaccine controversy: the history, use and safety of vaccinations. Westport: Praeger, 2005.

[3] Plotkin SL, Plotkin SA. A Short History of Vaccination. In: Plotkin S, Orenstein WA, editors. Vaccines. Philadelphia: W.B. Saunders, 1999: 1-12.

[4] World Health Organisation. (2010) Immunization. Available:http://www.who.int/topics/immunization/en/. Accessed 14/06/2010.

[5] Tackling negative perceptions towards vaccination. Lancet Infect Dis 2007;7(4):235.

[6] World Health Organization: Western Pacific Regional Office. (1999) Immunization safety surveillance: guidelines for managers of immunization programmes on reporting and investigating adverse events following immunization. WPRO/EPI/99.01. Available:http://www.who.int/immunization_safety/publications/aefi/en/AEFI_WPRO.pdf. Accessed 14/06/2010.

[7] Leask J, Chapman S, Cooper Robbins SC. "All manner of ills": The features of serious diseases attributed to vaccination. Vaccine 2010;28(17):3066-70.

[8] Nicoll A, Elliman D, Ross E. MMR vaccination and autism 1998. BMJ 1998;316(7133):715-6.

[9] Lamb RA, Krug RM. Orthomyxoviridae : the viruses and their replication. Fields Virology. Philadelphia.: Lippincott Williams and Wilkins., 2001: 1487-531.

[10] Nicoll A, Ciancio B, Tsolova S, Blank P, Yilmaz C. The scientific basis for offering seasonal influenza immunisation to risk groups in Europe. Euro Surveill 2008;13(43).

[11] World Health Organisation. (2010) Influenza (Seasonal). Available:http://www.who.int/mediacentre/factsheets/fs211/en/index.html. Accessed 14/06/2010.

[12] Kitler ME, Gavinio P, Lavanchy D. Influenza and the work of the World Health Organization. Vaccine 2002;20 Suppl 2:S5-14.

[13] Carrat F, Flahault A. Influenza vaccine: the challenge of antigenic drift. Vaccine 2007;25(39-40):6852-62.

[14] Couch RB, Kasel JA. Immunity to influenza in man. Annu Rev Microbiol 1983;37:529-49.

[15] Brett IC, Johansson BE. Immunization against influenza A virus: comparison of conventional inactivated, live-attenuated and recombinant baculovirus produced purified hemagglutinin and neuraminidase vaccines in a murine model system. Virology 2005;339(2):273-80.

[16] Potter CW. A history of influenza. J Appl Microbiol 2001;91(4):572-9.

[17] Johnson NP, Mueller J. Updating the accounts: global mortality of the 1918-1920 "Spanish" influenza pandemic. BullHist Med 2002;76(1):105-15.

[18] Crosby AW. America's forgotten Pandemic: The influenza of 1918. New York: Camridge University Press, 1989.

[19] Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. Emerg Infect Dis 2006;12(1):15-22.

[20] Kilbourne ED. Influenza pandemics of the 20th century. Emerg Infect Dis 2006;12(1):9-14.

[21] European Medicines Agency. (2010) Authorisation Procedures. Available:http://www.ema.europa.eu/influenza/vaccines/authorisation_procedures.htm. Accessed 12/06/2010.

[22] European Medicines Agency. (2008) CHMP Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (Revision) EMEA/CPMP/VEG/4717/2003- Rev.1. Available:http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003869.pdf. Accessed 15/08/2012.

[23] World Health Organisation: Expert Committee on Biological Standardization. (2007) Regulatory Preparedness for Human Pandemic Influenza Vaccines. WHO/BS/07.2074. Available:http://www.who.int/biologicals/publications/trs/areas/vaccines/influenza/Human_pandemic_Influenza_Vaccines_BS2074_01Feb08.pdf. Accessed 21/08/2012.

[24] World Health O. Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries. Weekly epidemiological record 2009;84(21):185-90.

[25] Swine influenza A (H1N1) infection in two children--Southern California, March-April 2009. MMWR MorbMortalWklyRep 2009;58(15):400-2.

[26] World Health O. New influenza A(H1N1) virus infections: global surveillance summary. Weekly epidemiological record 2009;84(20):173-9.

[27] (2009) World Health Organization. Influenza A(H1N1) - update 47. Available:http://www.who.int/csr/don/2009_06_11/en/index.html. Accessed 13/05/2010

[28] (2009) Transcript of statement by Margaret Chan, Director-General of the World Health Organization. Available:http://www.who.int/mediacentre/influenzaAH1N1_presstranscript_20090611.pdf. Accessed 14/10/2011.

[29] Petrosillo N, Di BS, Drapeau CM, Grilli E. The novel influenza A (H1N1) virus pandemic: An update. Ann Thorac Med 2009;4(4):163-72.

[30] Preliminary analysis of influenza A(H1N1)v individual and aggregated case reports from EU and EFTA countries. Euro Surveill 2009;14(23):19238.

[31] Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360(25):2605-15.

[32] Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quinones-Falconi F, Bautista E, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 2009;361(7):680-9.

[33] Rello J, Rodriguez A, Ibanez P, Socias L, Cebrian J, Marques A, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. Crit Care 2009;13(5):R148.

[34] Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 2009;302(17):1872-9.

[35] Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 2009;361(20):1935-44.

[36] Garske T, Legrand J, Donnelly CA, Ward H, Cauchemez S, Fraser C, et al. Assessing the severity of the novel influenza A/H1N1 pandemic. BMJ 2009;339:b2840.

[37] Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza vaccine. MMWR MorbMortalWklyRep 2009;58(19):521-4.

[38] Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N Engl J Med 2009;361(20):1945-52.

[39] World Health O. New influenza A (H1N1) virus: global epidemiological situation. Weekly epidemiological record 2009;84(25):249-57.

[40] Greenbaum JA, Kotturi MF, Kim Y, Oseroff C, Vaughan K, Salimi N, et al. Pre-existing immunity against swine-origin H1N1 influenza viruses in the general human population. Proc Natl Acad Sci U S A 2009;106(48):20365-70.

[41] Itoh Y, Shinya K, Kiso M, Watanabe T, Sakoda Y, Hatta M, et al. In vitro and in vivo characterization of new swine-origin H1N1 influenza viruses. Nature 2009;460(7258):1021-5.

[42] World Health O. Strategic Advisory Group of Experts on Immunization - report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic, 7 July 2009. Weekly epidemiological record 2009;84(30):213-9.

[43] Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009;374(9688):451-8.

[44] Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California1. JAMA 2009;302(17):1896-902.

[45] World Health Organization (2009) Transcript of Virtual Press conference with Dr Keiji Fukuda, Assistant Director-General ad. Interim for Health Security and Environment 27 April 2009 Available:http://www.who.int/mediacentre/swineflu_presstranscript_2009_04_27.pdf. Accessed 24/08/2012.

[46] Nicoll A, Coulombier D. Europe's initial experience with pandemic (H1N1) 2009 - Mitigation and delaying policies and practices. Euro Surveill 2009;14(29).

[47] Department of Health website. (2007) Pandemic Flu – A national framework for responding to an influenza pandemic. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_080745.pdf. Accessed 24/08/2012.

[48] Health Protection Agency. ((2009)) Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the second wave. Available:http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1258560552857. Accessed 24/08/2012.

[49] UK. (2009) Swine Flu: UK Planning Assumptions. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_104843.pdf. Accessed 13/12/2012.

[50] European Medicines Agency. (2009) CHMP/BWP. EU recommendation for the emergent novel H1N1 influenza vaccine composition EMEA/CHMP/BWP/340831/2009/Rev 1. Available:http://www.emea.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500015392.pdf. Accessed 15/08/2012.

[51] Strategic Advisory Group of Experts on Immunization - report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic, 7 July 2009. Weekly epidemiological record 2009;84(30):213-9.

[52] Donaldson L. (2009) Further details about the H1N1 swine flu vaccination programme 2009-2010. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_104315.pdf. Accessed 27/04/2010.

[53] Mereckiene J, Cotter S, Weber JT, Nicoll A, D'Ancona F, Lopalco PL, et al. Influenza A(H1N1)pdm09 vaccination policies and coverage in Europe. Euro Surveill 2012;17(4).

[54] Dalton I. (2009) A (H1N1) swine flu influenza: phase two of the vaccination programme; children over 6 months and under 5 years. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_109825.pdf. Accessed 28/04/2010.

[55] European Medicines Agency. (2009) Guideline on the conduct of pharmacovigilance for vaccines for pre- and post-exposure prophylaxis against infectious diseases. Available:http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011272.pdf. Accessed 30/11/2012.

[56] European Medicines Agency. (2009) CHMP assessment report for Pandemrix (H1N1). EMEA/CHMP/619109/2009 Available:http://www.ema.europa.eu/humandocs/PDFs/EPAR/pandemrix/Pandemrix-H-832-PU-17-AR.pdf. Accessed 12/06/2010.

[57] Donaldson L. (2009) The H1N1 swine flu vaccination programme 2009-2010 Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_107190.pdf. Accessed 15/10/2009.

[58] The European Medicines Agency, The European Centre for Disease Prevention and Control, The Heads of Medicines Agencies. (2009) European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring. Available:http://www.emea.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500044933.pdf. Accessed 20/11/2009.

[59] Edwards IR, Olsson S, Lindquist M, Hugman B. Global Drug Surveillance: The WHO Programme for International Drug Monitoring. In: Strom BL, editor. Pharmacoepidemiology. Chichester: John Wiley & Sons, Ltd, 2007: 161-83.

[60] Chen RT, Davis RL, Rhodes PH. Special Methodological Issues in Pharmacoepidemiology Studies of Vaccine Safety. In: Strom BL, editor. Pharmacoepidemiology. Chichester: John Wiley & Sons, Ltd, 2007: 455-85.

[61] MHRA. Pandemic vaccines and antivirals: safety review. Drug Saftey Update;4(3: H1).

[62] Jones JK. Determining Causation from Case Reports. In: Strom BL, editor. Pharmacoepidemiology. Chichester: John Wiley & Sons, Ltd, 2007: 555-70.

[63] Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. Drug Saf 2006;29(5):385-96.

[64] Begaud B, Moride Y, Tubert-Bitter P, Chaslerie A, Haramburu F. False-positives in spontaneous reporting: should we worry about them? Br J Clin Pharmacol 1994;38(5):401-4.

[65] Banzhoff A, Haertel S, Praus M. Passive surveillance of adverse events of an MF59-adjuvanted H1N1v vaccine during the pandemic mass vaccinations. Hum Vaccin 2011;7(5):539-48.

[66] Black S, Eskola J, Siegrist CA, Halsey N, Macdonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet 2009;374(9707):2115-22.

[67] Dieleman J, Sturkenboom M, Hviid A, Kilpi T, Castot A, Storsaeter J, et al. (2009) Background rates of events of specific interest with respect to vaccinations. Eurovaccine 2009. Available:http://ecdc.europa.eu/en/activities/diseaseprogrammes/Eurovaccine/Documents/0912-eurovaccine-ID20-Dieleman-background-rates.pdf. Accessed 21/08/2012.

[68] VAESCO. About us. Available:http://vaesco.net/vaesco/about-us.html. Accessed 21/08/2012.

[69] Mereckiene J, Cotter S, Nicoll A, Levy-Bruhl D, Ferro A, Tridente G, et al. National seasonal influenza vaccination survey in Europe, 2008. Euro Surveill 2008;13(43).

[70] European Centre for Disease Prevention and Control. (2010) Conducting health communication activities on MMR vaccination. Stockholm: ECDC. Available:http://ecdc.europa.eu/en/publications/Publications/1008_TED_conducting_health_communication_activities_on_MMR_vaccination.pdf. Accessed 21/08/2012.

[71] Euopean Medicines Agency. (1997) CPMP Note for guidance on clincial safety data management: periodic safety update reports for marketed drugs. CPMP/ICH/288/95 Available:http://www.ema.europa.eu/pdfs/human/ich/028895en.pdf. Accessed 25/04/2011.

[72] European Medicines Agency. (2009) CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine. EMEA/359381/2009. Available:http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500051739.pdf. Accessed 21/08/2012.

[73] Mitchell AA. Studies of Drug-Induced Birth Defects. In: Strom BL, editor. Pharmacoepidemiology. Chichester: John Wiley & Sons, Ltd, 2007: 501-14.

[74] Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis 2008;8(1):44-52.

[75] Wyszynski DF. Pregnancy exposure registries: academic opportunities and industry responsibility. Birth Defects Res A Clin Mol Teratol 2009;85(1):93-101.

[76] Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barre syndrome. Drug Saf 2009;32(4):309-23.

[77] Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barre syndrome and the 1978-1979 influenza vaccine. N Engl J Med 1981;304(26):1557-61.

[78] Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981. Lack of an association with influenza vaccination. JAMA 1982;248(6):698-700.

[79] Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. AmJ Epidemiol 2009;169(3):382-8.

[80] Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N Engl J Med 1998;339(25):1797-802.

[81] Ang CW, Jacobs BC, Laman JD. The Guillain-Barre syndrome: a true case of molecular mimicry. Trends Immunol 2004;25(2):61-6.

[82] Petrovsky N, Aguilar JC. Vaccine adjuvants: current state and future trends. Immunol Cell Biol. 2004;82(5):488-96.

[83] Mereckiene J, Cotter S, D'Ancona F, Giambi C, Nicoll A, Levy-Bruhl D, et al. Differences in national influenza vaccination policies across the European Union, Norway and Iceland 2008-2009. Euro Surveill 2010;15(44).

[84] Ropero-Alvarez AM, Kurtis HJ, Danovaro-Holliday MC, Ruiz-Matus C, Andrus JK. Expansion of seasonal influenza vaccination in the Americas. BMC Public Health 2009;9:361.

[85] Fauci AS. Seasonal and pandemic influenza preparedness: science and countermeasures. J Infect Dis. 2006;1(194) Suppl 2:S73-6.

[86] Garoon JP, Duggan PS. Discourses of disease, discourses of disadvantage: a critical analysis of National Pandemic Influenza Preparedness Plans. Soc Sci Med. 2008;67(7):1133-42.

[87] European Centre for Disease Prevention and Control. The 2009 A(H1N1) pandemic in Europe. Stockholm: ECDC; 2010.

[88] Pandemic alert level 6: scientific criteria for an influenza pandemic fulfilled. Euro Surveill 2009;14(23):19237.

# 2. Aims and Objectives

During the summer of 2009, European regulatory authorities sought to identify and fund institutions and initiatives capable of addressing gaps in their respective influenza A(H1N1)pdm09 vaccine post-marketing surveillance strategies. To this end, the ECDC funded the VAESCO consortium to carry out two collaborative studies. The Pharmacoepidemiology unit at the University of Bath were invited by the VAESCO consortium to contribute UK General Practice Research Database (GPRD) data to these studies.

It is in this context that the aims and objectives of this PhD thesis were devised. The primary aims of the thesis were:

1. To contribute to the post marketing safety surveillance of the influenza A(H1N1)pdm09 vaccine using GPRD data.

2. To assess the performance of the GPRD as a vaccine safety surveillance tool.

3. To illustrate the potential of the VAESCO working model as a platform for collaborative vaccine safety studies.

We sought to achieve these aims by completing the objectives set out below:

a) To estimate the uptake of influenza A(H1N1)pdm09 vaccine and seasonal influenza vaccine by individuals in clinical risk groups in the UK and to identify demographic factors associated with vaccine uptake in this population.

b) To estimate the uptake of influenza A(H1N1)pdm09 vaccine by pregnant women in the UK and to identify demographic factors associated with vaccine uptake in this population.

c) To estimate the 10 year background incidence rate of autoimmune and neurological diseases earmarked by regulatory authorities for enhanced surveillance based on a priori safety concerns. To investigate variation in these rates across age categories, seasons, calendar years and countries.

d) To use a case control study to estimate whether the risk of Guillain-Barré syndrome in the 6 weeks following influenza A(H1N1)pdm09 vaccination was comparable to that among individuals who did not receive the vaccine.

e) To use a self-controlled case series study to estimate whether the incidence of Guillain-Barré syndrome in the 6 week post influenza A(H1N1)pdm09 vaccination risk period was different to the incidence in other time periods.

f) To use a cohort study to estimate whether the hazard of first, second or third trimester foetal death in pregnant women vaccinated against influenza A(H1N1)pdm09 was greater than that among unvaccinated pregnant women.

Objectives c, d and e were addressed as part of collaborative European vaccine safety studies.

# 3. Materials and Methods

In this chapter I introduce the GPRD, describe its strengths and limitations with regard to the specific study objectives and briefly outline the working models implemented in both the independent and collaborative studies.

## 3.1 The General Practice Research Database (GPRD)

*UK General Practice*

In the UK, general practitioners (GPs) are commonly referred to as the "gatekeepers" of healthcare: since the early 20$^{th}$ century, in addition to handling encounters in general practice, they have also been responsible for referring patients for all non-urgent further care. Diagnoses, procedures and treatments administered outside general practice are routinely reported back to the GP and recorded in a patient's record.

Patient information is recorded electronically in GP practices, primarily using a set of clinical and administrative codes called Read codes. There are currently over 100,000 Read codes, allowing a GP to record detailed diagnostic, procedural, administrative and lifestyle information. Prescriptions are issued electronically, with coded details of the prescribed product automatically transcribed into the patient's record. In addition to these coded data, the recording of unstructured textual information in association with a Read or prescription code is possible. This information, commonly referred to as 'free text', generally contains elaborations on the information in the coded record. Documents detailing encounters outside the GP practice, such as hospital/specialist letters or discharge summaries, may also be kept in paper or electronic format, with relevant data entered under in a patient's record using appropriate Read codes.

*GPRD*

The GPRD is a database containing the collated medical records of patients registered with GPs in the UK. The GPRD collects anonymised data from all consenting GP practices using Vision computer systems [1]. In an effort to standardise data entry, and make the routinely collected clinical data more useful in research, contributing practices are asked to follow a set of data recording guidelines which advise how and when data should be recorded. As a result, data contained in the database includes demographic details, diagnoses and symptoms that lead to hospital admissions, referrals to specialists or changes in prescriptions, lab tests, prescriptions issued by

the GP, pregnancies, contraception, immunisations, hospital discharge summaries, hospital clinic summaries, specialist letters and deaths [2]. The recording guidelines also suggest how data should be recorded in the free text. In an effort to further promote consistent recording of key lifestyle and procedural information a number of structured data entry areas are available in Vision systems [1]. These data entry areas support the systematic recording of information on a range of indicators such as smoking status, alcohol consumption, immunisations and test results.

*Data quality*

In theory, the GP record should contain a complete record of a patient's medical history. However, in practice, the level of information recorded in the GP record will depend on factors such as the administrative quality of the primary and secondary care providers and the recording practices of the individual entering the data. As a result the quality of all data submitted to the GPRD by a practice is monitored by checking the continuity of reporting and by comparing the mortality rates in submitted data against those expected for that practice. Each practice is assigned an 'up-to-standard' (UTS) date reflecting the date from which the database provider considered data contributed by a practice to have met these minimum quality criteria and to have reached a standard suitable for research purposes. At a patient level, quality checks ensure registration, birth, death, age and sex information recorded in a patient's record meet a number of basic criteria. Patients not meeting these criteria are flagged [1]. The age and sex distribution of the GPRD population is representative of the UK population as a whole, however the Welsh population and larger practices are both overrepresented (Appendix 1).

Despite these checks, researchers using GPRD data are given access to all coded data for all patients; however ideally they should use only patient data recorded in "acceptable" periods after their practice's UTS date. In certain situations, such as when investigating disease prevalence or the incidence of a very rare condition, invalid patients and non-UTS data might be used with caution.

Even when working with data from valid, UTS records, consideration must be given to the impact coding errors or peculiar coding practices might have on the data. Such errors can range from the random incorrect entry of a single piece of information to the continued systematic miscoding of a condition by a particular individual or practice. While such problems may not affect routine clinical practice greatly, in research they can result in misclassification. Consideration of such issues is study

specific and will therefore be considered later, in the context of the data used in this thesis.

*Data Protection and ethics*

Collection, handling and distribution of GPRD data has been designed to conform with current data protection regulations. Bespoke data collection software is used to retrieve the full electronic medical record of every patient registered at a participating practice. Anonymised identifiers are assigned to all practices and patients by the data collection software. Strong identifiers (NHS numbers, addresses, telephone numbers, etc.) are removed from the dataset and staff identifiers are encrypted. Patients are provided with information on the nature of their practices' participation in the GPRD and can choose to opt out, in which case their record will be deleted. This dataset is sent to the GPRD team at the MHRA using a tracked postal service.

Upon receiving a practice dataset at the MHRA the coded portion of the data is separated from the free text and compiled into several tables. The quality of the coded data is then checked and made available to named users; in order to become a named user a researcher must attend a training day at the GPRD. Free text is only made available to researchers who commission its manual review and anonymisation.

The GPRD has a single Multi-Centre Ethics approval for all observational studies using GPRD data (Trent MREC, ref: 05/MRE04/87). As a result any GPRD study that does not require direct patient involvement can be carried out following protocol approval by an Independent Scientific Advisory Committee (ISAC) [1]. ISAC comprises individuals with a wide range of epidemiological, statistical and subject matter expertise. ISAC may request study specific MREC approval be sought if a protocol proposes an ethical issue of particular concern. All of the work presented in this thesis was covered under the MREC approval

*Data Access*

Upon receiving ISAC approval and paying all relevant licence fees, GPRD data can be accessed in a number of ways. The most comprehensive option is to obtain a copy of the entire GPRD dataset and host it in-house: this offers the greatest amount of independence in data checking, manipulation and extraction. A second option is to request a study specific cohort from the GPRD research team: this offers relatively little independence, leaving the majority of data extraction to the GPRD research team. A third, and relatively recent option, is to access GPRD data using online data

extraction tools. This offers researchers the freedom to define, extract and manage their own data while removing much of the burden involved in managing an entire flat file dataset. This option also offers the advantage of providing data that is updated on a monthly basis.

These three options offer access to the coded data only; free text data associated with these records cannot be routinely made available as it may contain identifiable information such as patient, doctor or hospital names. Researchers can request anonymised free text information associated with a patient or a defined set of codes at a cost of 5 pence per word. More recently, it has become possible to request a search of the free text for certain key words of interest and obtain the free text for any entry containing at least one of the key words. Given the data quality issues described above, information stored in the free text can prove vital in confirming the occurrence of an event. However, while a large amount of information is recorded in the free text, important information such as hospital letters and discharge summaries are sometimes not recorded therefore further verification might be required.

Further verification can be obtained by requesting additional data from GPs or by linking to other data sources. At the request of researchers, the GPRD team will send patient specific, ISAC-approved questionnaires to a practice or ask a practice for any paper medical records they might have for a patient. Response rates for such methods are high [3, 4] but the costs involved (£60-£110 per questionnaire) can also be prohibitively high. The GPRD has data linkages with a number of other healthcare data sources such as Hospital Episode Statistics (HES), disease registries and Office of National Statistics (ONS) mortality data. These linkages can be used to assess whether a large amount of secondary care information was not received/recorded by the GP. The cost of linkage is dependent on the data source being linked to, and the size of the study population. Data linkage is only available for approximately 65% of English practices [1]. The number of GPRD data linkages available is currently increasing under a UK wide initiative to expand the availability of routinely collected healthcare data for research. Under this initiative, access to the GPRD and the various other data sources will be obtained through the newly created Clinical Practice Research Datalink (CPRD). In addition to increasing the number of linkages, the CPRD will also attempt to increase the study population by recruiting practices using non-Vision computer systems [1]. As all studies in this thesis were carried out before the rebranding of the data source I refer to it as the GPRD throughout the thesis.

As of June 2010, the GPRD contained data from 589 GP practices, or 5.8% of UK practices. Historic data were available on 11.7 million patients while over 5 million patients, or ~8.4% of the UK population, were registered and contributing data with up-to-standard (UTS) practices (GPRD August 2010 release note).

*Immunisations*

Vaccine utilisation and safety studies require accurate recording of immunisation status [5]. In the UK, the seasonal influenza vaccination program is primarily administered in primary care.

Prior to the pandemic vaccination campaign GPs regularly recorded seasonal influenza vaccinations administered in GP practices [6]. However, to my knowledge the quality of recording of vaccination status in electronic health records has not been validated.
In advance of the pandemic vaccination campaign a set of Read codes were created to allow GPs to record specifically influenza A(H1N1)pdm09 vaccinations (as opposed to seasonal). The guidance published alongside these codes urged GPs to record all influenza A(H1N1)pdm09 vaccinations using these pandemic vaccination specific Read codes [7].

Vision computer systems allowed seasonal and pandemic influenza immunisations to be recorded by the GP in three ways: as an immunisation procedure, as a clinical procedure or as a prescription. Vaccinations recorded as an immunisation procedure were entered in an immunisation-specific data entry area which prompted GPs to enter a Read code as well as other information such as whether the vaccine was accepted or refused. GPs entering vaccination information as a clinical procedure entered a Read code only and those entering a prescription entered the product details only, therefore for the purpose of this thesis all vaccinations recorded as clinical procedures and prescriptions were assumed to have been successful vaccination encounters while those immunisation procedures flagged as "refused" were excluded.

Owing to the two dose vaccination schedule recommended in some children and immunosuppressed adults, individuals might have two influenza A(H1N1)pdm09 vaccination records. In other cases individuals might have two or more records due to miscoding or use of a code in the incorrect way. In such cases the first and second vaccinations recorded in an individual's record were classified as their first and second vaccination; all further vaccinations were assumed to relate to the earlier vaccinations

and were ignored. The potential for misclassification of vaccination status due to vaccination in non-GP settings and incorrect coding was considered in the interpretation of all study findings.

*Autoimmune and neurological conditions*

A number of the studies in this thesis involved determining the incidence of an autoimmune or neurological disease. Identifying incident events on the GPRD required careful consideration of how such events present to healthcare and how they are subsequently handled. First presentation with most neurological and autoimmune conditions is to the GP, who will most likely make a working diagnosis based on the reported and observed symptoms and refer the patient on to a specialist for confirmation of the diagnosis. The specialist's diagnosis should then be sent to the GP and recorded in the patient's record; this should be the case even where the first presentation was not in general practice. The entire diagnostic process, from first presentation to confirmation of diagnosis, may be recorded in a number of different ways depending on the final diagnosis, the quality of secondary care administration and the recording practices of the person entering the data. A code for the disease of interest could be entered in the GP's records at any point in this process. The situation is further complicated by the presence of non-specific Read codes and by the possibility that a code could be entered at a follow-up encounter, days, months or even years after the diagnosis.

Given the potential for differential recording of diagnosis dates, determining exact and consistent index dates required further work which could include:

- Manual review of each patient's record to determine the index date based on the sequence of specific and supporting codes in a patient's record.
- Creation of an automated algorithm to determine the index date based on the sequence of specific and supporting codes in a patient's record.
- Request of free text information for all patients/relevant codes
- Communication with GPs of all patients with a relevant code
- Request of the paper medical record of all relevant patients
- Linkage with HES/registry data

Each of these options would provide different levels of certainty with associated costs and time lags. The decision as to which method(s) to use therefore depended on the study question, study deadline and study budget.

*Pregnancies*

Investigation of the potential risks associated with vaccine exposure in pregnancy using the GPRD required the identification of pregnancies. A number of research groups have created algorithms to identify pregnancies and determine their outcome, end date and start date on the GPRD [8, 9]; our research group at the University of Bath have created a similar algorithm [10, 11]. This algorithm was governed by a set of rules which classify pregnancies based on the type, timing and sequence of codes observed in a woman's record. Briefly, this algorithm involved the following basic steps: Read codes were classified according to the level of evidence they provided about pregnancy occurrence, pregnancy outcome and gestational age. Pregnancies were then identified, based on the presence of codes supporting pregnancy occurrence and the outcome of each pregnancy was determined using any available outcome codes. The end dates of deliveries were set to the earliest pregnancy outcome in a series of outcome codes and the end dates of terminations and losses were set to the latest pregnancy outcome in a series of outcome codes. Where available, the estimated date of delivery and last menstrual period records were used to determine pregnancy start dates, where these were not available other gestational age related records were used (e.g. 6/12/24 week exam). If none of the above records were available the pregnancy start date was set to a default offset from the end date: 40 weeks for deliveries and 10 weeks for losses/terminations. Where sufficient evidence of pregnancy occurrence existed but no outcome code was identified, evidence of postnatal care was used to infer pregnancy lengths and outcomes.

Work has been carried out to refine this algorithm based on increasing knowledge of healthcare encounters in pregnancy and GP recording practices. For the purpose of this thesis, deliveries that had been flagged as antenatal deaths or potential stillbirths were all manually reviewed to assess the accuracy of gestational ages set by the algorithm.

When considering drug safety in pregnancy a number of outcomes can be studied, however the nature of GPRD data limits the number of outcomes available. Congenital malformations are of concern, particularly given the wide publicity that has surrounded associations between malformations and drugs such as thalidomide and valproate. It has been shown that the GPRD is a valid source for studying congenital malformations [11], however given the very low incidence of most malformations, obtaining sufficient sample sizes to provide robust risk estimates is difficult for all but the most common malformations. Spontaneous abortion and stillbirth are relatively

common, severe pregnancy complications which pregnant women often link with exposures based on temporality alone. This is particularly problematic during mass vaccination campaigns as hundreds of thousands of women might receive vaccination while at high background risk for these outcomes [12]. Drug exposures may alter the risk of infants being born prematurely or small for their gestational age however these outcomes are not recorded accurately enough in the GPRD to allow valid investigation of their risk factors.

*Covariates*

A range of covariates are routinely collected by GPs and recorded in the GPRD, including age, sex and year of birth (month of birth for those aged <16), a practice identifier allowed the identification of individuals registered with the same practice and a family identifier identified individuals who live together.

Deprivation is recorded in the GPRD using either Townsend scores or Indices of Multiple Deprivation (IMD). These are both indicators of deprivation that are assigned to geographic areas. Townsend scores are calculated using household level data from the 2001 census. In total four indicators are used: percentage unemployment, percentage of overcrowded households, percentage no car/vans ownership and percentage of non-home owners. In the Townsend score each factor carries the same weighting. IMD scores are calculated using seven domains of deprivation. Each domain covers a different aspect of deprivation (eg. income deprivation, employment deprivation, crime, living environment deprivation etc.) and within each domain several indicators are used to assign a score. Indicator data is collected from a range of administrative sources with only three of the 37 different indictors originating from census data. IMD domains are weighted to allow a greater influence of the more important domains on the overall score. The GPRD team assign deprivation scores to individual patients based on the deprivation score for the geographic area in which they reside, these areas have an average population of 1,500 residents. Patients can also be categorized into quintiles of deprivation based on where their area score ranks amongst the nationwide scores. Recording of both of these deprivation indicators is incomplete in the GPRD therefore in order to obtain a patient level deprivation indicator for the maximum number of possible patients we used Townsend quintile and, where this was not available, we used IMD quintile instead. Increasing deprivation quintile indicates increasing deprivation therefore the patients in deprivation quintile 5 are the most deprived and those in quintile 1 the least deprived.

IMD scores, but not Townsend scores, are also available at a practice level in the GPRD (ie. based on the area in which the practice is located); we therefore obtained the IMD quintile for the practice at which each patient was registered and included this in our model. Other potential practice level predictors investigated included practice location and practice size.

At the beginning of the vaccination campaign a list of diagnostic (Read) and prescription (Multilex) codes were compiled by the primary care information service (PRIMIS+) for use in the UK national influenza vaccine uptake survey [7]. We have used the same code list to identify this sub-population in the studies included in this thesis. A GP or patient may decide whether the patient is in a clinical risk group based on factors other than the presence of one of these Read codes in their record. Where this decision differs from that determined by the Read code there will be some misclassification of clinical risk group status.

Lifestyle factors such as smoking status, alcohol consumption and BMI are recorded for many patients in the GPRD however these measures are not always recorded in a standardised fashion. Pre-existing, in-house algorithms were therefore used to categorise patients according to the available measurements.

Identification of individuals with influenza infection is difficult in most retrospective data sources as infected individuals do not always seek medical attention and, where they do, the resultant clinical diagnosis is usually of acute upper respiratory tract infection (URTI) or influenza-like-illness (ILI). Both of these diagnoses have been found to have a poor predictive value for true influenza infection. Lab confirmation of influenza infection is not common. As a result while ILI and URTI were included as a time varying covariate in some studies in this thesis, their impact must be interpreted with caution.

As GPRD data is collected routinely in clinical practice a number of other potentially relevant covariates are not recorded, including genetic factors. Information on a GP's perception of a patient's health, of the safety of the influenza A(H1N1)pdm09 vaccine and of the risk posed by influenza A(H1N1)pdm09 infection is also not available. The potential impact of unmeasured confounding will therefore be considered in the interpretation of the results.

For all categorical variables with missing data a separate "missing" category was created and included in the models. The results in the missing category were carefully inspected to identify any potential biases introduced.

## 3.3 Working model

While a number of the studies contributing to this PhD were carried out independently within the University of Bath Pharmacoepidemiology unit, due to the rare nature of many vaccine safety outcomes, some were carried out as part of larger, collaborative, pan-European studies.

*University of Bath Pharmacoepidemiology unit*

The University of Bath pharmacoepidemiology unit is based in the Pharmacy Practice Research Group within the Department of Pharmacy and Pharmacology at the University of Bath. The unit consists of academic and research staff as well as post-graduate research students. The unit works primarily with data from the UK GPRD with epidemiological, statistical and database management expertise all available within the group.

All studies carried out within the unit follow standard operating procedures. These begin with detailed study feasibility, design and planning discussions. Based on these discussions study protocols are drafted. Protocols detail the creation of code lists and algorithms to identify exposures, outcomes and covariates, data extraction procedures and statistical analyses. Where necessary, manual review of patient records is pursued using specially developed electronic patient record visualisation software and additional information is requested from the GPRD for verification where feasible.

For the duration of this PhD the unit held a full GPRD licence allowing it to both host GPRD datasets locally and access GPRD GOLD data online. The data used in this PhD is from either the December 2010 version of the GPRD or online GPRD data. The December 2010 GPRD data was hosted locally on an Oracle database and was accessed primarily using SQL Developer and, to a lesser extent, MS Access. Once downloaded from the GPRD servers, all online GPRD data was managed in a similar manner to flat file data. All in-house statistical analyses were carried out using STATA10/11/12

*VAESCO*

As the primary UK partner in the VAESCO consortium, the pharmacoepidemiology unit at the University of Bath was responsible for contributing UK GPRD data to the ECDC funded VAESCO studies.

While each of the studies differed slightly, a similar collaborative working model was used across studies. This model began with study design discussions focusing on the study question, the strengths and limitations of potential study designs, the possibility of bias and confounding and initial comparisons of the type of information available in the different data sources. Following agreement on the study design to be used for a particular study a protocol was drafted which was edited and discussed by all partners until a final protocol was agreed upon. Detailed comparisons of the information to be used in each data source were carried out in an effort to produce homogenous exposure, outcome and covariate measures. Based on these comparisons, final datasets were defined and extracted. Comparison and combination of data from different sources was facilitated by transformation to a standard format using Jerboa (Erasmus MC, Rotterdam). Jerboa is a data processing program developed specifically for use in collaborative drug and vaccine safety studies. It is written in Java so that it can be freely installed and run across settings using different data processing or statistical software. All data code was cross validated in SAS. Where analyses required that person level data be shared, Jerboa enabled personal identifiers and exact event dates to be removed to ensure complete anonymisation. Study management was the responsibility of the Brighton Collaboration and data management and statistical analyses were coordinated by Erasmus Medical Centre, Rotterdam.

While this collaborative working model primarily sought to increase the homogeny of data contributed from different sources, each partner was nonetheless considered the "expert" on their own data source and was therefore granted a degree of autonomy in identifying, extracting/collecting and describing their own data. As a result in each VAESCO study I was responsible for:

- Providing general, but primarily GPRD-focused, input to study design discussions.
- Drafting and submitting ISAC protocols to obtain scientific and ethical approval to conduct the study in the GPRD (see Appendix 5 for VAESCO ISAC protocols).
- Identifying Read code lists for identification of potential cases in the GPRD

- Deciding on GPRD case verification methods based on the agreed study aims, timelines and budget
- Developing SQL programs to extract case information from the GPRD
- Developing data entry forms in MS Access to allow the independent, side-by-side review of coded and free text data on cases and the extraction of VAESCO relevant data in a pre-specified, Jerboa compatible format.
- Reviewing and extracting case information using these data entry forms
- Comparing the results of my case review with those of another reviewer (Corinne de Vries) and resolving any discrepancies.
- Running the Jerboa analysis program and uploading encrypted, compressed data to Erasmus MC.
- Reviewing proposed statistical analysis plans
- Interpreting the results of statistical analyses
- Reviewing draft manuscripts

Additionally, in the two GBS studies I was also responsible for:

- Developing SQL programs to match cases to controls
- Developing data entry forms in MS Access to allow the independent, side-by-side review of coded and free text data on exposures and covariates and the extraction of VAESCO relevant data in a pre-specified, Jerboa compatible format.
- Reviewing and extracting exposure and covariate information using these data entry forms.
- Comparing the results of my exposure and covariate review with those of another reviewer (Corinne de Vries) and resolving any discrepancies.

[1] 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.

[2] Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf 2004;27(12):871-81.

[3] Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69(1):4-14.

[4] Gelfand JM, Margolis DJ, Dattani H. The UK General Practice Research Database. In: Strom BL, editor. Pharmacoepidemiology. Chichester: John Wiley & Sons, Ltd, 2007: 337-46.

[5] Chen RT, Davis RL, Rhodes PH. Special Methodological Issues in Pharmacoepidemiology Studies of Vaccine Safety. In: Strom BL, editor. Pharmacoepidemiology. Chichester: John Wiley & Sons, Ltd, 2007: 455-85.

[6] Department of Health. Begum F, Pebody R. (2009) Influenza vaccine uptake among the 65 years and over and under 65 years at risk in England, Winter season 2008-09. Available:http://www.immunisation.nhs.uk/publications/FluVaccineUptake_Winter0809.pdf. Accessed 02/12/2011.

[7] Department of Health. PRIMIS+. (2010) Influenza A (H1N1)v Uptake Survey 2009/10, ImmForm, Read Codes Version 1.0. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_107347.pdf. Accessed 15/08/2012.

[8] Hardy JR, Holford TR, Hall GC, Bracken MB. Strategies for identifying pregnancies in the automated medical records of the General Practice Research Database. Pharmacoepidemiol Drug Saf 2004;13(11):749-59.

[9] Devine S, West S, Andrews E, Tennis P, Hammad TA, Eaton S, et al. The identification of pregnancies within the general practice research database. Pharmacoepidemiol Drug Saf 2010;19(1):45-50.

[10] Snowball JM, de Vries CS. Determination of pregnancy on the General Practice Research Database. Pharmacoepidemiol Drug Saf 2007;16(S1):S118.

[11] Charlton RA. The General Practice Research database as an alternative to registers for studying drug safety in pregnancy: anticonvulsants as a case study. Bath: University of Bath; 2012.

[12] Black S, Eskola J, Siegrist CA, Halsey N, Macdonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet 2009;374(9707):2115-22.

# 4. Results

## 4.1 Introductory statement

In this section I present manuscripts describing the studies carried out as part of this PhD. Preceding this I would like to highlight a number of points.

- The VAESCO background incidence rate study investigated the rate of anaphylaxis, autoimmune hepatitis, Bell's palsy, generalised convulsions, demyelinating diseases, encephalitis, GBS, optic neuritis, transverse myelitis, multiple sclerosis and thrombocytopenia. In this section I present a manuscript describing the rate of the event I am leading the publication of, facial nerve palsy. The methods described in the manuscript can be considered largely representative of those used in estimating the rate for each condition.

- In an effort to allow the reader to clearly distinguish the work I have carried out myself from that primarily carried out by collaborators I have summarised my contribution to each manuscript in table 4.1.

**Table 4.1** Personal contribution to manuscripts (L = Lead, C = Contributor)

| Study | Study design | ISAC approval | GPRD data extraction | Statistical analysis | Discussion of results | Reporting of results |
|---|---|---|---|---|---|---|
| **Uptake (risk groups)** | L | L | L | L | L | L |
| **Uptake (pregnancy)** | L | L | L | L | L | L |
| **Background rates (facial palsy)** | C | L | L | L | C | L |
| **GBS (Case control)** | C | L | L | C | C | C |
| **GBS (SCCS)** | C | L | L | C | C | C |
| **Pregnancy (Foetal death)** | L | L | L | L | L | L |

- The work presented in this section is based on edited versions of both published and unpublished manuscripts. All of the unpublished manuscripts are currently under review for publication in international journals (Table 4.2).

**Table 4.2** Publication status of manuscripts

| **Study** | **Journal** | **Status** |
|---|---|---|
| **Facial nerve palsy background rates** | *Vaccine* | Under internal review |
| **Uptake (clinical risk groups)** | *Vaccine* | Published |
| **Uptake (pregnancy)** | *Human vaccines and Immunother.* | Published |
| **GBS CC** | *BMJ* | Published |
| **GBS SCCS** | *PLoS ONE* | Published |
| **Foetal loss** | *PLoS ONE* | Published |

- As each section was written as a stand-alone manuscript there may be some overlap with material presented in the introduction and methods sections.

- In the immediate aftermath of the pandemic vaccination campaign a safety signal linking influenza A(H1N1)pdm09 vaccination with narcolepsy emerged. We contributed GPRD data to a VAESCO study investigating this signal. However as this study was not a pre-specified objective of this thesis I do not present it among the results.

## 4.2 Factors associated with uptake of seasonal and pandemic influenza vaccine among clinical risk groups in the UK: an analysis using the General Practice Research Database

**The work presented in this section is based on work published in:**

*Sammon, C. J., McGrogan, A., Snowball, J. and De Vries, C. Factors associated with uptake of seasonal and pandemic influenza vaccine among clinical risk groups in the UK: an analysis using the General Practice Research Database. Vaccine. 2012;30(14):2483-9*

**The version presented herein has been edited for inclusion in this thesis therefore the views expressed may not represent those of authors who collaborated on the published manuscript.**

| | |
|---|---|
| Word Count (Abstract): | 296 |
| Word Count (Full text): | 2,882 |
| Number of tables: | 6 |
| Number of figures: | 1 |

**Abstract**

**Background:** Influenza vaccine uptake rates are low compared with uptake rates of many other vaccines. It is unclear how this differs between risk groups in the population and between pandemic and non-pandemic influenza vaccines.

**Aim:** This study sought to estimate uptake rates of pandemic and seasonal influenza vaccines among clinical risk groups in the UK during the 2009/2010 influenza season and to identify predictors of vaccine uptake in this cohort.

**Methods:** Uptake rates were calculated using data from the UK General Practice Research Database (GPRD). Predictors of vaccination were identified using a modified Poisson regression with robust standard error estimates.

**Results:** Uptake of pandemic influenza vaccine in clinical risk groups was 40.3% and uptake of seasonal influenza vaccine was 61.3%. Factors found to be predictive of seasonal and pandemic influenza vaccination included age and the total number of underlying health conditions an individual had. At risk individuals in those age groups in which universal vaccination of the general population was recommended were more likely to have been vaccinated than individuals in age groups in which only clinical risk groups were recommended for vaccination; hence children in clinical risk groups were more likely to receive pandemic than seasonal influenza vaccine. In older people, having a history of Guillain Barré syndrome was associated with a reduced likelihood of receipt of both seasonal ($IRR_{adj}$ 0.83, $CI_{95}$ 0.77-0.90) and pandemic influenza vaccines ($IRR_{adj}$ 0.82, $CI_{95}$ 0.73-0.92).

**Discussion:** Uptake of pandemic influenza vaccine was lower than that of seasonal influenza vaccine among those at a clinically high risk of influenza related morbidity. This suggests that vaccination strategies may need to be altered during future pandemics. Recommending universal vaccination within age categories in which there is a large proportion of high risk individuals could be considered as this may result in higher uptake among clinical risk groups.

## Introduction

Influenza is an acute respiratory disease that commonly occurs following infection with influenza viruses. In many individuals the disease is self-limiting with patients experiencing the classic symptoms of influenza (such as fever, sore throat and cough) followed by recovery within one to two weeks. However, in some individuals infection can result in the development of more serious complications such as pneumonia, respiratory failure and death. Individuals with the following underlying health conditions are known to be at a particularly high risk of suffering from these more serious symptoms [1;2]: asthma, chronic obstructive pulmonary disease (COPD), chronic heart disease, chronic kidney disease, diabetes, chronic liver disease, stroke/transient ischaemic attack, central nervous system degeneration, and immunosuppression. These health conditions are therefore considered 'clinical risk groups' for seasonal influenza; individuals in these groups are recommended for vaccination during annual influenza immunisation programs in countries throughout the world [3-8].

In the early stages of the 2009/10 H1N1 pandemic, epidemiological evidence suggested that individuals in seasonal influenza clinical risk groups were also among those at the highest risk of complications following H1N1 infection [9]. This led a number of public health organisations, including the World Health Organisation, to recommend that they be one of the groups prioritised for vaccination in mass H1N1 immunisation campaigns [9-11]. Consequently, in many countries, including the UK, all individuals in seasonal influenza clinical risk groups were recommended to receive both seasonal influenza vaccine (SIV) and pandemic influenza vaccine (PIV) during the 2009/10 influenza season. In addition to those in clinical risk groups, all individuals aged greater than 65 were recommended to receive SIV [49] whereas all those aged 6 months up to 5 years old were recommended to receive PIV [50]. Pregnant women were also recommended to receive PIV [51].

High vaccination coverage is vital to the success of any vaccination campaign. Annual SIV coverage varies widely across Europe with the majority of countries reporting uptake rates of less than 50% among clinical risk groups [12]. Uptake rates have been shown to vary by a range of factors such as: age [13-18], sex [15;17-21], chronic illness [20;21], socioeconomic factors [15;16;18;20;22] and ethnicity [20;21;23;24]. In the UK, uptake rates among those in clinical risk groups aged <65 years have ranged from 40% to 48% over the last 5 years [13]. Surveys conducted during the 2009/10 H1N1 pandemic revealed that in many countries there was a widespread

public perception that the pandemic was not serious or that PIV was not safe [25]. Reporting of associations between pandemic influenza vaccination and the neurological disorder Gullain Barré syndrome (GBS) in the mainstream media [52, 53] may have contributed to the perception that PIV was not safe, particularly among those with a history of the condition. Such perceptions may have decreased PIV uptake substantially, and indeed coverage data from the UK and the US suggest that while uptake of SIV did not change in 2009/10, it was considerably higher than that of PIV [14;26-28]. In this study we have estimated uptake rates and factors predictive of uptake of both PIV and SIV among clinical risk groups in UK general practice during the 2009/10 influenza season.

**Materials and methods**

This study was carried out using the UK General Practice Research Database (GPRD). The GPRD is a primary care database containing the anonymised records of ~8.4% of the UK population. Patient data that is routinely available in the database includes demographic details, diagnoses and symptoms leading to hospital admissions, referrals to specialists, laboratory tests, prescriptions issued by the GP, pregnancies, contraception, immunisations, hospital discharge summaries, hospital clinic summaries and deaths [29]. The GPRD operates a continuous quality control procedure which requires that all data submitted by practices be considered of a standard sufficient for research purposes (up-to-standard) [30]. As of August 2010 the GPRD contained data from 589 practices with up-to-standard data.

The study population consisted of all patients registered with a practice contributing to the GPRD who, at the beginning of the UK H1N1 vaccination campaign, had an underlying health condition that placed them in a 'clinical risk group'[1]. We identified all such patients using the list of diagnostic (Read) and prescription (Multilex) codes compiled by the primary care information service (PRIMIS+) for use in the UK national influenza vaccine uptake survey [31]. People who were not in a clinical risk group, but who were recommended for vaccination solely because of their age were not included in the study population.

Any SIVs and PIVs administered between 31/08/2009 and 21/06/2010 were identified using either Read or Multilex codes [31]. Where patients had more than one

[1] The underlying health conditions which place individuals in a 'clinical risk group' are: asthma, chronic obstructive pulmonary disease (COPD), chronic heart disease, chronic kidney disease, diabetes, chronic liver disease, stroke/transient ischaemic attack, central nervous system degeneration, and immunosuppression

vaccination event coded during the study period we assumed the first entry to be their date of vaccination.

Patient level factors that were investigated as potential predictors of vaccination included age, sex, BMI, alcohol consumption, smoking status, history of GBS and the total number of underlying health conditions a patient had. Practice level predictors investigated included geographic location of a practice at a national level and practice size, which was determined by categorizing practices according to their patient list size.

Deprivation was investigated at both patient and practice level. Patient level deprivation was estimated using the Townsend score [32] of patients' area of residence, or, where this was not available, the area indices of multiple deprivation (IMD) score [33]. Practice deprivation was estimated using the IMD score of a practice's area.

Bivariate analyses were carried out to identify the variables suitable for inclusion in the multivariate model. Any variable found to be predictive of either SIV or PIV uptake at a significance level of $p<0.2$ was considered for inclusion in both multivariate models. Where a variable did not reach this level of significance in the bivariate analysis the decision as to whether it was suitable for inclusion in our multivariate model was made based on the perceived clinical relevance of that variable. A modified Poisson regression using robust standard error estimates to account for clustering by practice [34] was then carried out using all independent variables that remained following the bivariate analyses stage. From this we estimated the incidence rate ratios (IRR) of vaccination and the associated 95% confidence intervals ($CI_{95}$). All analyses were carried out twice, firstly using receipt of PIV as the dependant variable and secondly using receipt of SIV as the dependant variable. Variables were included in both the PIV and SIV models if deemed to be significant in one. Interaction terms and stratified models were used to investigate interaction between predictors of vaccination. All analyses were carried out using STATA10.

***Results***

A total of 708,609 patients were included in our study population. Population characteristics are given in table 4.3 and table 4.4. The overall PIV uptake rate was 40.3% and the SIV uptake rate was 61.3%. Of the study population, 65.3% had a record of vaccination with at least one of the two influenza vaccines. 36.3% of these

had a record of vaccination against both PIV and SIV, while 4.0% were vaccinated with PIV-only and 25.0% with SIV-only. These exclusive rates varied widely across age groups (Figure 4.1). Children in risk groups who were aged from 6 months up to 5 years old were the only group in which the majority of individuals vaccinated received only PIV.

**Table 4.3** Distribution of study variables and results of bivariate and main multivariate analyses investigating predictors of influenza A(H1N1)pdm09 vaccine uptake in clinical risk groups

| | | Pandemic influenza vaccine | | | | |
|---|---|---|---|---|---|---|
| | % | (n/n)[a] | Unadj. IRR | (95% CI) | Adj. IRR | (95% CI) |
| **Sex** | | | | | | |
| Male | 42.2 | (146,617/347,322) | ref. | - | ref. | |
| Female | 38.4 | (138,875/361,287) | 0.91 | (0.90,0.92) | 0.94 | (0.93,0.94) |
| **Age** | | | | | | |
| 0.5 – 4 | 50.2 | (2,758/5,497) | 1.13 | (1.09,1.17) | 1.27 | (1.21,1.34) |
| 5 – 19 | 37.0 | (17,725/47,944) | 0.83 | (0.81,0.85) | 0.91 | (0.88,0.94) |
| 20 – 39 | 31.6 | (21,864/69,136) | 0.71 | (0.70,0.73) | 0.76 | (0.74,0.77) |
| 40 – 64 | 44.4 | (103,136/232,111) | ref. | - | ref. | |
| 65 – 79 | 43.5 | (97,920/225,143) | 0.98 | (0.95,1.01) | 0.92 | (0.89,0.95) |
| 80 – 110 | 32.7 | (42,089/128,778) | 0.74 | (0.71,0.77) | 0.70 | (0.67,0.73) |
| **Patient deprivation quintile[b]** | | | | | | |
| 1 (least deprived) | 41.8 | (31,402/75,118) | 1.04 | (0.99,1.09) | 1.03 | (0.98,1.08) |
| 2 | 42.0 | (25,661/61,168) | 1.04 | (1.01,1.08) | 1.04 | (1.01,1.08) |
| 3 | 40.2 | (23,124/57,533) | ref. | - | ref. | |
| 4 | 36.7 | (18,423/50,211) | 0.91 | (0.88,0.95) | 0.92 | (0.89,0.96) |
| 5 (most deprived) | 34.7 | (12,654/36,440) | 0.86 | (0.82,0.91) | 0.88 | (0.83,0.93) |
| Unknown | 40.7 | (174,228/428,139) | 1.01 | (0.94,1.10) | 0.90 | (0.82,0.98) |
| **BMI** | | | | | | |
| <20 | 35.7 | (15,031/42,083) | 0.85 | (0.83,0.87) | 0.92 | (0.91,0.94) |
| 20-24 | 38.7 | (58,194/150,359) | 0.92 | (0.91,0.93) | 0.98 | (0.97,0.99) |
| 25-30 | 41.9 | (82,277/196,515) | ref. | - | ref. | |
| 30-34 | 43.5 | (50,092/115,187) | 1.04 | (1.03,1.05) | 1.01 | (1.00,1.02) |
| 35+ | 44.6 | (25,840/57,988) | 1.06 | (1.05,1.08) | 1.02 | (1.01,1.04) |
| Unknown | 36.9 | (54,058/146,477) | 0.88 | (0.83,0.93) | 0.83 | (0.81,0.86) |
| **Alcohol consumption** | | | | | | |
| Non-drinker | 37.3 | (30,100/80,705) | 0.89 | (0.86,0.92) | 0.93 | (0.90,0.95) |
| Drinker | 41.9 | (173,483/413,843) | ref. | - | ref. | |
| Heavy drinker[c] | 39.7 | (14,335/36,074) | 0.95 | (0.93,0.97) | 0.91 | (0.89,0.93) |
| Unknown | 38.0 | (67,574/177,987) | 0.91 | (0.86,0.95) | 0.95 | (0.92,0.99) |
| **Smoking status** | | | | | | |
| Non-smoker | 39.8 | (119,645/300,338) | ref. | - | ref. | |
| Smoker | 34.5 | (29,284/84,920) | 0.87 | (0.85,0.89) | 0.82 | (0.81,0.84) |
| Ex-smoker | 43.8 | (93,856/214,201) | 1.10 | (1.08,1.12) | 1.03 | (1.02,1.05) |
| Unknown | 39.1 | (42,707/109,150) | 0.98 | (0.92,1.05) | 1.02 | (0.98,1.07) |
| **History of Guillain Barré syndrome** | | | | | | |
| No | 40.3 | (285,319/708,105) | ref. | - | ref. | |
| Yes | 34.3 | (173/504) | 0.85 | (0.76,0.96) | 0.82 | (0.73,0.92) |
| **Total number of risk groups** | | | | | | |
| 1 | 37.6 | (178,420/474,564) | ref. | - | ref. | |
| 2 | 44.4 | (76,814/173,184) | 1.18 | (1.16,1.20) | 1.20 | (1.18,1.22) |
| >2 | 49.7 | (30,258/60,861) | 1.32 | (1.29,1.35) | 1.35 | (1.31,1.38) |
| **Practice region** | | | | | | |
| England | 37.2 | (197,765/531,373) | ref | - | ref. | |
| Northern Ireland | 57.5 | (11,195/19,459) | 1.55 | (1.35,1.76) | 1.63 | (1.42,1.88) |
| Scotland | 55.9 | (28,869/51,644) | 1.50 | (1.38,1.63) | 1.58 | (1.43,1.74) |
| Wales | 47.5 | (22,459/47,261) | 1.28 | (1.17,1.39) | 1.34 | (1.21,1.48) |
| Unknown | 42.8 | (25,204/58,872) | 1.15 | (1.04,1.27) | 1.36 | (1.23,1.51) |

**a) n/n** represents the number vaccinated divided by the total number of individuals in that group. **b)** Deprivation scores were categorized into quintiles with category 1 containing the least deprived quintile and category 5 the most deprived. Patient deprivation scores were assigned to patients based on the level of deprivation in the area in which they reside. **c)** Heavy drinkers are defined as individuals possessing a record indicating consumption of excessive amounts of alcohol; >42 units/week for males, >31 units/week for females.

**Table 4.4** Distribution of study variables and results of bivariate and main multivariate analyses investigating predictors of seasonal influenza vaccine uptake in clinical risk groups.

| | | Seasonal influenza vaccine | | | | |
|---|---|---|---|---|---|---|
| | % | (n/n)[a] | Unadj. IRR | (95% CI) | Adj. IRR | (95% CI) |
| **Sex** | | | | | | |
| Male | 61.0 | (211,927/347,322) | ref. | - | ref. | |
| Female | 61.6 | (222,645/361,287) | 1.01 | (1.00,1.02) | 1.00 | (0.99,1.00) |
| **Age** | | | | | | |
| 0.5 – 4 | 26.0 | (1,429/5,497) | 0.46 | (0.43,0.49) | 0.51 | (0.47,0.55) |
| 5 – 19 | 34.5 | (16,530/47,944) | 0.61 | (0.59,0.63) | 0.65 | (0.63,0.67) |
| 20 – 39 | 37.1 | (25,660/69,136) | 0.66 | (0.64,0.67) | 0.68 | (0.67,0.70) |
| 40 – 64 | 56.6 | (131,341/232,111) | ref. | - | ref. | |
| 65 – 79 | 74.8 | (168,307/225,143) | 1.32 | (1.30,1.34) | 1.27 | (1.25,1.29) |
| 80 - 110 | 70.9 | (91,305/128,778) | 1.25 | (1.22,1.28) | 1.20 | (1.17,1.23) |
| **Patient deprivation quintile[b]** | | | | | | |
| 1 (least deprived) | 65.8 | (49,394/75,118) | 1.04 | (1.01,1.08) | 1.04 | (1.00,1.07) |
| 2 | 65.6 | (40,137/61,168) | 1.04 | (1.02,1.07) | 1.03 | (1.00,1.05) |
| 3 | 62.9 | (36,204/57,533) | ref. | - | ref. | |
| 4 | 60.6 | (30,449/50,211) | 0.96 | (0.94,0.99) | 0.98 | (0.95,1.00) |
| 5 (most deprived) | 59.5 | (21,688/36,440) | 0.95 | (0.91,0.98) | 0.98 | (0.94,1.01) |
| Unknown | 60.0 | (256,700/428,139) | 0.95 | (0.90,1.00) | 0.92 | (0.85,0.98) |
| **BMI** | | | | | | |
| <20 | 49.3 | (20,744/42,083) | 0.75 | (0.73,0.76) | 0.95 | (0.94,0.96) |
| 20-24 | 61.5 | (92,498/150,359) | 0.93 | (0.92,0.94) | 0.98 | (0.97,0.98) |
| 25-30 | 66.1 | (129,930/196,515) | ref. | - | ref. | |
| 30-34 | 66.2 | (76,299/115,187) | 1.00 | (1.00,1.01) | 1.01 | (1.00,1.02) |
| 35+ | 65.2 | (37,801/57,988) | 0.99 | (0.98,1.00) | 1.03 | (1.02,1.04) |
| Unknown | 52.8 | (77,300/146,477) | 0.80 | (0.76,0.84) | 0.85 | (0.83,0.87) |
| **Alcohol consumption** | | | | | | |
| Non-drinker | 61.3 | (49,460/80,705) | 0.93 | (0.92,0.95) | 0.96 | (0.94,0.98) |
| Drinker | 65.6 | (271,618/413,843) | ref. | - | ref. | |
| Heavy drinker[c] | 58.0 | (20,918/36,074) | 0.88 | (0.87,0.90) | 0.93 | (0.92,0.95) |
| Unknown | 52.0 | (92,576/177,987) | 0.79 | (0.76,0.83) | 0.98 | (0.96,1.01) |
| **Smoking status** | | | | | | |
| Non-smoker | 61.7 | (185,237/300,338) | ref. | - | ref. | |
| Smoker | 51.3 | (43,563/84,920) | 0.83 | (0.82,0.85) | 0.86 | (0.85,0.88) |
| Ex-smoker | 68.4 | (146,618/214,201) | 1.11 | (1.10,1.12) | 1.02 | (1.01,1.02) |
| Unknown | 54.2 | (59,154/109,150) | 0.88 | (0.83,0.93) | 1.02 | (0.98,1.06) |
| **History of Guillain Barré syndrome** | | | | | | |
| No | 61.3 | (434,294/708,105) | ref. | - | ref. | |
| Yes | 55.2 | (278/504) | 0.90 | (0.83,0.97) | 0.83 | (0.77,0.90) |
| **Total number of risk groups** | | | | | | |
| 1 | 56.5 | (267,931/474,564) | ref. | - | ref. | |
| 2 | 68.3 | (118,201/173,184) | 1.21 | (1.20,1.22) | 1.14 | (1.13,1.16) |
| >2 | 79.6 | (48,440/60,861) | 1.41 | (1.39,1.43) | 1.22 | (1.19,1.24) |
| **Practice region** | | | | | | |
| England | 59.8 | (318,002/531,373) | ref | - | ref. | |
| Northern Ireland | 70.0 | (13,626/19,459) | 1.17 | (1.04,1.32) | 1.25 | (1.09,1.43) |
| Scotland | 66.8 | (34,523/51,644) | 1.12 | (1.04,1.20) | 1.18 | (1.09,1.29) |
| Wales | 63.8 | (30,141/47,261) | 1.06 | (1.01,1.13) | 1.12 | (1.04,1.20) |
| Unknown | 65.0 | (38,280/58,872) | 1.09 | (1.03,1.76) | 1.27 | (1.20,1.34) |

a**) n/n** represents the number vaccinated divided by the total number of individuals in that group. **b)** Deprivation scores were categorized into quintiles with category 1 containing the least deprived quintile and category 5 the most deprived. Patient deprivation scores were assigned to patients based on the level of deprivation in the area in which they reside. **c)** Heavy drinkers are defined as individuals possessing a record indicating consumption of excessive amounts of alcohol; >42 units/week for males, >31 units/week for females.

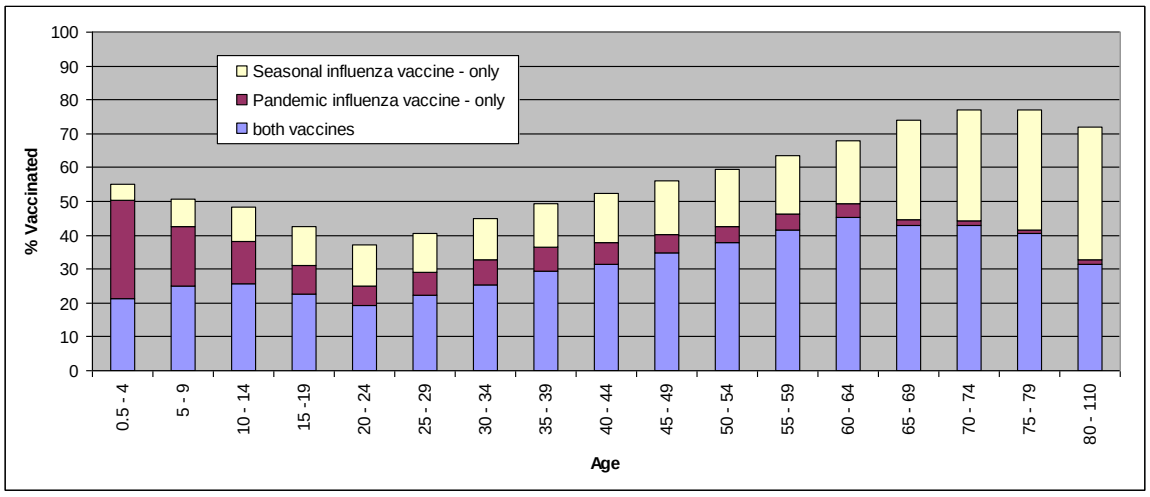


**Figure 4.1** Vaccination uptake in clinical risk groups according to age, number and type of vaccine received.

The results of the main multivariate regression models are shown in table 4.3 and table 4.4. Age was a strong predictor of vaccination. Uptake of both vaccines varied significantly across different age groups with the likelihood of receiving SIV increasing in each age category from childhood up to 65-80 year olds. The association between PIV and age was bimodal with the highest uptake rates achieved in those aged 6 months up to 5 years old ($IRR_{adj}$ 1.28, $CI_{95}$ 1.22-1.35) and in those aged 40-64 years old (reference category). Predictors of vaccination differed across age strata. Uptake rates and immunisation policies in different age strata are summarised in Table 4.7 and the results of age-stratified models are given in table 4.5 and table 4.6.

Overall, females were slightly less likely to receive PIV than males ($IRR_{adj}$ 0.94, $CI_{95}$ 0.93-0.94) while sex was not meaningfully associated with SIV uptake ($IRR_{adj}$ 1.00, $CI_{95}$ 0.99-1.00). Stratification by age category revealed that the association between sex and PIV (but not SIV) uptake was only observed in women aged 65-110 years ($IRR_{adj}$ 0.86, $CI_{95}$ 0.85-0.87). Overweight and obese individuals (BMI >24) were more likely to be vaccinated with PIV and SIV than those of normal weight or underweight (BMI <25). Overweight 5-64 year old individuals were more likely to be vaccinated with PIV and SIV than those of normal weight while this association was observed with PIV but not with SIV in those aged 65-110 years. BMI was missing for 96% of those aged 6 months to 5 years, this is to be expected as BMI is not typically calculated for children of such an age. BMI was therefore not included in the stratified model for this age group. (table 4.5 and table 4.6.).

Smoking status and alcohol consumption were both predictors of PIV, with smokers ($IRR_{adj}$ 0.82, $CI_{95}$ 0.81-0.84) and non-drinkers ($IRR_{adj}$ 0.92, $CI_{95}$ 0.90-0.95) being less likely to be vaccinated than non-smokers and drinkers respectively. Slightly weaker associations were noted between these predictors and SIV. The estimates for those patients with unknown/missing data for smoking status and alcohol consumption were consistent with this group being made up of an unbiased mixture of each of the known groups, suggesting that this data may be missing at random. People living in the most deprived areas were less likely to be vaccinated with PIV than those from less deprived areas. Associations between deprivation category and influenza vaccination were weak, however the risk estimates suggested a possible trend towards decreasing uptake with increasing deprivation. Risk estimates for alcohol consumption, smoking status and patient deprivation did not vary greatly across age strata.

Individuals who had more than two diseases indicating at-risk status were 35% more likely to be vaccinated with PIV ($IRR_{adj}$ 1.35, $CI_{95}$ 1.31-1.38) and 22% more likely to be vaccinated with SIV ($IRR_{adj}$ 1.22, $CI_{95}$ 1.19-1.24) than those with only a single high risk condition. These associations were stronger among those aged <65 years than in those aged >65 years (table 4.5 and table 4.6).

Patients with a history of GBS were 18% less likely to have received PIV ($IRR_{adj}$ 0.82, $CI_{95}$ 0.73-0.92) and 17% less likely to have received SIV ($IRR_{adj}$ 0.83, $CI_{95}$ 0.77-0.90) than those without a prior GBS diagnosis. After stratifying by age category the associations were only observed in those aged 65-110 years for PIV ($IRR_{adj}$ 0.70, $CI_{95}$ 0.59-0.82) and SIV ($IRR_{adj}$ 0.78, $CI_{95}$ 0.71-0.85). No children aged from 6 months and up to 5 years old had a history of GBS therefore this variable was excluded from their stratified model. People in Northern Irish, Scottish and Welsh practices all had significantly higher uptake of PIV than those in English practices. SIV uptake was also significantly higher in non-English practices than English practices however the magnitude of the association was considerably smaller than that observed with PIV. Practice size and practice level deprivation were not significantly associated with uptake of either vaccine. Testing for interactions between predictors other than age revealed a number of significant interactions; however inclusion of such terms did not alter the risk estimates materially.

**Table 4.5** Results of age-stratified multivariate analyses investigating predictors of influenza A(H1N1)pdm09 vaccine uptake in clinical risk groups.

| | Pandemic influenza vaccine | | | | | |
|---|---|---|---|---|---|---|
| | 6months - 4 yrs | | 5yrs - 64yrs | | 65yrs - 110yrs | |
| | adj. IRR | (ci95) | adj. IRR | (ci95) | adj. IRR | (ci95) |
| **Sex** | | | | | | |
| Male | ref. | | ref. | | ref. | |
| Female | 0.94 | (0.90,1.00) | 0.98 | (0.97,0.99) | 0.86 | (0.85,0.87) |
| **Patient deprivation quintile**[a] | | | | | | |
| 1 (least deprived) | 1.13 | (0.98,1.31) | 1.03 | (0.99,1.08) | 1.04 | (0.98,1.10) |
| 2 | 0.98 | (0.86,1.13) | 1.04 | (1.01,1.08) | 1.05 | (1.00,1.09) |
| 3 | ref. | | ref. | | | |
| 4 | 0.93 | (0.80,1.08) | 0.91 | (0.88,0.95) | 0.92 | (0.88,0.97) |
| 5 (most deprived) | 0.76 | (0.63,0.92) | 0.89 | (0.85,0.94) | 0.86 | (0.79,0.93) |
| Unknown | 0.97 | (0.85,1.10) | 0.94 | (0.88,1.02) | 0.85 | (0.75,0.96) |
| **BMI** | | | | | | |
| <20 | -[c] | - | 0.92 | (0.90,0.94) | 0.84 | (0.82,0.87) |
| 20-24 | - | - | 0.94 | (0.93,0.95) | 0.96 | (0.95,0.97) |
| 25-30 | - | - | ref. | | | |
| 30-34 | - | - | 1.03 | (1.02,1.04) | 1.02 | (1.01,1.04) |
| 35+ | - | - | 1.05 | (1.03,1.07) | 1.04 | (1.02,1.06) |
| Unknown | - | - | 0.82 | (0.80,0.85) | 0.77 | (0.73,0.81) |
| **Alcohol consumption** | | | | | | |
| Non-drinker | -[d] | - | 0.94 | (0.91,0.96) | 0.90 | (0.87,0.93) |
| Drinker | - | - | ref. | | | |
| Heavy drinker[b] | - | - | 0.92 | (0.90,0.94) | 0.95 | (0.92,0.98) |
| Unknown | - | - | 0.92 | (0.89,0.94) | 0.95 | (0.88,1.03) |
| **Smoking status** | | | | | | |
| Non-smoker | -[d] | - | ref. | | | |
| Smoker | - | - | 0.84 | (0.83,0.86) | 0.82 | (0.79,0.84) |
| Ex-smoker | - | - | 1.05 | (1.04,1.07) | 1.03 | (1.01,1.05) |
| Unknown | - | - | 1.01 | (0.97,1.05) | 1.12 | (1.00,1.26) |
| **History of Guillain Barré syndrome** | | | | | | |
| No | -[e] | - | ref. | | | |
| Yes | - | - | 1.02 | (0.87,1.20) | 0.70 | (0.59,0.82) |
| **Total number of risk groups** | | | | | | |
| 1 | ref. | | ref. | | | |
| 2 | 1.08 | (1.03,1.14) | 1.22 | (1.20,1.24) | 1.16 | (1.13,1.18) |
| >2 | 1.34 | (1.01,1.76) | 1.51 | (1.48,1.55) | 1.26 | (1.23,1.30) |
| **Practice region** | | | | | | |
| England | ref. | | | | | |
| Northern Ireland | 1.41 | (1.20,1.66) | 1.55 | (1.37,1.76) | 1.75 | (1.47,2.08) |
| Scotland | 1.47 | (1.32,1.63) | 1.48 | (1.37,1.60) | 1.71 | (1.50,1.96) |
| Wales | 1.23 | (1.10,1.37) | 1.28 | (1.18,1.40) | 1.40 | (1.23,1.60) |
| Unknown | 0.95 | (0.79,1.14) | 1.37 | (1.25,1.51) | 1.44 | (1.26,1.65) |

**a)** Deprivation scores were categorized into quintiles with category 1 containing the least deprived quintile and category 5 the most deprived. Patient deprivation scores were assigned to patients based on the level of deprivation in the area in which they reside. **b)** Heavy drinkers are defined as individuals possessing a record indicating consumption of excessive amounts of alcohol; >42 units/week for males, >31 units/week for females. **c)** BMI excluded from model as >95% missing data. **d)** Smoking status and alcohol consumption excluded from model as not relevant for this age group. **e)** History of GBS excluded from model as no patients in this age category had an existing diagnosis.

**Table 4.6** Results of age-stratified multivariate analyses investigating predictors of seasonal influenza vaccine uptake in clinical risk groups.

| | Seaasonal influenza vaccine | | | | | |
|---|---|---|---|---|---|---|
| | 6months - 4 yrs | | 5yrs - 64yrs | | 65yrs - 110yrs | |
| | adj. IRR | (ci95) | adj. IRR | (ci95) | adj. IRR | (ci95) |
| **Sex** | | | | | | |
| Male | ref. | | ref. | | ref. | |
| Female | 0.87 | (0.80,0.96) | 1.00 | (1.00,1.01) | 0.98 | (0.98,0.99) |
| **Patient deprivation quintile**[a] | | | | | | |
| 1 (least deprived) | 0.99 | (0.79,1.25) | 1.03 | (0.99,1.07) | 1.05 | (1.02,1.08) |
| 2 | 0.84 | (0.66,1.08) | 1.02 | (1.00,1.05) | 1.03 | (1.00,1.07) |
| 3 | ref. | | ref. | | ref. | |
| 4 | 0.89 | (0.70,1.13) | 0.98 | (0.95,1.01) | 0.97 | (0.94,1.00) |
| 5 (most deprived) | 0.92 | (0.68,1.23) | 0.98 | (0.93,1.03) | 0.97 | (0.94,1.00) |
| Unknown | 0.88 | (0.72,1.09) | 0.98 | (0.93,1.04) | 0.88 | (0.81,0.95) |
| **BMI** | | | | | | |
| <20 | -[c] | - | 0.81 | (0.80,0.83) | 0.94 | (0.93,0.96) |
| 20-24 | - | - | 0.91 | (0.90,0.92) | 0.99 | (0.98,1.00) |
| 25-30 | - | - | ref. | | ref. | |
| 30-34 | - | - | 1.05 | (1.04,1.06) | 0.99 | (0.99,1.00) |
| 35+ | - | - | 1.07 | (1.06,1.08) | 0.99 | (0.98,1.00) |
| Unknown | - | - | 0.77 | (0.75,0.79) | 0.87 | (0.85,0.89) |
| **Alcohol consumption** | | | | | | |
| Non-drinker | -[d] | - | 0.98 | (0.96,1.00) | 0.93 | (0.91,0.95) |
| Drinker | - | - | ref. | | ref. | |
| Heavy drinker[b] | - | - | 0.95 | (0.93,0.97) | 0.94 | (0.92,0.96) |
| Unknown | - | - | 0.86 | (0.84,0.89) | 0.98 | (0.94,1.01) |
| **Smoking status** | | | | | | |
| Non-smoker | -[d] | - | ref. | | ref. | |
| Smoker | - | - | 0.89 | (0.88,0.91) | 0.86 | (0.84,0.88) |
| Ex-smoker | - | - | 1.07 | (1.06,1.08) | 1.01 | (1.00,1.02) |
| Unknown | - | - | 0.96 | (0.92,1.00) | 1.11 | (1.04,1.18) |
| **History of Guillain Barré syndrome** | | | | | | |
| No | -[e] | - | ref. | | ref. | |
| Yes | - | - | 0.98 | (0.86,1.12) | 0.78 | (0.71,0.85) |
| **Total number of risk groups** | | | | | | |
| 1 | ref. | | ref. | | ref. | |
| 2 | 0.92 | (0.83,1.02) | 1.25 | (1.23,1.27) | 1.08 | (1.07,1.09) |
| >2 | 1.58 | (1.02,2.46) | 1.55 | (1.52,1.58) | 1.14 | (1.12,1.16) |
| **Practice region** | | | | | | |
| England | ref. | | ref. | | ref. | |
| Northern Ireland | 1.83 | (1.46,2.29) | 1.29 | (1.14,1.45) | 1.21 | (1.04,1.40) |
| Scotland | 1.63 | (1.29,2.07) | 1.21 | (1.12,1.31) | 1.17 | (1.05,1.30) |
| Wales | 0.89 | (0.60,1.33) | 1.07 | (0.99,1.15) | 1.14 | (1.05,1.24) |
| Unknown | 0.90 | (0.69,1.19) | 1.56 | (1.46,1.66) | 1.17 | (1.10,1.24) |

**a)** Deprivation scores were categorized into quintiles with category 1 containing the least deprived quintile and category 5 the most deprived. Patient deprivation scores were assigned to patients based on the level of deprivation in the area in which they reside. **b)** Heavy drinkers are defined as individuals possessing a record indicating consumption of excessive amounts of alcohol; >42 units/week for males, >31 units/week for females. **c)** BMI excluded from model as >95% missing data. **d)** Smoking status and alcohol consumption excluded from model as not relevant for this age group. **e)** History of GBS excluded from model as no patients in this age category had an existing diagnosis.

Table 4.8 shows uptake rates for each of the underlying health conditions constituting 'clinical risk groups' stratified by age. In every age group, high uptake of both vaccines was noted among people with diabetes. Among those aged 5 years up to 110 years old, people with immunosupression had notably high uptake. Comparatively low uptake of both vaccines was observed across all age categories in individuals with central nervous system degeneration (multiple sclerosis, cerebral palsy, etc) and among individuals aged younger than 5 years and older than 64 years with a history of stroke/TIA. In contrast, among individuals aged from 5 up to 64 years with a previous stroke/TIA higher uptake was observed.

**Table 4.7** Comparison of seasonal and influenza A(H1N1)pdm09 vaccine uptake rates in clinical risk groups across age groups and immunisation policies.

| Age group | Influenza vaccine | Immunisation policy | Uptake rate in clinical risk groups (%) |
|---|---|---|---|
| 6 months - 4 years | Seasonal | clinical risk groups | 26.0 |
| | Pandemic | entire age group | 50.2 |
| 5 years - 64 years | Seasonal | clinical risk groups | 49.7 |
| | Pandemic | clinical risk groups | 40.9 |
| 65 years – 110 years | Seasonal | entire age group | 73.4 |
| | Pandemic | clinical risk groups | 39.6 |

**Discussion**

Except for in young children, the uptake of SIV in clinical risk groups during the 2009 UK pandemic vaccination campaign far exceeded that of PIV. Several factors including age, number of underlying health conditions and history of GBS were found to be predictive of both pandemic and seasonal influenza vaccine uptake.

One of the main strengths of this study was the large sample size from a well validated primary care database. A limitation of using such a database for this study is that information on the GPs' and patients' personal views regarding susceptibility to influenza related morbidity and the influenza vaccination's effectiveness and safety is not available. This type of data can be strongly predictive of vaccine uptake [18;35-

37]. However, many of the surveys collecting this type of information may suffer from recall and response bias. Such biases are not an issue when using the GPRD. Reassuringly our estimate of ~15% of the population being in a 'clinical risk group' is similar to that identified by others [14]. As GP practices are contractually obliged to accurately record vaccinations in a patient's record [55], and as GP practices are likely to use the information in these records to complete payment claims, recording of vaccinations in the GPRD should be relatively complete. Despite this, as SIV is available in pharmacies, supermarkets and workplaces misclassification of seasonal influenza vaccination status may have occurred. In our study population, negative misclassification of vaccinations administered outside the GP practice should have been mitigated as vaccines were only available free of charge to individuals in clinical risk groups if they were administered by GP practices.

**Table 4.8** Seasonal influenza and influenza A(H1N1)pdm09 vaccine uptake in each 'clinical risk group' across age strata.

| | Age | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 6months - 4 years | | | 5 years – 64 years | | | 65 years -110 years | | |
| Risk Group[a] | total n | PIV % | SIV % | total n | PIV % | SIV % | total n | PIV % | SIV % |
| Chronic heart disease | 1,579 | 45.8 | 23.4 | 60,075 | 41.9 | 52.3 | 146,359 | 40.2 | 73.2 |
| Chronic kidney disease | 51 | 47.1 | 33.3 | 26,956 | 42.4 | 50.2 | 133,168 | 38.9 | 75.5 |
| Chronic respiratory disease | 3,386 | 52.8 | 27.2 | 171,322 | 40.6 | 48.9 | 90,360 | 45.4 | 77.9 |
| Diabetes | 61 | 65.6 | 55.7 | 76,815 | 49.0 | 64.5 | 84,972 | 44.5 | 75.6 |
| Stroke/Transient ischaemic attack | 53 | 43.4 | 13.2 | 9,583 | 43.3 | 57.2 | 34,306 | 35.1 | 70.3 |
| Chronic liver disease | 28 | 53.6 | 42.9 | 12,302 | 34.8 | 40.0 | 4,852 | 38.8 | 69.4 |
| Immunosuppression | 54 | 46.3 | 24.1 | 18,546 | 53.6 | 57.0 | 8,712 | 54.2 | 81.7 |
| Central nervous system degen. | 397 | 46.1 | 23.4 | 21,115 | 34.5 | 38.3 | 23,529 | 32.0 | 67.4 |

a) clinical risk groups are not mutually exclusive as an individual may have a multitude of the underlying health conditions listed

The national immunisation policy may explain some of the differences between SIV and PIV uptake in different age categories. In the UK, one of two immunisation policies was implemented in each age category: vaccination of all individuals in that age category or vaccination of only those in clinical risk groups. Vaccination of an entire age category was only employed where evidence suggested a large proportion of people of that age were at a high risk of prolonged or more serious morbidity resulting from influenza infection. As a result within some age groups different policies were implemented for SIV and PIV: all those aged 6 months to up to 5 years were advised to be vaccinated with PIV and all those aged >64 were advised to be vaccinated with SIV. In both age categories, the other vaccine (SIV and PIV respectively) was only offered to people who were in clinical risk groups. As illustrated in Table 4.7, where immunisation policies differed within an age category, *for both*

*vaccines* the uptake by people in clinical risk groups was higher if the vaccine had also been offered to people in their age category who were not in clinical risk groups. Amongst 5 – 64 year olds only those in clinical risk groups were invited for PIV and SIV vaccination and in this age group the difference in uptake rates between the two vaccines was considerably less. Overall this suggests that immunisation policies that cover entire age groups are associated with higher uptake of influenza vaccines by individuals in clinical risk groups. Associations between immunisation policy and influenza vaccine uptake have been investigated in Canada, Spain and Finland. SIV uptake rates in a region that implemented an age based immunisation policy were compared with rates in regions with the standard risk group based immunisation policy. In each case vaccine uptake amongst people in clinical risk groups was found to be higher in those regions with the broader, age-based vaccination policy [38-40]. The CDC have suggested this may be because targeting entire age groups simplifies the overall public health message regarding influenza vaccines and removes the need for identification of high risk individuals by GPs [41].

Given the reports of an increased risk of H1N1 influenza related complications in obese individuals [42;43] it is unsurprising that we observed higher PIV uptake in individuals with higher BMI. The fact there were no such reports for SIV may explain the slightly weaker association between SIV and BMI. Notably all associations between BMI and vaccine uptake were of a small magnitude and therefore may be sensitive to the presence of missing data. Individuals with normal or slightly low BMI may be overrepresented among those with unknown/missing BMI if recording of low BMI is deemed to be less clinically relevant by GPs. If this were true, our results suggest we would have underestimated any association between high BMI and high vaccine uptake. Our results also suggest a weak association between increasing deprivation and decreasing influenza vaccine uptake. A similar, albeit slightly stronger trend was observed for Carstairs deprivation score in a recent study of influenza vaccine uptake in the UK [44]. Differences in these results might be explained by differences between the measures contributing to the Carstairs score and those contributing to our composite (Townsend or IMD) score. In addition, the low uptake observed in those with missing deprivation data might obscure the true association between deprivation and vaccine uptake.

The decreased likelihood of vaccination among individuals with a history of GBS may reflect GP and patient concerns surrounding the potentially increased risk of GBS recurrence following influenza vaccination. Recent data suggests it may be the influenza infection itself, and not the vaccine, that carries the highest risk of GBS

[45;46]. If this is true then any decision not to vaccinate against influenza in an effort to prevent GBS recurrence may have the opposite effect.

The difference in unadjusted and adjusted incidence rate ratios comparing uptake in Wales, Scotland and Northern Ireland to England resulted from the inclusion of the deprivation variable in the model; individuals in non-English countries had a much greater proportion of individuals missing deprivation score than English practices, and uptake was much lower in this group. Differences in the handling of the pandemic and the pandemic vaccination campaign in Wales, Scotland, Northern Ireland and England might have led to the differences in uptake that were observed in the unadjusted analysis. A review of the pandemic vaccination campaign in Northern Ireland highlighted their decision to split bulk packs of vaccines on a pro rata basis, allowing wider distribution of the earliest vaccine supplies, as key to the high uptake obtained there [54]. In England bulk packs were not split [54] while no literature could be found to confirm what policy was adopted on this in Wales and Scotland. Closer investigation of the policies implemented in each devolved administration might provide other reasons for the disparities observed.
The uptake rates observed across the clinical risk groups varied and were similar to those reported in the HPA Pandemic H1N1 and seasonal influenza vaccine uptake surveys [14;28]. Our finding that the likelihood of influenza vaccination increased with increasing number of risk groups has been reported previously for both SIV and PIV in Spain [21;47].

Overall, uptake of PIV in clinical risk groups was low compared with that achieved in many other countries, while uptake of SIV was similar to that achieved in previous seasons in the UK. Our results suggest that recommending universal vaccination of certain age categories may increase influenza vaccination rates among clinically at risk individuals of that age. Given the low PIV uptake achieved in the UK it may be worth considering recommendation of universal vaccination during future pandemics where the consequences of poor vaccine uptake in clinical risk groups might have more serious consequences. Such policy changes may also be required for SIV if the UK are to meet the European Council's recommended 2014/15 target of 75% SIV uptake among all risk groups [48]. However, before any policy changes are made consideration would need to be given to the cost effectiveness of such a strategy, that is, whether the costs associated with vaccinating millions of individuals at low-risk of influenza complications would be acceptable given the potential savings that would be brought about through increasing uptake in clinical risk groups. The recent

introduction of universal influenza immunisation in the United States may provide the opportunity to observe the relative merits of introducing such a policy.

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[1] Monto AS. Epidemiology of influenza. Vaccine 2008 12;26 Suppl 4:D45-D48.

[2] Nicoll A, Ciancio B, Tsolova S, Blank P, Yilmaz C. The scientific basis for offering seasonal influenza immunisation to risk groups in Europe. Euro Surveill 2008;13(43).

[3] Blank PR, Szucs TD. Increasing influenza vaccination coverage in recommended population groups in Europe. Expert Rev Vaccines 2009;8(4):425-33.

[4] Ropero-Alvarez AM, Kurtis HJ, novaro-Holliday MC, Ruiz-Matus C, Andrus JK. Expansion of seasonal influenza vaccination in the Americas. BMC Public Health 2009;9:361.

[5] Fiore AE, Shay DK, Broder K, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009;58(RR-8):1-52.

[6] An Advisory Committee Statement (ACS), National Advisory Committee on Immunization (NACI). Statement on Seasonal Trivalent Inactivated Influenza Vaccine (TIV) for 2009-2010. Canada Communicable Disease Report 2010;35.

[7] National Health and Medical Research Council (Australia), Nolan T, Immunise Australia Program, et al. The Australian immunisation handbook. 9th ed. Canberra: NHMRC, 2008.

[8] van Essen GA, Palache AM, Forleo E, Fedson DS. Influenza vaccination in 2000: recommendations and vaccine use in 50 developed and rapidly developing countries. Vaccine 2003;21(16):1780-5.

[9] World Health Organisation. Strategic Advisory Group of Experts on Immunization – report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic, 7 July 2009. Weekly epidemiological record 2009;84(30):213-9.

[10] European Centre for Disease Prevention and Control. (2009) ECDC Interim Risk Assessment: Influenza A(H1N1) 2009 pandemic. European Centre for Disease Prevention and Control. Available:http://www.reliefweb.int/rw/RWFiles2009.nsf/FilesByRWDocUnidFilename/SODA-7U5TH8-full_report.pdf/$File/full_report.pdf. Accessed 20/09/2010

[11] Centers for Disease Control and Prevention. Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep 2009;58(RR-10):1-8.

[12] Mereckiene J, Cotter S, Nicoll A, et al. National seasonal influenza vaccination survey in Europe, 2008. Euro Surveill 2008;13(43).

[13] Department of Health. Begum F, Pebody R. (2009) Influenza vaccine uptake among the 65 years and over and under 65 years at risk in England, Winter season 2008-09.

Available:http://www.immunisation.nhs.uk/publications/FluVaccineUptake_Winter0809.pdf. Accessed 28/04/2010

[14] Department of Health. Begum F, Pebody R. (2010 ) Seasonal influenza vaccine uptake among the 65 years and over and under 65 years at risk in England - Winter season 2009-10.
Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_118645.pdf. Accessed 20/09/2010

[15] Endrich MM, Blank PR, Szucs TD. Influenza vaccination uptake and socioeconomic determinants in 11 European countries. Vaccine 2009;27(30):4018-24.

[16] Kohlhammer Y, Schnoor M, Schwartz M, Raspe H, Schafer T. Determinants of influenza and pneumococcal vaccination in elderly people: a systematic review. Public Health 2007;121(10):742-51.

[17] Chen Y, Yi QL, Wu J, Li F. Chronic disease status, self-perceived health and hospital admissions are important predictors for having a flu shot in Canada. Vaccine 2007;25(42):7436-40.

[18] Muller D, Szucs TD. Influenza vaccination coverage rates in 5 European countries: a population-based cross-sectional analysis of the seasons 02/03, 03/04 and 04/05. Infection 2007;35(5):308-19.

[19] Jimenez-Garcia R, Hernandez-Barrera V, de Andres AL, Jimenez-Trujillo I, Esteban-Hernandez J, Carrasco-Garrido P. Gender influence in influenza vaccine uptake in Spain: time trends analysis (1995-2006). Vaccine 2010;28(38):6169-75.

[20] Coupland C, Harcourt S, Vinogradova Y, et al. Inequalities in uptake of influenza vaccine by deprivation and risk group: time trends analysis. Vaccine 2007;25(42):7363-71.

[21] Rodriguez-Rieiro C, Dominguez-Berjon MF, Esteban-Vasallo MD, et al. Vaccination coverage against 2009 seasonal influenza in chronically ill children and adults: analysis of population registries in primary care in Madrid (Spain). Vaccine 2010;28(38):6203-9.

[22] Breeze E, Mangtani P, Fletcher AE, Price GM, Kovats S, Roberts J. Trends in influenza vaccination uptake among people aged over 74 years, 1997-2000: survey of 73 general practices in Britain. BMC Fam Pract 2004;5:8.

[23] Lu PJ, Singleton JA, Rangel MC, Wortley PM, Bridges CB. Influenza vaccination trends among adults 65 years or older in the United States, 1989-2002. Arch Intern Med 2005;165(16):1849-56.

[24] Centers for Disease Control and Prevention. Racial/ethnic disparities in influenza and pneumococcal vaccination levels among persons aged > or =65 years--United States, 1989-2001. MMWR Morb Mortal Wkly Rep 2003;52(40):958-62.

[25] Poland GA. The 2009-2010 influenza pandemic: effects on pandemic and seasonal vaccine uptake and lessons learned for seasonal vaccination campaigns. Vaccine 2010;28 Suppl 4:D3-13.

[26] Centers for Disease Control and Prevention. Interim results: state-specific influenza A (H1N1) 2009 monovalent vaccination coverage - United States, October 2009-January 2010. MMWR Morb Mortal Wkly Rep 2010;59(12):363-8.

[27] Centers for Disease Control and Prevention. Interim results: state-specific seasonal influenza vaccination coverage - United States, August 2009-January 2010. MMWR Morb Mortal Wkly Rep 2010;59(16):477-84.

[28] Begum F, Pebody R. Department of Health. (2010) Pandemic H1N1 (Swine) Influenza Vaccine Uptake amongst Patient Groups in Primary Care in England 2009/10.
Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_121014.pdf. Accessed 12/11/2010

[29] Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf 2004;27(12):871-81.

[30] General Practice Research Database. (2011) Facts and Figures.
Available:http://www.gprd.com/gprd/factsandfigures.asp. Accessed 12/11/2010

[31] Department of Health. PRIMIS+. (2010) Influenza A (H1N1)v Uptake Survey 2009/10, ImmForm, Read Codes Version 1.0 (excluding pregnancy).
Available:http://www.dh.gov.uk/en/Publichealth/Flu/Swineflu/InformationandGuidance/Vaccinationprogramme/DH_107355. Accessed 11/05/2010

[32] Townsend P, Beattie A, Phillimore P. Health and deprivation inequality and the north. London: Croom Helm, 1988.

[33] Noble M, McLennan D, Wilkinson K, Whitworth A, Barnes H. (2008) The English Indices of Multiple Deprivation 2007. Communities and Local Government: London, Social Disadvantage Research Centre, University of Oxford.
Available:http://www.communities.gov.uk/publications/communities/indicesdeprivation07. Accessed 21/09/2010

[34] Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159(7):702-6.

[35] Kroneman M, van Essen GA, John PW. Influenza vaccination coverage and reasons to refrain among high-risk persons in four European countries. Vaccine 2006;24(5):622-8.

[36] Mangtani P, Breeze E, Stirling S, Hanciles S, Kovats S, Fletcher A. Cross-sectional survey of older peoples' views related to influenza vaccine uptake. BMC Public Health 2006;6:249.

[37] Holm MV, Blank PR, Szucs TD. Developments in influenza vaccination coverage in England, Scotland and Wales covering five consecutive seasons from 2001 to 2006. Vaccine 2007;25(46):7931-8.

[38] Kwong JC, Rosella LC, Johansen H. Trends in influenza vaccination in Canada, 1996/1997 to 2005. Health Rep 2007;18(4):9-19.

[39] Jimenez-Garcia R, Rodriguez-Rieiro C, Hernandez-Barrera V, et al. Effectiveness of age-based strategies to increase influenza vaccination coverage among high risk subjects in Madrid (Spain)
1. Vaccine 2011;29(16):2840-5.

[40] Honkanen PO, Keistinen T, Kivela SL. The impact of vaccination strategy and methods of information on influenza and pneumococcal vaccination coverage in the elderly population. Vaccine 1997;15(3):317-20.

[41] CDC's Advisory Committee on Immunization Practices (ACIP) Recommends Universal Annual Influenza Vaccination. CDC Division of Media Relations 2010 February 24. Available:http://www.cdc.gov/media/pressrel/2010/r100224.htm. Accessed 17/01/2011

[42] Louie JK, Acosta M, Winter K, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA 2009;302(17):1896-902.

[43] Centers for Disease Control and Prevention. Intensive-care patients with severe novel influenza A (H1N1) virus infection - Michigan, June 2009. MMWR Morb Mortal Wkly Rep 2009;58(27):749-52.

[44] Norbury M, Fawkes N, Guthrie B. Impact of the GP contract on inequalities associated with influenza immunisation: a retrospective population-database analysis
2. Br J Gen Pract 2011;61(588):e379-e385.

[45] Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database
1. Am J Epidemiol 2009;169(3):382-8.

[46] Dieleman J, Romio S, de Vries CS, Sammon CJ, Andrews N, Hviid A. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe
1. BMJ 2011;343:d3908.

[47] Rodriguez-Rieiro C, Esteban-Vasallo MD, Dominguez-Berjon MF, et al. Coverage and predictors of vaccination against 2009 pandemic H1N1 influenza in Madrid, Spain. Vaccine 2011;29(6):1332-8.

[48] European Commision. Proposal for a Council recommendation on seasonal influenza vaccination. COM(2009) 353 final/2.

Available:http://ec.europa.eu/health/ph_threats/com/Influenza/docs/seasonflu_rec2009_en.pdf. Accessed 12/09/2010

[49] Donaldson L, Beasley C, Ridge K. (2010) The influenza immunisation programme 2009/10.
Available:https://www.cas.dh.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=101187. Accessed 30/07/2013.

[50] Dalton I. (2009) A (H1N1) swine flu influenza: phase two of the vaccination programme; children over 6 months and under 5 years.
Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_109825.pdf. Accessed 28/04/2010.

[51] Donaldson L. (2009) Further details about the H1N1 swine flu vaccination programme 2009-2010.
Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_104315.pdf. Accessed 27/04/2010.

[52] Mail Online. (2009) Swine flu jab link to killer nerve disease: Leaked letter reveals concern of neurologists over 25 deaths in America. Available: http://www.dailymail.co.uk/news/article-1206807/Swine-flu-jab-link-killer-nerve-disease-Leaked-letter-reveals-concern-neurologists-25-deaths-America.html.Accessed 31/07/2013

[53] The Telegraph. (2009) Doctors told to watch for Guillain-Barre syndrome during Swine flu vaccination programme. Available: http://www.telegraph.co.uk/health/swine-flu/6038460/Doctors-told-to-watch-for-Guillain-Barre-syndrome-during-Swine-flu-vaccination-programme.html.Accessed 31/07/2013

[54] The Department of Health, Social Services and Public Safety. (2010) The 2009 pandemic - Learning from Experience, A report of the Northern Ireland response to the 2009 influenza pandemic
Available:http://www.dhsspsni.gov.uk/northern_ireland_report_of_the_2009_influenza_pandemic_-_november_2010_-_final_version.pdf. Accessed 30/07/2013

[55] Primary Medical Services (Directed Enhanced Services - Pandemic Influenza (H1N1) Vaccination Scheme) and Statement of Financial Entitlements (Amendment) (No. 6) Directions 2009. Available: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_107719.pdf. Accessed 22/08/2013

## *4.3* Pandemic influenza vaccination during pregnancy; an investigation of vaccine uptake during the 2009/10 pandemic vaccination campaign in Great Britain

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**Abstract**

**Background:** Pregnant women in Great Britain were recommended to receive influenza A(H1N1)pdm09 vaccines during the 2009/10 influenza pandemic, however uptake of the vaccines by pregnant women was reported to have been very low.

**Aim:** We sought to estimate uptake of influenza A(H1N1)pdm09 vaccines and to investigate predictors of vaccine uptake in pregnant women in Great Britain during the 2009/10 pandemic.

**Methods:** Uptake rates were calculated using data from the UK General Practice Research Database (GPRD). Predictors of vaccination were identified using a Cox proportional hazards model.

**Results:** Uptake of influenza A(H1N1)pdm09 vaccines by pregnant women was 21.6%. Pregnant women with an underlying health condition increasing the risk of influenza-related complications had a higher vaccination rate than pregnant women without such conditions. The hazard ratio comparing these two groups decreased logarithmically throughout pregnancy from 9.3 in the first week to 1.3 by the end of pregnancy. Increasing maternal age (HR 1.01, $CI_{95}$ 1.00 – 1.01), having a previous delivery recorded (HR 1.22, $CI_{95}$ 1.17 – 1.27) and living in Scotland (HR 2.55, $CI_{95}$ 2.30 – 2.84) or Wales (HR 1.38, $CI_{95}$ 1.20 – 1.59) as opposed to England were all also associated with an increase in vaccination uptake rates throughout pregnancy.

**Discussion:** Uptake of influenza A(H1N1)pdm09 vaccines by pregnant women was low. None of the potential predictors evaluated in this study were strong enough to account for this, however information on health beliefs and GP recommendation were not available. If the low rates reported here are to be improved new strategies to increase uptake of influenza vaccine in pregnant women need to be identified, evaluated and implemented.

**Introduction**

The emergence and rapid global spread of a mutated strain of influenza (influenza A(H1N1)pdm09 ) in spring 2009 resulted in the declaration of the first influenza pandemic of the 21st century[1]. Data collected early in the pandemic suggested that the risk of serious complications or death following infection with influenza A(H1N1)pdm09 might be much higher in pregnant women than in the general population [2]. This finding refocused attention upon an ongoing debate about the risks of influenza infection in pregnancy and the relative merits of vaccinating pregnant women against influenza [3-8].

Retrospective cohort studies have found increased rates of cardiopulmonary hospitalisations among pregnant women not in influenza clinical risk groups during weeks 21-26 (RR 2.52 $CI_{95}$ 1.74-3.65), 27-31 (RR 2.62 $CI_{95}$ 1.82-3.76), 32-36 (RR 3.21 $CI_{95}$ 2.32-4.44) and 37-42 (RR 4.67 $CI_{95}$ 3.42-6.39) of pregnancy relative to the post-partum period [51] and in the second (RR 1.50 $CI_{95}$ 1.01-2.23) and third (RR 2.81 $CI_{95}$ 1.98-3.99) trimester relative to the first [52] in addition to increased rates of respiratory hospitalisations in second (RR 1.87 $CI_{95}$ 1.11-3.17) and third (RR 2.40 $CI_{95}$ 1.70-3.40) trimesters during the influenza season relative to the non-influenza season [53] and in the first (RR 1.67 $CI_{95}$ 1.00-2.77) second (RR 2.09 $CI_{95}$ 1.34-3.26), and third (RR 5.14 $CI_{95}$ 3.62-7.31) trimesters relative to the year before pregnancy [53]. Notably, these studies have lack lab confirmed endpoints. However it has also been suggested that during the 1918 pandemic the case fatality rate for pregnant women [54, 55, 56, 57] may have been higher than many of the estimates for the general population [56, 57, 58] and that during the 1957 pandemic pregnant women were overrepresented among those who died. As in the general population, influenza vaccination may result in pregnant women experiencing mild side effects [59, 60, 61, 62], however the risk of serious maternal or foetal adverse events in vaccinated women has not been found to be increased relative to non-vaccinated [63, 64] and pneumococcal vaccinated women [65]. Despite all of this, studies of influenza vaccine safety in pregnancy are lacking [5].

As a result, the most thorough reviews carried out to date have come to a common set of conclusions [5, 6]: seasonal influenza vaccination is warranted in the second and third trimesters in healthy pregnant women; in any trimester in pregnant women with underlying health conditions; during pandemics, influenza vaccination is warranted in any trimester regardless of underlying health conditions. Interestingly such conclusions have not been widely reflected in public health policy and while countries such as the US and Canada have been recommending seasonal influenza

vaccination for pregnant women for several years, authorities in many other countries have been reluctant to make similar recommendations; until 2008 only 10 out of 27 European countries [9] and 7 out of 43 countries in the Americas [10] recommended routine seasonal influenza vaccination for pregnant women.

Despite this historic reluctance to vaccinate pregnant women against seasonal influenza, the limited early data on the risk of pandemic influenza in pregnant women was readily accepted by public health bodies and during the 2009/10 pandemic vaccination campaign many countries recommended all pregnant women receive A(H1N1)pdm09 influenza vaccines regardless of their underlying health status [11]. The main difference in recommendations between these countries was in the recommended trimester of vaccination: some recommended second and third trimester vaccination only, while others, including the UK, recommended vaccination in any trimester [12-14]. This represented a considerable shift in influenza vaccination policy in the UK as, before the pandemic, the only pregnant women recommended for seasonal influenza vaccination were those who had underlying health conditions known to increase the risk of influenza-related complications independent of pregnancy [15, 16].

In the UK, vaccination of pregnant women with pandemic influenza A(H1N1)pdm09 vaccines began on 21 October 2009 and ended in the summer of 2010 [17]. A national survey of more than 90% of English GP practices has since reported a pandemic vaccine coverage of 14.9% in pregnant women [18]. The public health impact of such low vaccination coverage does not appear to have been great, possibly reflecting the fact that the pandemic was ultimately much less severe than first anticipated. However, such low uptake of a vaccine by a high risk group warrants further investigation: identifying particular demographic groups or gestational periods in which there was low vaccine uptake may inform targeting of promotional campaigns during future influenza seasons. In this study we describe the uptake of pandemic influenza vaccine by pregnant women in the UK during the 2009/10 pandemic reporting on the (gestational) time to vaccination and investigating a number of potential predictors of vaccine uptake.

**Methods**

This study was carried out using the UK General Practice Research Database (GPRD). The GPRD is a primary care database containing the anonymised records of ~8.4% of the UK population [42]. Patient data routinely available in the database includes demographic details, diagnoses and symptoms leading to hospital admissions,

immunisations, pregnancies, laboratory tests, referrals to specialists, prescriptions issued by the GP, contraception, hospital discharge and clinic summaries and deaths [43]. The GPRD operates a continuous quality control procedure which assesses whether or not they consider data submitted by a practice to be of a standard sufficient for research purposes (up-to-standard) [42]. Pregnant women have been identified on the GPRD using an algorithm similar to those applied elsewhere[44, 45]. In summary this algorithm identifies individual pregnancies based on records of pregnancy losses or deliveries and estimates each pregnancy's start and end dates using all pregnancy-related events in a woman's record. This algorithmic approach to pregnancy identification on the GPRD has been tested against manual review of electronic and paper medical records [46]. Quality of comorbidity recording in pregnancy is similar to that in the general population, although lifestyle factors are more commonly recorded by midwives during pregnancy using a paperbased system kept by the pregnant woman.

Pregnancy outcome data was available on all pregnancies starting before 01 April 2010, and with very few exceptions, any woman with a pregnancy ending after the start of the vaccination campaign (21 October 2009) was eligible for pandemic vaccination at some time during their pregnancy. The study population therefore consisted of all women with a pregnancy ending after 21 October 2009 and starting before 01 April 2010. Only pregnancies ending in delivery were included in our study population. Women who were vaccinated with influenza A(H1N1)pdm09 vaccine before their pregnancy start date were excluded from the study. Patients from Northern Irish practices were also excluded from the study population as vaccination of pregnant women in Northern Ireland was coordinated through acute trusts, as opposed to GPs [47].

Pandemic influenza vaccinations were identified using influenza A(H1N1)pdm09 vaccine specific medical and product codes; codes which had been created to allow differential recording of seasonal and pandemic vaccinations on GP systems [48]. Where a woman had more than one pandemic vaccination recorded, the first record of vaccination was considered to be on the vaccination date.

Kaplan Meier curves for vaccine uptake by gestational age were constructed. Cox regression modelling was used to identify predictors of pandemic influenza vaccine uptake. The following population characteristics were considered potential predictors of vaccine uptake and their associations with uptake rates were evaluated: whether a

woman was in one of the clinical risk groups*, maternal age (years), record of a previous delivery (yes/no), pre-pregnancy alcohol consumption (drinker, non-drinker, heavy drinker), pre-pregnancy smoking status (smoker, non-smoker, ex-smoker), pre-pregnancy BMI (<20, 20-24, 25-29, >29), Indices of Multiple Deprivation (IMD) score of a patients' practice (quintiles) and the country in which a patients' practice was located (England, Scotland, Wales). All factors were coded as categorical variables with the exception of maternal age, which was included as a continuous variable. Where missing data existed for a variable, a separate "unknown" category was created to identify these women in the models. Survival time began on the first day of the estimated LMP date and delayed entry was used for pregnancies beginning before the start of the vaccination campaign. To account for the change in exposure prevalence over calendar time estimates were stratified by the calendar month of estimated LMP date. Variables that were significant in the multivariate model at $p<0.05$ or found to alter the hazard ratio of another variable by >10% were included in the final model. Interactions between variables were investigated by introducing multiplicative interaction terms into the model. Linearity of the association with maternal age was checked using plots of standardized residuals and deviation was addressed by the introduction of polynomial terms into the model. The proportionality assumption was examined graphically using plots of the scaled Schoenfeld residuals and log-log survival probabilities over time and was investigated formally by testing for non-zero slope in a linear regression of the scaled Schoenfeld residuals over time. Where non-proportionality was suggested interaction terms between the offending predictor and log time were introduced into the model; any significant interactions with log time were included in the final model. Robust standard error estimates were used to account for clustering by practice. As a sensitivity analysis, uptake rates were estimated restricting the study population to pregnancies beginning before the start of the vaccination campaign; all such women were recommended for vaccination during the two peak months of vaccination. All analyses were performed using STATA10[49].

**Results**

Overall uptake of pandemic influenza vaccine by pregnant women was 21.6%. The probability of vaccination in the first trimester was 7%, the probability of vaccination by the end of the second trimester was 24% and the probability of vaccination by the end of week 40 of pregnancy was 32%.

* Underlying health conditions warranting inclusion in a clinical risk group: asthma, chronic heart disease, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, chronic neurodegenerative disease, diabetes, immunosuppresion and stroke/transient ischemic attack.

Figure 4.2 shows the relationship between gestational age and date of vaccination among vaccinated women using a Lexis diagram. Notable gaps in vaccination are observed around major holidays (25-Dec-2009, 31-Dec-2009). As can be seen from this figure, uptake of vaccination in pregnancy was highest in the first two months following the introduction of the vaccine. After January, fewer pregnant women received A/H1N1 vaccine. This was particularly evident for vaccinations early in the 1st and in the 3rd trimester.

Univariate analyses suggested the strongest predictor of vaccination in pregnancy was being in a clinical risk group. The Kaplan Meier failure curve for those in a clinical risk group versus those not in a risk group (Figure 4.3) suggested that the main difference in the probability of vaccination between these two groups arose in the first trimester. Examination of the scaled Schoenfeld residuals also suggested non proportionality therefore an interaction term between clinical risk group and (log) time was introduced into our Cox model. As shown in Table 4.10 and Figure 4.4, on any day in the first week of pregnancy those in a clinical risk group were 9.2 times more likely to be vaccinated than those without an underlying health condition. This ratio decreased throughout the pregnancy such that by the end of the first trimester (end of week 12) the rate of vaccination in those in a clinical risk group had decreased to 2.48 times that of those not in a clinical risk group. The hazard ratio remained much more stable over the second and third trimesters; by gestational week 40 it was 1.30.

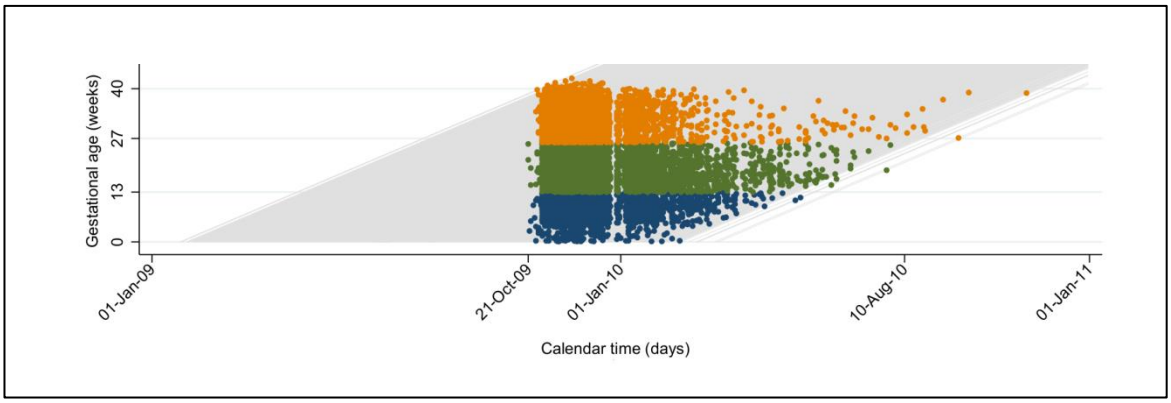


**Figure 4.2** Lexis diagram showing the relationship between gestational age and calendar date of vaccination in vaccinated women. Grey lines represent vaccinated women. Blue dots represent first trimester vaccinations, green dots represent second trimester vaccinations and orange dots represent third trimester vaccinations.

**Table 4.9** Characteristics of pregnant women recommended for A(H1N1)pdm09 vaccination

| | Total (n) | Vaccinated % |
|---|---|---|
| **Total** | 54,694 | 21.7 |
| **Maternal age (continuous)** | - | - |
| **Underlying health condition** | | |
| No | 52,160 | 21.1 |
| Yes | 2,534 | 33.1 |
| **Record of previous delivery** | | |
| No | 28,942 | 19.6 |
| Yes | 25,752 | 23.9 |
| **Smoking status** | | |
| Smoker | 13,251 | 19.6 |
| Non-smoker | 29,773 | 22.4 |
| Ex-smoker | 10,900 | 23.0 |
| Missing | 770 | 9.0 |
| **Alcohol consumption** | | |
| Drinker | 30,824 | 23.2 |
| Non-Drinker | 13,104 | 19.8 |
| Heavy drinker[a] | 1,486 | 16.7 |
| Missing | 9,280 | 19.7 |
| **Practice region** | | |
| England | 45,573 | 19.3 |
| Scotland | 4,947 | 40.0 |
| Wales | 4,174 | 25.1 |
| **Practice IMD score[b]** | | |
| 1 (least deprived) | 9,562 | 25.3 |
| 2 | 10,586 | 22.2 |
| 3 | 11,069 | 21.5 |
| 4 | 12,092 | 19.6 |
| 5 (most deprived) | 11,369 | 20.4 |
| unknown | 16 | 31.3 |
| **Pre-pregnancy BMI** | | |
| <20 | 4,884 | 21.7 |
| 20-24 | 17,341 | 23.5 |
| 25-29 | 8,870 | 24.0 |
| >29 | 6,393 | 24.6 |
| Unknown | 17,206 | 17.5 |

**a)** Heavy drinkers are defined as individuals possessing a record indicating consumption of excessive amounts of alcohol; >42 units/week for males, >31 units/week for females. **b)** IMD scores were categorized into quintiles with category 1 containing the least deprived quintile and category 5 the most deprived. IMD scores were assigned to patients based on the level of deprivation in the area in which their practice is located.

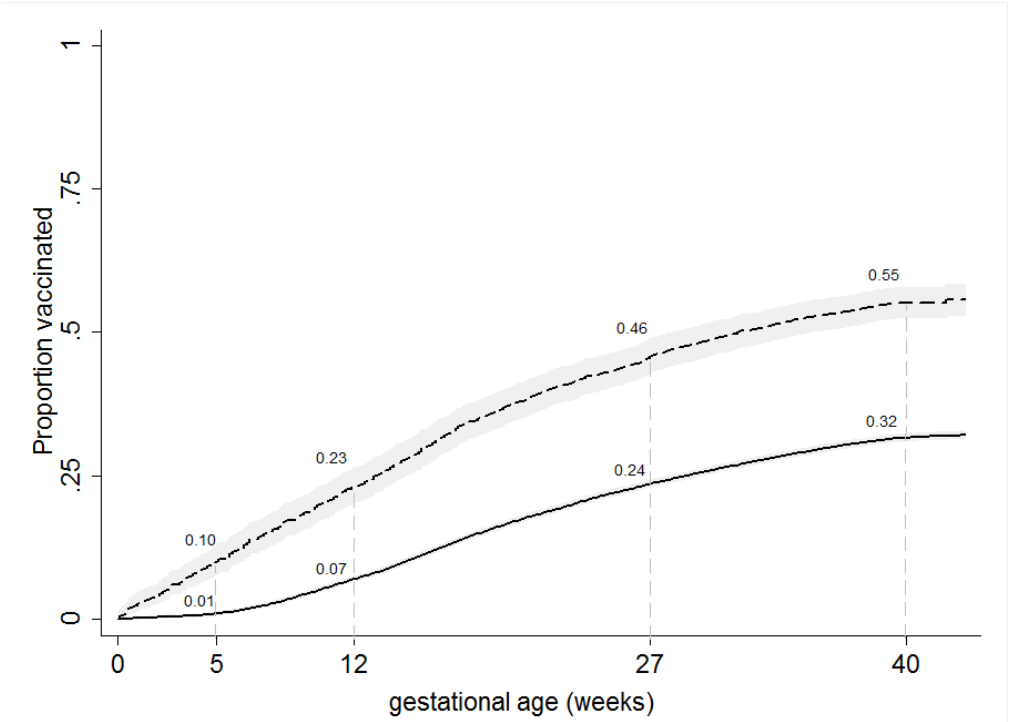


**Figure 4.3** Kaplan Meier curve showing the proportion of pregnant women vaccinated over gestational age by clinical risk group. Separate curves fitted for those in a clinical risk group (dashed line) and those not in a clinical risk group (solid line). Shaded regions show 95% CI. The dashed lines (grey) highlight the difference in the proportion vaccinated at different time points.

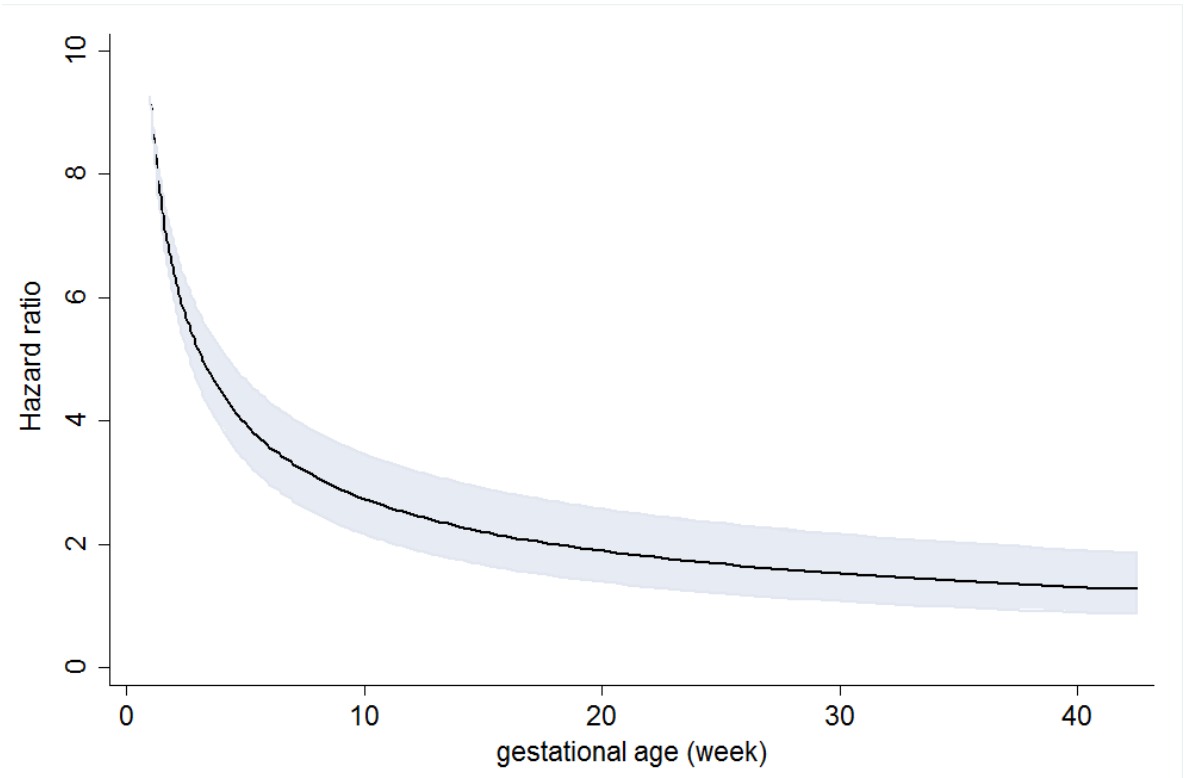


**Figure 4.4** Change in hazard ratio for those in a clinical risk group versus those not in a clinical risk group over gestational age (red line). Shaded blue region shows 95% CI for the change.

**Table 4.10** Unadjusted and adjusted hazard ratios for A(H1N1)pdm09 vaccination among pregnant women recommended for vaccination

| | unadj. HR | (95% CI) | adj. HR | (95% CI) |
|---|---|---|---|---|
| **Total** | | | | |
| **Maternal age (continuous)** | 1.02 | (0.01 - 1.02) | 1.01 | (1.00 - 1.01) |
| **Underlying health condition** | | | | |
| No | ref. | - | ref. | - |
| Yes | 9.17 | (6.73-12.49) | 9.21 | (6.78 – 12.53) |
| ***Interaction with log(t)*** | ***0.59*** | ***(0.53 -0.65)*** | ***0.59*** | ***(0.53 - 0.65)*** |
| **Record of previous delivery** | | | | |
| No | ref. | - | ref. | - |
| Yes | 1.27 | (1.21 - 1.32) | 1.22 | (1.17 - 1.27) |
| **Smoking status** | | | | |
| Smoker | 0.87 | (0.82 - 0.93) | 0.88 | (0.84 - 0.93) |
| Non-smoker | ref. | - | ref. | - |
| Ex-smoker | 1.04 | (0.98 - 1.10) | 1.00 | (0.95 - 1.05) |
| Missing | 0.34 | (0.26 - 0.44) | 0.36 | (0.28 - 0.47) |
| **Alcohol consumption** | | | | |
| Drinker | ref. | - | ref. | - |
| Non-Drinker | 0.83 | (0.78 - 0.89) | 0.88 | (0.82 - 0.94) |
| Heavy drinker[a] | 0.62 | (0.53 - 0.73) | 0.72 | (0.62 - 0.83) |
| Missing | 0.82 | (0.75 - 0.88) | 0.89 | (0.83 - 0.95) |
| **Practice region** | | | | |
| England | ref. | - | ref. | - |
| Scotland | 2.53 | (2.29 - 2.79) | 2.55 | (2.30 - 2.84) |
| Wales | 1.35 | (1.19 - 1.54) | 1.38 | (1.20 - 1.59) |
| **Practice IMD score[b]** | | | | |
| 1 (least deprived) | 1.28 | (1.07 - 1.54) | 1.20 | (1.04 – 1.38) |
| 2 | 1.09 | (0.91 - 1.30) | 1.07 | (0.93 – 1.23) |
| 3 | 1.07 | (0.89 - 1.27) | 1.06 | (0.93 – 1.22) |
| 4 | 0.95 | (0.79 - 1.13) | 1.00 | (0.87 – 1.15) |
| 5 (most deprived) | ref. | - | ref. | - |
| unknown | 1.23 | (1.06 - 1.41) | 0.62 | (0.55 – 0.71) |
| **Pre-pregnancy BMI** | | | | |
| <20 | 0.93 | (0.87 - 1.01) | | |
| 20-24 | ref. | - | | |
| 25-29 | 1.02 | (0.96 - 1.08) | | |
| >29 | 1.06 | (1.00 - 1.13) | | |
| Unknown | 0.74 | (0.70 - 0.78) | | |

**a)** Heavy drinkers are defined as individuals possessing a record indicating consumption of excessive amounts of alcohol; >42 units/week for males, >31 units/week for females. **b)** IMD scores were categorized into quintiles with category 1 containing the least deprived quintile and category 5 the most deprived. IMD scores were assigned to patients based on the level of deprivation in the area in which their practice is located.

With every 1 year increase in maternal age the hazard of vaccination increased by 1% (HR 1.01, $CI_{95}$ 1.00 – 1.01). On any day of pregnancy, women who had a record of a previous successful pregnancy were 1.2 times more likely than women with no recorded deliveries (HR 1.22, $CI_{95}$ 1.17 – 1.27) to be vaccinated. This association was observed independent of maternal age. Those in Scottish (HR 2.55, $CI_{95}$ 2.30 – 2.84) and Welsh practices (HR 1.38, $CI_{95}$ 1.20 – 1.59) had a higher rate of vaccination than those in English practices throughout pregnancy. The hazard of vaccination was higher in women registered with practices in the least deprived areas than women registered at practices in the most deprived areas (HR 1.20, $CI_{95}$ 1.04 – 1.38).

The rate of vaccination among smokers was 13% lower than the rate among non-smokers while the rate of vaccination among ex smokers was similar to that among non-smokers. Women with missing smoking status were substantially less likely to have a vaccination recorded than smokers (HR 0.36, $CI_{95}$ 0.28 – 0.47). Non drinkers and heavy drinkers had vaccination rates that were lower than those among drinkers. Those with missing data on alcohol consumption also had slightly lower vaccination rates than drinkers.

There were no meaningful differences in the rate of vaccination across all BMI categories and none of the multiplicative interaction terms were found to be significant. Stratification by calendar month of LMP did not materially alter the risk estimates (data not shown). Restriction of the study population to pregnancies beginning before the vaccination campaign increased the uptake rate to 26%.

**Discussion**

At 21.6%, we report low uptake of pandemic vaccine among pregnant women registered with UK general practices. This is markedly lower than the 40.3% uptake rate observed among other groups recommended for vaccination [19]. We have identified a number of predictors of vaccination uptake, none of which are strong enough to account for the extremely low uptake achieved. Uptake was highest among those in a clinical risk group and those living in Scotland; however uptake in these groups only reached 33.1% and 40% respectively.

Using the GPRD for this study, we were able to provide robust estimates for predictors of vaccine uptake using data on over 50,000 pregnancies. Vaccination details and other covariates such as underlying health status were collected in routine clinical practice thus minimizing the likelihood of recall bias. We have described previously the

limitations of using the GPRD to identify predictors of pandemic vaccination [19]. While pregnant women in the included countries were vaccinated primarily by GPs, in approximately 20% of practices midwives may have administered the vaccine [20]. Practices are contractually obliged to ensure all vaccinations, including those administered by midwives, are accurately recorded in GP records [21] however where such recording is poor, vaccination status may have been misclassified resulting in underestimation of uptake rates. Missing data on smoking status, alcohol consumption, BMI and deprivation may have obscured associations between each of these variables and vaccine uptake. For example, uptake was low in women missing pre-pregnancy BMI data, if such women are more likely to have normal BMI (a plausible situation given that normal BMI is of less clinical relevance than high or low BMI) then uptake will have been overestimated in those with normal BMI. Such overestimation could have resulted in the hazard ratios comparing uptake in those with higher BMI to those with normal BMI not reaching statistical significance. In addition, it has been shown that the use of a deprivation measure aggregated at practice postcode level underestimates patient socioeconomic inequalities [50].

The number of births on the GPRD, as determined by our algorithm, is proportional to that reported in the literature [22], supporting the accuracy of pregnancy recording on the GPRD. Information on pregnancy start dates (dates of last menstrual periods) are not available for many pregnancies on the GPRD therefore the start dates of approximately 80% of pregnancies were defaulted to 40 weeks before delivery. Pregnant women's perceptions about the pandemic and the pandemic vaccine are strong predictors of uptake in pregnant women [23-25]. In addition, healthcare provider recommendations have also been found to be predictive of uptake [23-25]. The GPRD does not contain data on these factors.

Both our study and the English pandemic influenza vaccine uptake survey used similar study periods and collected data from GP practices however the vaccination uptake we report for English practices (19.3%) is somewhat higher than that reported by the HPA (14.9%) [18]. This is likely to result from either a lack of precision in our estimates or differences in the study period or denominators used in each study (in their report the HPA acknowledge that a coding error may have inflated their denominator of pregnant women [18]). The uptake we observed in Scotland and Wales were higher than that in England. Such differences in uptake may result from different implementation of the immunisation campaign in each country; in Northern Ireland, where the immunisation of pregnant women was coordinated through acute trusts, uptake was reported to be 57.1% [26].

Uptake among pregnant women in other European countries varied widely with Netherlands achieving 63% uptake [27], while Germany [28], Spain, Hungary, Estonia and Slovenia [13] all reported uptake of <10%. Uptake in France [29, 30] and Portuga l[13] was similar to that observed in England and Wales while uptake in the Republic of Ireland (~33%) [13] fell between that we report here for Wales (25%) and Scotland (40%). It has been suggested that the high uptake observed in the Netherlands may reflect the high level of trust the Dutch public were reported to have in their government [27, 31]. With the exception of Northern Ireland and the Netherlands, uptake in Europe was generally lower than that reported in the USA (42-86%) [23-25, 32, 33] and Canada (76%) [34]; this is likely to reflect the fact that seasonal influenza vaccination has been recommended for all pregnant women in these countries for a number of years while, before the pandemic, only those with chronic illnesses had been recommended for influenza vaccination in most European countries.

Our finding, that uptake in clinical risk groups was much higher than that in pregnant women, is surprising, given that individuals in clinical risk groups and pregnant women were both vaccinated primarily by their GP. This difference in uptake may reflect concerns among pregnant women or their healthcare providers about vaccine related adverse pregnancy outcomes. While all individuals involved in the care of pregnant women were advised to recommend pandemic vaccination it is unclear to what extent they did; anecdotal reports suggested that British healthcare professionals were sceptical about the need for, and safety of the pandemic vaccine, although to our knowledge this has not been evaluated systematically. The difference in uptake may also reflect the fact that individuals in clinical risk groups have been recommended for seasonal influenza vaccination for many years while pregnant women have not. The high uptake observed in women who were both pregnant *and* in a clinical risk group is in line with this.

While the UK government recommended vaccination in any trimester of pregnancy, our vaccination rates suggest that many pregnant women and/or GPs avoided first trimester exposure. First trimester uptake was particularly low in those not in clinical risk groups. Literature reviews have found little evidence to support first trimester seasonal influenza vaccination [5, 6], and the evidence supporting first trimester pandemic influenza vaccination is based on limited data from this and previous pandemics [5, 6, 35]. This paucity of evidence led many European countries not to vaccinate pregnant women against influenza A(H1N1)pdm09 during their first

trimester [13] and may also have led to the low uptake observed in the UK. Post-marketing surveillance of pandemic vaccination campaigns has resulted in the publication of studies supporting the safety of influenza vaccination in any trimester of pregnancy [36-39]. The low uptake we report here suggests it is vital that the results of such studies are communicated in a clear and understandable way to pregnant women and their healthcare providers.

Since the 2010/11 influenza season the UK government has recommended immunisation of all pregnant women in any trimester with seasonal influenza vaccine which, like the pandemic vaccines, contains the A(H1N1)pdm09 strain. A survey of English GP practices reported uptake of the seasonal influenza vaccine by pregnant women to have increased to 38% in the 2010/11 season [40]. While this is an improvement on the uptake we report for the pandemic vaccine in 2009/10 it is still well below the levels of vaccine coverage observed in other high risk groups [40]. Further to this, reports from the 2011/12 season suggest seasonal influenza vaccine uptake in pregnant women may have decreased to 27.4% [41]. While similar reasons for low uptake among pregnant women have been consistently identified [23-25, 27, 32] few formal investigations of strategies to increase uptake rates have been carried out. The uptake observed in Northern Ireland [26] suggests the increased involvement of acute trusts in vaccination of pregnant women should be investigated, while a recent study reporting higher uptake of seasonal influenza vaccine among general practices in which midwives were involved in recommending and administering the vaccine to pregnant women suggests the increased involvement of midwives should be looked into further [20]. The low uptake we report here suggests that more strategies to increase uptake of influenza vaccine among pregnant women need to be identified, evaluated and implemented if influenza vaccination of pregnant women is to prove a successful public health intervention.

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[1] (2009) Transcript of statement by Margaret Chan, Director-General of the World Health Organization. Available:http://www.who.int/mediacentre/influenzaAH1N1_presstranscript_20090611.pdf. Accessed 14/10/2011.

[2] Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009;374(9688):451-8.

[3] Ayoub DM, Yazbak FE. Re: "Delivering influenza vaccine to pregnant women". AmJ Epidemiol 2007;165(3):351-2.

[4] Ayoub DM, Yazbak FE. A closer look at influenza vaccination during pregnancy. Lancet Infect Dis 2008;8(11):660-1.

[5] Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis 2008;8(1):44-52.

[6] Skowronski DM, De SG. Is routine influenza immunization warranted in early pregnancy? Vaccine 2009;27(35):4754-70.

[7] Naleway AL, Smith WJ, Mullooly JP. Delivering influenza vaccine to pregnant women. Epidemiol Rev 2006;28:47-53.

[8] Tamma PD, Ault KA, del Rio C, Steinhoff MC, Halsey NA, Omer SB. Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol 2009;201(6):547-52.

[9] Mereckiene J, Cotter S, D'Ancona F, Giambi C, Nicoll A, Levy-Bruhl D, et al. Differences in national influenza vaccination policies across the European Union, Norway and Iceland 2008-2009. Euro Surveill 2010;15(44).

[10] Ropero-Alvarez AM, Kurtis HJ, Danovaro-Holliday MC, Ruiz-Matus C, Andrus JK. Expansion of seasonal influenza vaccination in the Americas. BMC Public Health 2009;9:361.

[11] Ng S, Wu P, Nishiura H, Ip DK, Lee ES, 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 Infect Dis 2011;11:230.

[12] Luteijn JM, Dolk H, Marnoch GJ. Differences in pandemic influenza vaccination policies for pregnant women in Europe. BMC Public Health 2011;11:819.

[13] Mereckiene J. (2010) Overview of pandemic (H1N1) 2009 influenza vaccination in Europe. Preliminary results of VENICE survey conducted in 2010. ESCAIDE, Lisbon. Available:http://ecdc.europa.eu/en/ESCAIDE/ESCAIDE%20Presentations%20library/ESCAIDE2010_Late_Breakers_Mereckiene.pdf. Accessed 05/12/2012.

[14] Hanquet G, Van Damme P, Brasseur D, De Cuyper X, Gregor S, Holmberg M, et al. Lessons learnt from pandemic A(H1N1) 2009 influenza vaccination. Highlights of a European workshop in Brussels (22 March 2010). Vaccine 2011;29(3):370-7.

[15] Department of H. Influenza. In: Salisbury D, Ramsay M, Noakes K, editors. Immunisation against infectious disease-"the Green Book", 2006: 185-200.

[16] Donaldson L, Beasley C, Ridge K. (2008) The Influenza Immunisation Programme 2008/09. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_086394.pdf. Accessed 18/10/2011.

[17] Davies S, Beasley C, Ridge K. (2010) The influenza immunisation programme 2010/11. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_116943.pdf. Accessed 18/10/2011.

[18] Department of Health website. Begum F, Pebody R. (2010) Pandemic H1N1 (Swine) Influenza Vaccine Uptake amongst Patient Groups in Primary Care in England 2009/10. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_121014.pdf. Accessed 15/08/2012.

[19] Sammon CJ, McGrogan A, Snowball J, de Vries CS. Factors associated with uptake of seasonal and pandemic influenza vaccine among clinical risk groups in the UK: An analysis using the General Practice Research Database. Vaccine 2011.

[20] Dexter LJ, Teare MD, Dexter M, Siriwardena AN, Read RC. Strategies to increase influenza vaccination rates: outcomes of a nationwide cross-sectional survey of UK general practice. BMJ Open 2012;2(3).

[21] Department of Health website. (2009) The Primary Medical Services (Directed Enhanced Services - Pandemic Influenza (H1N1) Vaccination Scheme) and Statement of Financial Entitlements (Amendment) (No. 6) Directions 2009. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_107719.pdf. Accessed 23/11/2012.

[22] Office for National Statistics. (2011) Births and Deaths in England and Wales, 2011 (Final). Available:http://www.ons.gov.uk/ons/dcp171778_279934.pdf. Accessed 01/12/2012.

[23] Steelfisher GK, Blendon RJ, Bekheit MM, Mitchell EW, Williams J, Lubell K, et al. Novel pandemic A (H1N1) influenza vaccination among pregnant women: motivators and barriers. Am J Obstet Gynecol 2011;204(6 Suppl 1):S116-23.

[24] Goldfarb I, Panda B, Wylie B, Riley L. Uptake of influenza vaccine in pregnant women during the 2009 H1N1 influenza pandemic. Am J Obstet Gynecol 2011;204(6 Suppl 1):S112-5.

[25] Ding H, Santibanez TA, Jamieson DJ, Weinbaum CM, Euler GL, Grohskopf LA, et al. Influenza vaccination coverage among pregnant women--National 2009 H1N1 Flu Survey (NHFS). Am J Obstet Gynecol 2011;204(6 Suppl 1):S96-106.

[26] Department of Health website. McClean E, Pebody R. (2010) Epidemiological report of pandemic (H1N1) 2009 in the UK. Available:http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1284475321350. Accessed 15/08/2012.

[27] van Lier A, Steens A, Ferreira JA, van der Maas NA, de Melker HE. Acceptance of vaccination during pregnancy: Experience with 2009 influenza A (H1N1) in the Netherlands. Vaccine 2012;[epub ahead of print].

[28] Walter D, Böhmer MM, Heiden Mad, Reiter S, Krause G, Wichmann O. Monitoring pandemic influenza A(H1N1) vaccination coverage in Germany 2009/10 – Results from thirteen consecutive cross-sectional surveys. Vaccine 2011;29(23):4008-12.

[29] Bone A, Guthmann JP, Nicolau J, Levy-Bruhl D. Population and risk group uptake of H1N1 influenza vaccine in mainland France 2009-2010: results of a national vaccination campaign. Vaccine 2010;28(51):8157-61.

[30] Blondel B, Mahjoub N, Drewniak N, Launay O, Goffinet F. Failure of the vaccination campaign against A(H1N1) influenza in pregnant women in France: results from a national survey. Vaccine 2012;30(38):5661-5.

[31] van der Weerd W, Timmermans DR, Beaujean DJ, Oudhoff J, van Steenbergen JE. Monitoring the level of government trust, risk perception and intention of the general public to adopt protective measures during the influenza A (H1N1) pandemic in The Netherlands. BMC Public Health 2011;11:575.

[32] Fisher BM, Scott J, Hart J, Winn VD, Gibbs RS, Lynch AM. Behaviors and perceptions regarding seasonal and H1N1 influenza vaccination during pregnancy. Am J Obstet Gynecol 2011;204(6 Suppl 1):S107-11.

[33] Drees M, Johnson O, Wong E, Stewart A, Ferisin S, Silverman PR, et al. Acceptance of 2009 H1N1 influenza vaccine among pregnant women in Delaware. Am J Perinatol 2012;29(4):289-94.

[34] Fabry P, Gagneur A, Pasquier JC. Determinants of A (H1N1) vaccination: cross-sectional study in a population of pregnant women in Quebec. Vaccine 2011;29(9):1824-9.

[35] Mosby LG, Rasmussen SA, Jamieson DJ. 2009 pandemic influenza A (H1N1) in pregnancy: a systematic review of the literature. Am J Obstet Gynecol 2011;205(1):10-8.

[36] Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. BMJ 2012;344:e2794.

[37] Fell DB, Sprague AE, Liu N, Yasseen AS, 3rd, Wen SW, Smith G, et al. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. Am J Public Health 2012;102(6):e33-40.

[38] 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. Am J Obstet Gynecol 2012;207(3):177 e1-8.

[39] Sammon CJ, McGrogan A, Snowball J, 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;7(12):e51734.

[40] Department of Health website. Begum F, Pebody R. (2011) Seasonal influenza vaccine uptake amongst GP patient groups in England. Winter season 2010-11. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_129856.pdf. Accessed 15/08/2012.

[41] Department of Health website. The Immunisation Team Newsletter - Issue 187 - March 2012. Available:https://www.wp.dh.gov.uk/immunisation/files/2012/03/VaccineUpdate_I187_Mar12_acc.pdf. Accessed 31/03/2012.

[42] General Practice Research Database website. (2011) Facts and Figures. Available:http://www.gprd.com/gprd/factsandfigures.asp. Accessed 18/10/2011.

[43] Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf 2004;27(12):871-81.

[44] Hardy JR, Holford TR, Hall GC, Bracken MB. Strategies for identifying pregnancies in the automated medical records of the General Practice Research Database. Pharmacoepidemiol Drug Saf 2004;13(11):749-59.

[45] Devine S, West S, Andrews E, Tennis P, Hammad TA, Eaton S, et al. The identification of pregnancies within the general practice research database. Pharmacoepidemiol Drug Saf 2010;19(1):45-50.

[46] 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;33(9):741-50.

[47] Health Protection Scotland. (2009) Immunisation of pregnant women against Influenza A H1N1(v) - Annex 2. Available:http://www.documents.hps.scot.nhs.uk/respiratory/swine-influenza/influenza-a-h1n1v-immunisation-pregnancy-briefing-paper-2009-12-03.pdf. Accessed 23/11/2012.

[48] Department of Health. PRIMIS+. (2010) Influenza A (H1N1)v Uptake Survey 2009/10, ImmForm, Read Codes Version 1.0. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_107347.pdf. Accessed 15/08/2012.

[49] StataCorp. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP, 2007.

[50] McLean G, Guthrie B, Watt G, Gabbay M, O'Donnell CA. Practice postcode versus patient population: a comparison of data sources in England and Scotland. Int J Health Geogr 2008;7:37

[51] Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148(11):1094-102.

[52] Hartert TV, Neuzil KM, Shintani AK, Mitchel EF Jr, Snowden MS, Wood LB, Dittus RS, Griffin MR. Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. Am J Obstet Gynecol 2003;189(6):1705-12.

[53] Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J, MacDonald N. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. CMAJ 2007;176(4):463-8.

[54] Harris JW. Influenza occurring in pregnant women. JAMA 1919;72:978–980

[55] Bland PB. Influenza in its relation to pregnancy and labor. Am J Obstet 1919;79:184–197

[56] Woolston WJ, Conley DO. Epidemic pneumonia (Spanish influenza) in pregnancy: effect in one hundred and one cases. JAMA 1918:71;1898-99

[57] Nuzum JW, Pilot I, Stange FH, Bunar BE. 1918 pandemic influenza and pneumonia in a large civil hospital. JAMA 1918;71:1562-65

[58] Francis T. Influenza: the newe acquayantance. Ann Intern Med 1953;39:203–21

[59] Yeager DP, Toy EC, Baker B 3rd. Influenza vaccination in pregnancy. Am J Perinatol 1999;16(6):283-6.

[60] Hulka JF. Effectiveness of polyvalent influenza vaccine in pregnancy: report of a controlled study during an outbreak of Asian influenza. Obstet Gynecol 1964;23:830-7.

[61] Deinard AS, Ogburn P Jr. A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome. Am J Obstet Gynecol 1981;140(3):240-5.

[62] Sumaya CV, Gibbs RS. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant. J Infect Dis. 1979;140(2):141-6.

[63] Black SB, Shinefield HR, France EK, Fireman BH, Platt ST, Shay D; Vaccine Safety Datalink Workgroup. Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol 2004;21(6):333-9

[64] Munoz FM, Englund JA. Vaccines in pregnancy. Infect Dis Clin North Am 2001;15(1):253-71.

[65] Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, Omer SB, Shahid NS, Breiman RF, Steinhoff MC. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008;359(15):1555-64.

## 4.4 The background incidence rate of facial nerve palsy: a multinational retrospective cohort study in Europe

**The work presented in this section is based on a manuscript currently in preparation for publication:**

*Cormac J Sammon, Leonoor Wijnans, Jeanne P Dieleman, Silvana Romio, Francisco J de Abajo, Consuelo Huerta, Miguel Gil , Ana Chacón, Belen oliva, Arturo Alvarez, Anders P Hviid, Henrik Svanström, Ditte Mølgaard-Nielsen, Giampiero Mazzaglia, Salvatore Mannino, Harald Heijbel, Lisen Arnheim Dahlström, Jonas Hallgren, Par Sparen, Nicoline van der Maas, Hester de Melker, Terhi Kipli, Jukka Ollgren, Tuija Leino, Mees Mosseveld, Martijn Schuemie, Jann Storsaeter, Svenn-Erik Mamelund, Kari Johansen, Piotr Kramarz, Daniel Weibel, Jan Bonhoeffer, CJM Sturkenboom and Corinne S de Vries. The background incidence rate of facial nerve palsy: a multinational retrospective cohort study in Europe.(manuscript in preparation).*

**The version presented herein has been edited for inclusion in this thesis therefore the views expressed may not represent those of authors who collaborated on the published manuscript.**

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**Abstract**

**Introduction:** Facial nerve palsy has been found to be associated with vaccination therefore in advance of the 2009 H1N1 pandemic the VAESCO consortium sought to estimate the background incidence rate of facial nerve palsy for use in post-marketing surveillance.

**Methods:** A collaborative retrospective cohort study was used to estimate the incidence rate of facial nerve palsy in eight European databases from 1996-2008. A common protocol was implemented at each study site and standardised analysis software (Jerboa®) was used to analyse, aggregate and encrypt data. Incidence rates were estimated by data source, age category, calendar year and calendar month. Prevalent cases and recurrent events were excluded.

**Results:** The age standardized incidence rate (per 100,000 person years) of facial nerve palsy was found to range from 5.33 in Sweden to 41.82 in Spain. Incidence rates from Sicily (IR 6.64) and Sweden (IR 5.33) were considerably lower than those in other sources and incidence rates from GP databases were higher than those from hospital databases. Incidence rates in all countries increased with age, peaking between the ages of 65 and 74 years. Incidence rates in Spain and Denmark increased over time, possibly due to registration practices in these data sources. Higher incidence rates were observed in winter months, most notably in BIFAP and HSD.

**Discussion:** In this study we confirm a number of previously reported variations in the background incidence rate of facial nerve palsy and provide detailed, precise and generalisable background incidence rates suitable for use in OE analyses in several European countries.

## Introduction

Facial nerve palsy (FNP) is a rare condition in which paralysis or paresis of cranial nerve VII, the facial nerve, results in an inability to control facial muscles. The incidence of facial nerve palsy ranges between 11 and 60 cases per 100,000 person years (PY) [1]. Trauma, stroke, malignancy and Lyme disease are among a number of the conditions known to cause facial palsy, however 75-80% of cases are routinely classified as idiopathic facial nerve palsy, a condition commonly referred to as Bell's palsy [2]. While Bell's palsy is by definition idiopathic, vascular, infectious and immunological aetiologies have all been suggested as potential causes. Associations with infection, and pathological similarities between facial nerve palsy and other neurological conditions such as Guillain-Barré syndrome, have led to a growing belief that many idiopathic cases of facial paralysis may have an autoimmune aetiology [2]. Consistent with this theory a number of sources have described the onset of facial palsy following immunisation [3-5].

In 2004, a cluster of 46 case reports in Switzerland, describing Bell's palsy occurring as an adverse event following inactivated intranasal influenza immunisation, led public health authorities to initiate a controlled epidemiological study [6]. This study verified the reported signal using both case control and case series analyses: the risk of Bell's palsy in vaccinated cases was estimated to be at least 19 times that in the unvaccinated. While a causal mechanism for this association has not yet been established it has been suggested that the E. coli heat labile enterotoxin adjuvant used in the inactivated intranasal vaccine may have provoked the adverse events. In the same year a study using Vaccine Adverse Event Reporting System (VAERS) data found that between 1991 and 2001 the proportion of spontaneous adverse events reported for Bell's palsy was higher for inactivated intramuscular influenza vaccine than for all other vaccines combined (proportional reporting ratio = 3.78) [7]. Controlled epidemiological studies carried out in electronic healthcare databases have not supported this finding, identifying a relative incidence of Bell's palsy in the 3 months after influenza vaccination of 0.92 (0.78 – 1.08) in the UK using an SCCS study design [8] and an odds ratio of Bell's palsy in the 28 days after influenza vaccination of 0.70 ($CI_{95}$ 0.2 – 2.8) in the USA using a case centred study design [9]. The evidence to date therefore suggests that while an association may have existed with the vaccine used in Switzerland, other influenza vaccines do not appear to be associated with Bell's palsy.

The inability to confirm the association observed in the VAERS data demonstrates the limitations of hypotheses generated using disproportionality analyses of spontaneous reports and highlights the need for verification of safety signals using controlled

epidemiological studies. However, before initiating expensive and lengthy epidemiological studies, safety signals must be thoroughly assessed in order to make preliminary regulatory decisions and establish whether further study is needed. Observed versus Expected (OE) analyses form a key aspect of any such assessment. OE analyses compare the number of events observed in individuals exposed to a certain drug or vaccine to the number expected based on the normal, or background incidence rate. The ratio of observed to expected events for the drug or vaccine of interest is then often compared to that for other drugs or vaccines to assess whether it is disproportionately high. The background incidence rates used to calculate the *expected* numbers of events for OE analyses can be obtained from the literature or, where suitable rates cannot be identified in the literature, can be estimated using de novo studies.

In advance of the 2009 H1N1 pandemic vaccination campaign, regulatory authorities identified several neurological and/or autoimmune adverse events of specific interest (AESI) [10-12]. Amidst concern that existing background rates for many of these events lacked the generalisability, detail and precision needed for use in OE analyses [10-12], the VAESCO consortium designed and carried out a study investigating the background rate of several AESI using eight healthcare databases based in seven different European countries. This manuscript describes the background incidence rate of facial nerve palsy calculated in this study.

## Methods

A collaborative retrospective cohort study was used to estimate the incidence rate of facial nerve palsy in eight European databases from 1996-2008 (Table 4.11). A common protocol was implemented at each site and standardised analysis software (Jerboa®) was used to analyse, aggregate and encrypt data.

**Table 4.11** Types of database and coding library used in the estimation of the background incidence rate of facial nerve palsy.

| Country | Data source | Coding library |
|---|---|---|
| ***GP - medical records*** | | |
| Netherlands | IPCI | ICPC |
| Spain | BIFAP | ICPC |
| United Kingdom (UK) | GPRD | READ |
| Italy (GP) | HSD | ICD9-CM |
| ***Hospital - inpatient and/or outpatient diagnoses*** | | |
| Italy (Hospital) | Sicilian Regional Database (SRD) | ICD9-CM |
| Sweden | MBR/NHR | ICD10 |
| Denmark | DCRS/NHDR | ICD10 |
| Finland | HILMO | ICD10 |

The study population comprised all individuals who were registered within one of the contributing databases at any time between 01 January 1996 and 31 December 2008 and for whom a valid start and end of follow-up could be defined. Follow-up began one year after the person was first registered in the database or one year after the start of data collection, whichever was latest. Follow-up ended on the date of death, transferring out of the study population or the end of data collection, whichever was earliest. Sex and date of birth were extracted for each patient, where exact birthdates were not available midpoints (i.e. 30 June) were used. Based on these criteria, Jerboa® compatible files containing the entire study population in a data source were created at each study site.

The databases in the study use one of four coding schemes to describe events: the International Classification of Diseases (ICD9-CM and ICD10); the International Classification of Primary Care (ICPC); and the READ Code classification (Table 4.11). Owing to differences between these coding schemes and the use of free text in most medical record databases, facial nerve palsy related terms were mapped according to a common terminology system, the Unified Medical Language System® (UMLS®). The UMLS is a biomedical terminology integration system handling more than 150 terminologies including the four used in this study. The mapping process was supplemented by a manual comparison and check of the code lists; the final code lists created using this methodology are shown in Table 4.12. All events recorded with one of these codes during the study period were identified in each database and Jerboa® compatible files containing information on these events were created at each study site.

At each study site, the population and event files were entered into Jerboa® to calculate age, sex, year and calendar month specific incidence rates of facial nerve palsy. 95% confidence intervals were calculated assuming a normal approximation to the binomial distribution. Age standardized rates were calculated based on the age distribution of the world population as presented by the WHO [13]. All subjects with an event before the start of follow-up were considered prevalent cases and were excluded. Only first events in an individual were considered. Sensitivity analyses compared the impact of disease free run-in periods of 0 years, 1 year and 3 years to define incident events.

Aggregated national population level data were used to estimate denominators in Finland. As a result, the Finnish data was not compatible with Jerboa®. The Finnish data was therefore analysed and anonymised in a similar fashion to Jerboa®, but using software other than Jerboa.

**Table 4.12** Clinical codes used to identify facial nerve palsy cases

| UMLS CONCEPT | Coding library | | | |
|---|---|---|---|---|
| | Read code | ICD10 | ICD9CM | ICPC |
| Bell's palsy | 2BR6.00 | G51.0 | 351.0 | N91 |
| Facial Hemiatrophy | - | - | - | - |
| Facial Nerve Diseases | F31..00<br>F310.00<br>F31y.00<br>F31yz00<br>F31z.00 | G51.9 | 351.9 | - |
| Facial weakness/facial droop* | - | | 781.94 | - |

*Not a UMLS concept

**Results**

The 8 databases contributed a total of 264,050,313 PY of data. The amount of person time contributed by each data source is shown in Figure 4.5, broken down by age category, season and calendar year. Most person time was contributed between the ages of 20 and 60 years with the amount of person time decreasing after approximately 60 years of age in all databases. In Italy (GP) no person time was contributed in those aged <10 and in Sweden the amount of person time contributed in those aged <5 was low. The amount of person time contributed in Spain increased each year up to 2007, after which it dropped. The large drop in overall person time observed in 2008 can be attributed to the lack of data from Sweden for this year.

Table 4.13 reports age standardised incidence rates of FNP for each country while figure 4.6 depicts the incidence rate of FNP in each database by age group, calendar year and calendar month. Numerators, denominators, incidence rates and 95% confidence intervals on which Figure 4.5 and 4.6 are based are presented in Appendix 2. Rates in GP medical record databases were generally higher than those in hospital discharge databases; Finland was the only hospital discharge database with rates as high as the GP medical record databases. The rate of facial nerve palsy in all databases increased from birth, peaking at approximately age 65 -74 years and then declining. The increase in incidence rates over time in Spain is likely to reflect improvements in the validity of data as opposed to true changes in the incidence of

facial nerve palsy (Dr Miguel Gil Garcia, BIFAP project coordinator – personal communication) therefore Spanish rates that are not stratified by calendar year may underestimate the true rate in the Spanish data source. The reason for the increasing incidence in Denmark is not clear but may be due to a similar reason. In Spain and Italy (GP) incidence rates were higher in winter than in summer months. This was also observed in other databases, although the differences were not as pronounced. No notable differences in the incidence rates by sex were observed (Appendix 2). The rates presented above used a disease-free run in period of one year; the use of disease-free run in periods of 1 and 3 years did not materially alter the results (data not shown).

**Table 4.13** Age standardised incidence rates of facial nerve palsy (per 100,000 PY) in each data source and their 95% confidence intervals.

| Country | Total | |
|---|---|---|
| | IR | $CI_{95}$ |
| ***GP - medical records*** | | |
| Netherlands | 21.88 | (12.81-30.94) |
| Spain | 41.82 | (37.08-46.56) |
| UK | 27.22 | (24.85-29.59) |
| Italy (GP) | 27.34 | (19.12-35.56) |
| ***Hospital - inpatient and/or outpatient diagnoses*** | | |
| Italy (Hospital) | 6.64 | (5.48-7.79) |
| Sweden | 5.33 | (4.67-5.99) |
| Denmark | 15.11 | (13.93-16.28) |
| Finland | 23.39 | (20.84-25.95) |

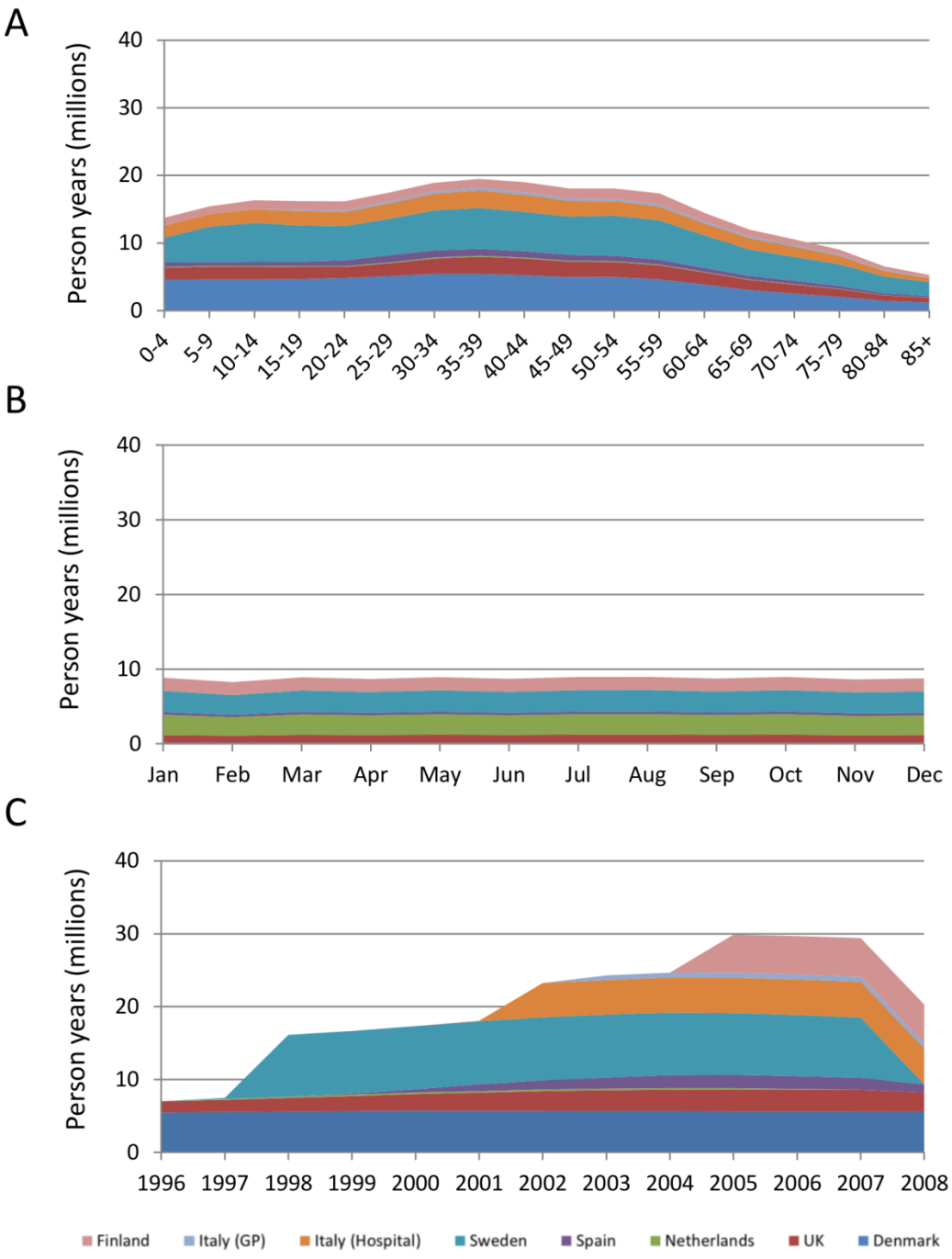


**Figure 4.5** Person time available for background rate calculation in each data source by age (A), calendar month (B) and calendar year (C). Data from Denmark and Sweden are absent from Figure 4.5(B) as rates were not stratified by calendar month in these data sources

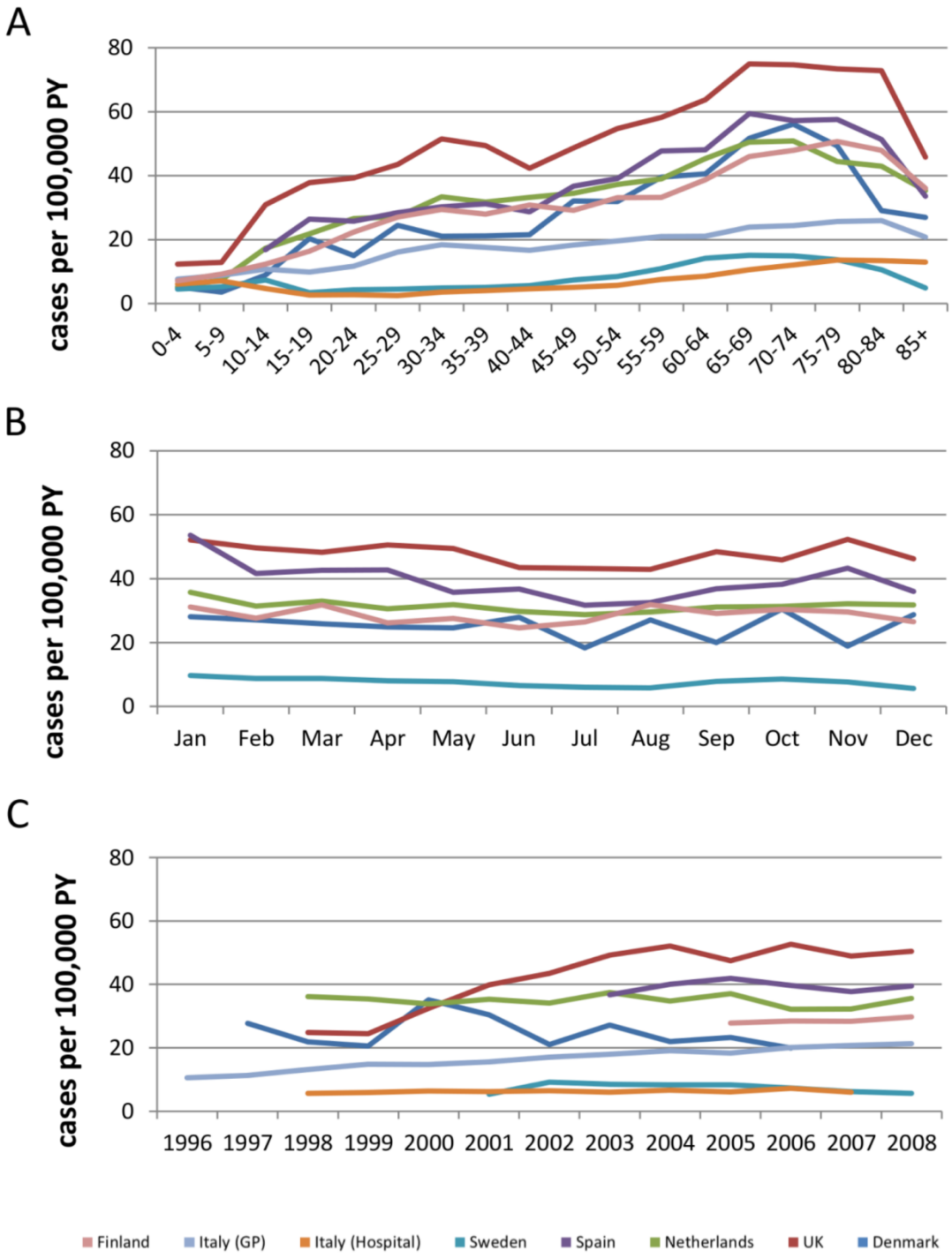


**Figure 4.6** Age(A), calendar month (B) and calendar year (C) specific incidence rates by data source. Data from Denmark and Sweden are absent from Figure 4.5(B) as rates were not stratified by calendar month in these data sources

**Discussion**

In this study we confirm a number of previously reported variations in the background incidence rate of facial nerve palsy and provide detailed, precise and generalisable background incidence rates suitable for use in OE analyses in several European countries. Age standardised incidence rates of facial nerve palsy ranged from 5.33/100,000 PY in Sweden to 41.82/100,000 PY in Spain.

The study used populations from 8 geographically diverse data sources, providing a total study population of more than 264 million PY of data. The use of a common protocol removed much of the heterogeneity in results that might normally be introduced by trivial differences in study definitions, thereby overcoming a problem often encountered when comparing rates from different sources. While this approach improved the comparability of our rates, substantial heterogeneity remained, most notably the difference in rates between GP databases and hospital based databases. The accuracy of incidence rates estimated from GP and hospital databases is dependent on the diagnosis under study. The databases using hospital data may underestimate the rate of facial palsy as they will miss cases that do not result in hospital admission; it has been suggested that hospital referral rates might be as low as 20% in some countries [14]. In contrast the vast majority of facial nerve palsy cases are likely to be seen by their GP and have their diagnosis or symptoms recorded in their GP's notes. However, rates in the GP databases may include events recorded as working diagnoses that were not subsequently confirmed resulting in overestimation of the background incidence rate; this is less likely in hospital databases as the diagnosis will usually be complete on discharge. Overall incidence rates reported for hospital based databases are expected to underestimate the true incidence. The exclusion of recurrent events, the inclusion of secondary FNP events and the underestimation of Spanish (and possibly Danish) rates due to the inclusion of data from years with poor quality should be taken into account in any interpretation of our rates.

As we include all cases of facial nerve palsy, regardless of their aetiology, some of the geographical variation observed in incidence rates might result from variation in aetiological factors. For example the high rate observed in those aged >50 is due, at least in part, to facial nerve palsy occurring as a result of stroke. Similarly geographical variation in the epidemiology of viral agents such as Lyme disease may explain differences. 2-25% of facial nerve palsy cases in some cohorts have been

identified as having Lyme disease [19], the incidence of which varies across and within European countries [20].

With the exception of Sweden, the rates we reported for Northern European data sources were similar to those reported in the literature [1]. The rates we reported for the two Italian databases were considerably lower than those previously reported in Sicilian (52.8) [15] and Roman Health districts (53.3) [16], however these studies included cases referred from areas outside the health districts which may have resulted in underestimation of the true denominator; in the Italian GP database the denominator is likely to be more accurate. The rate in Spain is higher than that previously reported in the same area of Spain; however consistent with VAESCO data, this lower rate was observed in a hospital database. The seasonal trends observed, particularly in Spain and Italy (GP), are in line with previous studies reporting a higher incidence of Bell's palsy in colder seasons. Excluding the Italian hospital based rates, the overall geographical distribution of our rates provides weak support for an association between facial nerve palsy and warmer countries [1] or more arid climates [17].

It has been suggested that the dissemination of rates and expected numbers of background events in advance of introducing a new drug or vaccine on the market would aid the interpretation of safety data by both regulatory authorities and the public [10, 18]. Our results suggest such information must be provided in enough detail to allow OE analyses to account for variability in the rates. In Table 4.14 we present the number of facial nerve palsy events that could be expected to occur in a 120 day period following vaccination based on our age specific rates, if vaccination did not alter the risk of facial nerve palsy.

While passive surveillance is moving towards more advanced signal detection techniques, it is likely that OE-type analyses, and therefore background incidence rates, will continue to play an important role in the assessment of drug and vaccine safety signals. The incidence rates presented here offer a detailed breakdown of the incidence of facial nerve palsy in Europe across time, age, season, country and data source. Preliminary versions of these rates have been used by the EMA in the post-marketing surveillance of the H1N1 vaccination campaign [12] and should prove particularly useful in assessing the post marketing safety of newly introduced intranasal vaccines.

**Table 4.14** Age stratified numbers of facial palsy events expected per million individuals in a 120 day post vaccination period

| Age category | GP - medical records | | | | | | | | *Hospital - inpatient and/or outpatient diagnoses* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Netherlands | | Spain | | UK | | Italy (GP) | | Italy (Hospital) | | Sweden | | Denmark | | Finland | |
| | IR | $CI_{95}$ | IR | $CI_{95}$ | IR | $CI_{95}$ | IR | $CI_{95}$ | IR | $CI_{95}$ | IR | $CI_{95}$ | IR | $CI_{95}$ | IR | $CI_{95}$ |
| **0-4** | 17 | (7.1, 35.2) | 40 | (32.4, 49.9) | 17 | (13.4, 20.2) | - | - | 15 | (11.9, 18.4) | 19.90 | (17.4, 22.7) | 25 | (22.7, 28) | 23 | (18.7, 28.8) |
| **5-9** | 12 | (3.9, 27.8) | 42 | (33.2, 53.1) | 24 | (20.7, 28.8) | - | - | 17 | (14.2, 21.1) | 23.25 | (21, 25.7) | 29 | (26.3, 31.9) | 30 | (24.9, 36.4) |
| **10-14** | 29 | (15.1, 52.1) | 102 | (87.7, 117.2) | 57 | (51.1, 63.3) | 55 | (15.3, 147.6) | 24 | (20.5, 28.3) | 15.57 | (13.8, 17.5) | 35 | (32.3, 38.5) | 41 | (34.6, 47.2) |
| **15-19** | 67 | (43, 99.3) | 124 | (109.7, 140.2) | 72 | (64.8, 78.9) | 87 | (64.4, 114.8) | 11 | (8.8, 13.9) | 8.72 | (7.4, 10.2) | 32 | (29.5, 35.4) | 54 | (46.9, 61.3) |
| **20-24** | 49 | (29.8, 77) | 129 | (116, 143.5) | 88 | (79.5, 96.1) | 85 | (65.5, 107.4) | 14 | (11.6, 17.5) | 8.98 | (7.6, 10.6) | 39 | (35.5, 41.8) | 74 | (65.6, 82.3) |
| **25-29** | 80 | (56.4, 111.5) | 143 | (130.5, 156.7) | 89 | (81.6, 97) | 93 | (74.7, 115.5) | 15 | (12.3, 18.1) | 8.16 | (6.9, 9.6) | 53 | (49.5, 56.8) | 89 | (80, 98.4) |
| **30-34** | 69 | (48.2, 96.3) | 169 | (155.6, 183.9) | 110 | (102.3, 118) | 100 | (81.8, 120.3) | 16 | (13.5, 19.2) | 11.74 | (10.2, 13.4) | 61 | (57, 64.5) | 97 | (87.5, 107.1) |
| **35-39** | 70 | (48.8, 96.6) | 162 | (148.7, 177.2) | 104 | (97.4, 111.9) | 103 | (85.2, 122.6) | 17 | (14, 19.7) | 13.31 | (11.7, 15.1) | 58 | (54.3, 61.6) | 92 | (82.9, 101.5) |
| **40-44** | 71 | (49.3, 98.6) | 139 | (125.8, 153.2) | 109 | (101.8, 116.7) | 94 | (77.7, 113.3) | 18 | (15.6, 21.6) | 15.10 | (13.4, 17) | 55 | (51.2, 58.5) | 101 | (92.3, 110.7) |
| **45-49** | 105 | (77.6, 140.2) | 160 | (145.2, 175.8) | 114 | (105.8, 121.7) | 121 | (101, 143.3) | 24 | (20.7, 27.9) | 16.55 | (14.7, 18.6) | 60 | (56.5, 64.3) | 96 | (87.2, 105.1) |
| **50-54** | 105 | (76.7, 140.5) | 180 | (163.6, 197.2) | 123 | (114.4, 131.1) | 128 | (107.3, 152.6) | 28 | (23.9, 32) | 18.78 | (16.9, 20.9) | 64 | (60.5, 68.5) | 109 | (99.7, 118.5) |
| **55-59** | 130 | (95.8, 172.9) | 191 | (173.8, 210.1) | 128 | (119.6, 137.2) | 157 | (133.3, 183.6) | 36 | (31.4, 40.9) | 24.67 | (22.4, 27.1) | 69 | (64.6, 73.3) | 109 | (100.2, 118.5) |
| **60-64** | 133 | (94.4, 183.2) | 210 | (189.2, 231.7) | 149 | (139.1, 159.6) | 158 | (133.2, 186.7) | 47 | (41.2, 52.8) | 28.14 | (25.5, 31) | 69 | (64.6, 74.1) | 127 | (116.6, 138.9) |
| **65-69** | 170 | (122.1, 230.5) | 246 | (222.7, 271.8) | 166 | (154.4, 177.9) | 195 | (166.9, 227.6) | 50 | (43.7, 55.9) | 34.70 | (31.5, 38.2) | 79 | (73.1, 84.5) | 151 | (137.9, 165.5) |
| **70-74** | 184 | (131.3, 252.3) | 246 | (221.9, 271.1) | 167 | (155.1, 180.3) | 188 | (158.4, 221.7) | 49 | (43, 55.7) | 39.75 | (36.1, 43.7) | 80 | (74, 86.7) | 157 | (142.6, 173.5) |
| **75-79** | 162 | (108.3, 233.6) | 241 | (215.7, 269.3) | 146 | (133.7, 159.3) | 189 | (157.5, 225.6) | 45 | (38.6, 52.2) | 44.89 | (40.8, 49.2) | 84 | (77.4, 91.8) | 167 | (150.3, 184.4) |
| **80-84** | 96 | (49.1, 169.6) | 239 | (208.9, 273.2) | 141 | (127, 156.7) | 169 | (134.7, 208.8) | 35 | (27.9, 42.5) | 44.17 | (39.6, 49.1) | 85 | (76.8, 94.1) | 158 | (138.7, 178.2) |
| **85+** | 89 | (39.5, 174.1) | 151 | (124.2, 180.8) | 116 | (102.6, 131.2) | 110 | (78.2, 151.8) | 16 | (10.9, 22.9) | 42.75 | (37.9, 48.1) | 68 | (60.1, 77.2) | 119 | (99.9, 140) |

[1] De Diego-Sastre JI, Prim-Espada MP, Fernández-García F. The epidemiology of Bell's palsy. RevNeurol 2005;41(05):287-90.

[2] Greco A, Gallo A, Fusconi M, Marinelli C, Macri GF, de Vincentiis M. Bell's palsy and autoimmunity. Autoimmunity Reviews 2012;12(2):323-8.

[3] Alp H, Tan H, Orbak Z. Bell's palsy as a possible complication of hepatitis B vaccination in a child. J Health Popul Nutr 2009;27(5):707-8.

[4] Chou CH, Liou WP, Hu KI, Loh CH, Chou CC, Chen YH. Bell's palsy associated with influenza vaccination: two case reports. Vaccine 2007;25(15):2839-41.

[5] Rath B, Linder T, Cornblath D, Hudson M, Fernandopulle R, Hartmann K, et al. All that palsies is not Bell's -the need to define Bell's palsy as an adverse event following immunization. Vaccine 2007;26(1):1-14.

[6] Mutsch M, Zhou W, Rhodes P, Bopp M, Chen RT, Linder T, et al. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med 2004;350(9):896-903.

[7] Zhou W, Pool V, DeStefano F, Iskander JK, Haber P, Chen RT. A potential signal of Bell's palsy after parenteral inactivated influenza vaccines: reports to the Vaccine Adverse Event Reporting System (VAERS)--United States, 1991-2001. Pharmacoepidemiol Drug Saf 2004;13(8):505-10.

[8] Rowhani-Rahbar A, Klein NP, Lewis N, Fireman B, Ray P, Rasgon B, et al. Immunization and Bell's palsy in children: a case-centered analysis. Am J Epidemiol 2012;175(9):878-85.

[9] Stowe J, Andrews N, Wise L, Miller E. Bell's palsy and parenteral inactivated influenza vaccine. Hum Vaccin 2006;2(3):110-2.

[10] Black S, Eskola J, Siegrist CA, Halsey N, Macdonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet 2009;374(9707):2115-22.

[11] The European Medicines Agency, The European Centre for Disease Prevention and Control, The Heads of Medicines Agencies. (2009) European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring. Available:http://www.emea.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500044933.pdf. Accessed 20/11/2009.

[12] Kurz X, Domergue F, Slattery J, Segec A, Szmigiel A, Hidalgo-Simon A. Safety monitoring of Influenza A/H1N1 pandemic vaccines in EudraVigilance. Vaccine 2011;29(26):4378-87.

[13] Ahmad O, Boschi-Pinto C, Lopez A, Murray C, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. GPE Discussion Paper Series: no31. Geneva: World Health Organization, 2000.

[14] Rowlands S, Hooper R, Hughes R, Burney P. The epidemiology and treatment of Bell's palsy in the UK. European Journal of Neurology 2002;9(1):63-7.

[15] Savettieri G, Salemi G, Rocca WA, Meneghini F, Santangelo R, Morgante L, et al. Incidence and lifetime prevalence of Bell's palsy in two Sicilian municipalities. Sicilian Neuro-Epidemiologic Study (SNES) Group. Acta Neurol Scand 1996;94(1):71-5.

[16] Monini S, Lazzarino AI, Iacolucci C, Buffoni A, Barbara M. Epidemiology of Bell's palsy in an Italian Health District: incidence and case-control study. Acta Otorhinolaryngol Ital 2010;30(4):198.

[17] Campbell KE, Brundage JF. Effects of climate, latitude, and season on the incidence of Bell's palsy in the US Armed Forces, October 1997 to September 1999. Am J Epidemiol 2002;156(1):32-9.

[18] Rasmussen TA, Jorgensen MR, Bjerrum S, Jensen-Fangel S, Stovring H, Ostergaard L, et al. Use of population based background rates of disease to assess vaccine safety in childhood and mass immunisation in Denmark: nationwide population based cohort study. BMJ 2012;345:e5823.

[19] Nigrovic LE, Thompson AD, Fine AM, Kimia A. Clinical Predictors of Lyme Disease Among Children With a Peripheral Facial Palsy at an Emergency Department in a Lyme Disease–Endemic Area. Pediatrics 2008;122(5)e1080-85

[20] European concerted action on lyme borreliosis. (2009) Epidemiology of European Lyme Borreliosis. Available: http://www.eucalb.com/. Accessed 13/08/2013

## 4.5 Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe

**The work presented in this section is based on work published in:**

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**Abstract**

**Objective:** To assess the association between influenza A(H1N1)pdm09 vaccine and Guillain-Barré syndrome.

**Design:** Case-control study.

**Setting:** Five European countries.

**Participants**: 104 patients with Guillain-Barré syndrome and its variant Miller-Fisher syndrome matched to one or more controls. Case status was classified according to the Brighton Collaboration definition. Controls were matched to cases on age, sex, index date, and country.

**Main outcome measures**: Relative risk estimate for Guillain-Barré syndrome after pandemic influenza vaccine.

**Results:** Case recruitment and vaccine coverage varied considerably between countries; the most common vaccines used were adjuvanted (Pandemrix and Focetria). The unadjusted pooled risk estimate for all countries was 2.8 (95% confidence interval 1.3 to 6.0). After adjustment for influenza-like illness/upper respiratory tract infection and seasonal influenza vaccination, receipt of pandemic influenza vaccine was not associated with an increased risk of Guillain-Barré syndrome (adjusted odds ratio 1.0, 0.3 to 2.7). The 95% confidence interval shows that the absolute effect of vaccination could range from one avoided case of Guillain-Barré syndrome up to three excess cases within six weeks after vaccination in one million people.

**Conclusions:** The risk of occurrence of Guillain-Barré syndrome is not increased after pandemic influenza vaccine, although the upper limit does not exclude a potential increase in risk up to 2.7-fold or three excess cases per one million vaccinated people. When assessing the association between pandemic influenza vaccines and Guillain-Barré syndrome it is important to account for the effects of influenza-like illness/upper respiratory tract infection, seasonal influenza vaccination, and calendar time.

## Introduction

During the 2009 influenza A (H1N1) pandemic, new monovalent adjuvanted and non-adjuvanted pandemic influenza A (H1N1) vaccines were introduced in Europe. Documented immunogenicity and safety was in line with the CHMP Note for Guidance, but safety data were limited [1-8]. Vaccination campaigns started in autumn 2009 at the peak of the pandemic in Europe.

A concern with the pandemic influenza A (H1N1) 2009 vaccine was the possible occurrence of neuroimmunological adverse events, including Guillain-Barré syndrome. A more than sevenfold increased risk of Guillain-Barré syndrome was observed in the 6 weeks following receipt of the swine-origin influenza A (H1N1) subtype A/NJ/76 vaccine applied in the United States in 1976 [9], when the vaccination campaign had to be discontinued abruptly. Subsequent prospective surveillance studies [10;11] and retrospective epidemiological studies [12;13] on seasonal influenza vaccines used in 1978, 1979, 1980, 1992, 1993, and beyond showed no or modest increases (up to twofold) in risk of Guillain-Barré syndrome. Even though the studies repeatedly showed risk estimates well below the sevenfold increase of 1976, they do not provide reassurance that there is no increase in risk after seasonal influenza vaccination. Small increases might surface only during mass vaccination campaigns.

Guillain-Barré syndrome is an acute polyneuropathy, which, in Europe, mostly presents as acute inflammatory demyelinating polyradiculoneuropathy leading to progressive symmetrical paresis [14-16]. Guillain-Barré syndrome is fatal in 3-10% of cases and leads to disability for more than six months in 20% [17]. The risk increases with age; reported incidence rates range between 0.4 and 4 per 100,000 person years [18].

The pathogenesis of the syndrome is not fully understood, but it is usually preceded by specific gastrointestinal and respiratory infections [21]. Some infections might induce the production of cross reactive antibodies to neural gangliosides [22], which cause inflammatory neural damage. In 2008, Nachamkin et al reported that the 1976 influenza A (H1N1) vaccine was capable of inducing cross reactive anti-GM1 in mice, supporting a causal relation between the vaccination and Guillain-Barré syndrome [23].

To date the role of influenza vaccinations as a trigger in Guillain-Barré syndrome remains controversial. Two recent studies from the United Kingdom found no

supporting evidence for a causal relation but rather identified influenza-like illness as a strong risk factor [21;24]. The results suggested a protective effect of seasonal vaccination, possibly through the prevention of influenza-like illness [21].

Prospective monitoring of vaccine safety is essential in maintaining public trust in vaccination campaigns [25]. This and the issues around Guillain-Barré syndrome in 1976 led the European Centre for Disease Prevention and Control (ECDC) to commission a prospective evaluation of any association between pandemic influenza vaccines and Guillain-Barré syndrome.

## Methods

*Setting*

The VAESCO (Vaccine Adverse Events Surveillance and Communication) consortium conducted a distributed case-control study. VAESCO is a growing network of organisations (public health institutes, regulatory agencies, and academic research centres) in Europe dedicated to improving the monitoring of safety of vaccines after licensing and was initiated by the European Centre for Disease Prevention and Control. Centres in Denmark, France, the Netherlands, Sweden, and the UK participated in this study. The respective databases captured a total source population of 50 million. All centres worked according to a common protocol with a standardised case definition and data collection form. Data were entered locally through a common electronic data entry system. At each centre, transformations were carried out using a standardised JAVA based program (Jerboa version 2.6.0, Erasmus University Medical Center, Rotterdam, Netherlands), which was verified using SAS [26]. Only completely anonymous and de-identified datasets with no individual dates of disease or exposure were shared for data pooling and centralised analysis. Consent forms, original data, and Jerboa input files were kept locally. Because of differences in healthcare structure and availability of registries, the type of source population from which cases and controls were recruited and the type of data sources differed by country (see table 4.15). The coordinating centre closely verified and queried data quality. The coordinating centre and the national lead investigators ensured that, as far as possible, information was collected in the same way from cases and controls. The study period ran between 1 November 2009 and 30 March 2010.

*Cases and controls*

For this study we included cases of Guillain-Barré syndrome and its variant Miller-Fisher syndrome. Each case was validated according to the standardised case definition of Guillain-Barré syndrome developed by the Brighton Collaboration for use in immunisation safety studies [14], using information obtained from the reporting neurologist (France, Sweden, and Netherlands) or from data in medical charts/records (UK, Denmark). All cases fulfilling the case definition for Guillain-Barré syndrome or Miller Fisher syndrome level 1 to 3 were included as well as any other cases with a diagnosis confirmed by a neurologist. A sensitivity analysis was conducted in which we restricted the cases to those meeting Brighton Collaboration definition levels 1-3 only.

The index date was the earliest date of first symptoms or diagnosis of Guillain-Barré syndrome. Table 4.15 summarises country specific approaches to identification of cases and controls. Each case was matched to up to 25 controls on age (plus or minus one year), sex, index date, and country.

*Exposure classification*

The primary exposure of interest was pandemic influenza vaccination during a risk window of one day to 42 days before the index date, reflecting the 6 week risk period observed in 1976. Exposure was further classified according to the brand of vaccine (Pandemrix, Focetria, Celvapan, Panenza, or other) and dose (first or second). Vaccination occurring more than six weeks before was classified as past exposure [9]. Unknown vaccination dates were categorised separately. Data on pandemic influenza vaccination were obtained from vaccine registries in Denmark and France, from general practitioner records in the UK and the Netherlands, and through structured interviews in Sweden.

*Control for confounding*

Information on the following covariates was collected with a standardised data collection form in each country: history of Guillain-Barré syndrome, Epstein-Barr virus infection, malignancy, immunosuppression, autoimmune disorder, gastrointestinal infections, influenza-like illness or upper respiratory tract infection, and other vaccinations (especially seasonal influenza vaccination). For influenza-like illness or upper respiratory tract infection, gastrointestinal infection, and seasonal influenza

vaccination, the risk window comprised the six weeks before the index date, not including the index date itself. Seasonal influenza vaccination (2009-10 season) more than six weeks before the index date was classified as past exposure. Information on covariates was retrieved from general practice records in the UK and the Netherlands, from hospital medical records in France, and by structured interview in Sweden. In Denmark, information on covariates was obtained through chart review of the cases only and therefore could not be used for statistical adjustments.

*Statistical analysis*

Matched odds ratios and 95% confidence intervals were calculated with multivariate conditional logistic regression. "No vaccination" in the six weeks before the index date served as the reference category. Variables considered for inclusion in the final model were those that were associated with Guillain-Barré syndrome in the univariate matched analysis at $p<0.1$; they were retained in the final model if they changed the point estimate of the association between the pandemic influenza vaccine and Guillain-Barré syndrome by more than 10% [27]. We conducted age stratified analyses to estimate the association with pandemic influenza vaccination in different age groups. We explored interactions between pandemic influenza vaccination and the main confounders by applying population restrictions but had insufficient power for statistical testing because of the low prevalence of exposure.

We carried out sensitivity analyses regarding disease and misclassification of exposure to pandemic influenza vaccination to assess robustness of the results. Exposure misclassification was addressed with three approaches: with all people with unknown dates of vaccination considered as exposed; with all people with unknown dates of vaccination considered as unexposed; and with all exposures more than six weeks before classified as non-exposure.

Risk estimates across countries were pooled with a meta-analytical approach to account for the differences in exposure prevalence. We used a random effects model to account for heterogeneity between countries [28]. For all analyses significance was accepted at a two sided $p<0.05$. Analyses were done in SPSS 15.0 for windows (release 15.0, 2006, SPSS, Chicago, IL).

**Table 4.15** Sources for cases, controls, exposure, and covariates by country in study of association between pandemic influenza A (H1N1) 2009 vaccine and Guillain-Barré syndrome

| Country | Cases | Controls | Matching | Exposure to H1N1 vacc | Covariates |
|---|---|---|---|---|---|
| UK | Each case identified from GPRD by using appropriate READ codes (F370.00, F370000, F370100, F370200, F370z00). Case verification done with free text, scanned hospital letters as well as GPs' notes regarding diagnostic procedures. No major selection expected | Controls selected randomly from General Practice Research Database, matched on age, sex, practice, and index date to case. Consent not required. No selection expected | Sex, age, practice, index date | From automated GP records, no recall bias. Non-differential misclassification possible as some vaccination outside of GP office | From GP record for cases and controls |
| Denmark | Cases identified from National Patient Register with primary discharge diagnoses only (ICD-10 code: G61.0). Case verification done after obtaining charts from cases. Potential small selection because of incomplete availability of charts | Controls selected randomly from Danish civil registration system. Up to 20 controls matched to case on age, sex, and index date. Consent not required. No selection expected | Sex, age, index date | From vaccination registry, no recall bias | From medical charts for cases only) |
| Netherlands | Cases identified prospectively through neurologists. Completeness verified retrospectively by checking against claims codes in each of reporting hospitals. Consent not required. Missing patients included retrospectively as far as possible. Verification of reporting against vaccination status showed incomplete reporting but non-differential regarding vaccinations | Controls were identified from GP of case patients. 10 patients randomly selected from list of registered patients and matched to case on age, sex, index date, and practice. Consent not required. No selection bias expected | Sex, age, practice, index date | From GP record. No recall bias Non-differential misclassification possible as some people might have been vaccinated outside of GP office | From GP records for cases and controls |
| France | Cases identified prospectively through neurologists in seven reference hospitals in France. All patients provided informed consent. Verified against pharmacy data (immunoglobulin prescriptions) and showed incomplete reporting (<50%). Vaccination status of non-reported cases could not be verified as linkage to vaccination registry required consent | Controls obtained from trauma unit in same hospital. Controls needed to provide informed consent. Response incomplete. Not possible to assess whether non-response differed by vaccination status and hence cannot exclude selection bias | Sex, age, hospital, index date | From registry. No recall bias | Medical records for both cases and controls |
| Sweden | Cases identified through seven neurology assessment labs covering a population of 9.4 million. Informed consent needed from all cases. Completeness of cases was checked in National Patient Registry for part of country. Recruitment incomplete because of delays in consent and non-consent. Not possible to assess whether non-response differed by vaccination status and hence cannot exclude selection bias | Controls selected randomly from Swedish national population registry. Controls needed to provide informed consent. Response incomplete. Not possible to assess whether non-response differed by vaccination status and hence cannot exclude selection bias | Sex, age, index date | By interview, cannot exclude recall bias | By interview for cases and controls. Charts reviewed for case verification |

**Results**

*Study population*

From a source population of about 50 million in the five countries, 154 cases of Guillain-Barré syndrome were identified. Of these, 104 could be matched to one or more controls. Many unmatched cases were from France, where timely recruitment of controls was problematic. Comparison of the number of patients with Guillain-Barré syndrome in hospital claims registries in the Netherlands suggested around 50% under-reporting of cases omitted for the study. The uptake of pandemic influenza A (H1N1) 2009 vaccine in excluded cases was similar to that in the included cases.

Most cases were men, aged 46-61 (table 4.16) and had Brighton Collaboration case classification level 1 to 3. In countries with retrospective chart or medical record review (Denmark and UK) the available information did not always allow for Brighton Collaboration classification, mostly because information regarding symptoms and diagnostic processes was not recorded to the required level of detail and could not be retrieved retrospectively. Acute inflammatory demyelinating polyradiculoneuropathy was the most common type of Guillain-Barré syndrome. Six patients (5.8%) had a disability score of 5 (ventilator treatment required) or 6 (fatal).

Chronic comorbidity was rare; malignancy and immunocompromise were the most common comorbid conditions, but these were no more prevalent among cases than controls. Acute infections in the six weeks leading up to the index date were more common and occurred mostly in cases (table 4.17). Most infections were influenza-like illness/upper respiratory tract infections. They were strongly associated with Guillain-Barré syndrome, with odds ratios ranging from 4.9 (95% confidence interval 1.6 to 15.5) in the UK to 19.3 (5.9 to 63.4) in the Netherlands.

*Vaccinations*

Pandemrix was the most widely used pandemic influenza A (H1N1) 2009 vaccine in the study population as this was the main brand used in Denmark, Sweden, and the UK. In the Netherlands Focetria was the predominant vaccine, but Pandemrix was used in children aged below 6. Other brands were used only rarely. Vaccine uptake was highest in the Netherlands and Sweden and was much lower (<10% of study population) in the UK, Denmark, and France (table 4.18). In each country, exposure to the vaccine in unmatched cases was similar to that in matched cases. Exposure

prevalence among unreported cases in the Netherlands was similar to that of cases in the study.

Seasonal influenza vaccination coverage in the Netherlands was similar to pandemic influenza vaccination coverage but consistently occurred earlier and therefore was more often classed as past exposure (table 4.18). In the UK seasonal influenza vaccination was more common than pandemic influenza vaccination, and there was evidence of an increased risk of Guillain-Barré syndrome with recent exposure to seasonal influenza vaccination (odds ratio 6.3 (1.8 to 22.0) with no adjustment for influenza-like illness/upper respiratory tract infections; 5.1 (1.4 to 18.6) with adjustment). In Sweden the recorded uptake of seasonal influenza vaccination was low and potentially incomplete. For Denmark and France, no information on seasonal influenza vaccination was available for controls. No cases were exposed to other types of vaccination in the six weeks before the index date.

*Guillain-Barré syndrome and pandemic influenza vaccination*

Unadjusted matched analyses resulted in risk estimates for Guillain-Barré syndrome with pandemic influenza vaccination that ranged from 1.3 to 2.5 in the UK, Sweden, and Netherlands (table 4.20). The risk estimate in Denmark, based on two exposed cases, was 9.5 (1.7 to 53). Both cases had extensive comorbidity but no influenza-like illness/upper respiratory tract infections or gastrointestinal infections recorded in the charts. We could not calculate an estimate for France because there was only one exposed case and no exposed controls. There was no difference in risk between Pandemrix and Focetria, although the products could not be compared within countries. Two doses of pandemic influenza vaccination as provided in the Netherlands seemed to be associated with a higher risk of Guillain-Barré syndrome (table 4.19).

The increase in risk of Guillain-Barré syndrome associated with pandemic influenza vaccination in the unadjusted analyses disappeared when we adjusted the results for influenza-like illness/upper respiratory tract infections and seasonal influenza vaccination. Adjusted risk estimates for the Netherlands and the UK, where information on both variables was available, were 0.6 (0.1 to 4.4) and 0.7 (0.1 to 4.1), respectively (table 4.19).

The test for homogeneity in effect estimates across the four countries was not significant (P=0.40), but, because of lack of power of the test and the differences observed, we used a random effects model for the weighted pooling. The crude

matched risk for Guillain-Barré syndrome was 2.8 (1.3 to 6.0). The random effects risk estimate adjusted for seasonal influenza vaccination and influenza-like illness/upper respiratory tract infections for the Netherlands, UK, and Sweden was 1.0 (0.3 to 2.7, P=0.81 for homogeneity). As Swedish data did not capture seasonal influenza vaccination well and might be subject to selection and recall bias, we conducted a sensitivity analysis without Sweden. The pooled adjusted odds ratio was 0.7 (0.2 to 2.5) (table 4.20). Denmark could not be included in the adjusted analyses because information on influenza-like illness/upper respiratory tract infections and seasonal influenza vaccination was unavailable for the controls.

*Restricted and stratified analyses*

Among individuals without influenza-like illness/upper respiratory tract infections, the risk of Guillain-Barré syndrome was higher in vaccinated than unvaccinated individuals, however this association was non-significant, unstable and shrank on adjustment for seasonal influenza vaccination (table 4.20). Influenza-like illness/upper respiratory tract infections had a strong confounding effect in people without seasonal influenza vaccination. As recorded seasonal influenza vaccination in Sweden was possibly incomplete we could explore confounding only by influenza-like illness/upper respiratory tract infections, which again was substantial (matched odds ratio for Swedish population without influenza-like illness/upper respiratory tract infections was 1.3, 0.2 to 8.1).

Cases in children were rare (9%, table 4.16). Most cases were in people aged 19-59 (n=57, 55%), in whom uptake of pandemic influenza A (H1N1) 2009 vaccine was low (exposure in controls 4%). Uptake of the vaccine was higher in those aged over 60 (10% in controls). Risk estimates for those aged 19-59 and 60 and over did not differ significantly (4.9 (1.3 to 17.9) *v* 2.7 (0.8 to 9.1)). Below the age of 19 the risk estimate seemed high but this was unstable because of too few exposed people (one case and two controls).

**Table 4.16** Recruitment of cases with Guillain-Barré syndrome and coverage with influenza A(H1N1)pdm09 vaccine by country.

| | Netherlands | Sweden | UK* | Denmark† | France | Pooled |
|---|---|---|---|---|---|---|
| Brand used | Focetria (Pandemrix in children) | Pandemrix | Pandemrix (Celvapan, Focetria) | Pandemrix | Pandemrix (Celvapan, Focetria, Panenza) | — |
| Vaccination coverage (%)‡ | 33 | 62 | 8 | 6 | 7-8 | |
| Approximate source population (million) | 16 | 9.4 | 3.5 | 5.5 | 10-20 | 49.4 |
| Expected No of cases in study period§ | 100 | 59 | 22 | 34 | 62-25 | 299 |
| No of cases recruited | 33 | 26 | 34 | 24 | 37 | 154 |
| No of cases with ≥1 control | 25 | 18 | 30 | 24 | 7 | 104 |
| Total No of controls | 227 | 60 | 300 | 590 | 21 | 1198 |
| Total study population | 252 | 78 | 330 | 614 | 28 | 1302 |
| **Characteristics of cases (No (%) unless stated otherwise)** | | | | | | |
| Mean (SD) age (years) | 46 (23) | 55 (20) | 48 (23) | 48 (19) | 61 (16) | 50 (22) |
| Age ≤18 | 4 (16) | 0 | 4 (13) | 1 (4) | 0 | 9 (9) |
| Age 19-59 | 13 (52) | 9 (50) | 16 (53) | 16 (67) | 3 (43) | 57 (55) |
| Age ≥60 | 8 (32) | 9 (50) | 10 (33) | 7 (29) | 4 (57) | 38 (37) |
| Male | 14 (56) | 13 (73) | 17 (57) | 14 (57) | 4 (58) | 62 (60) |
| Brighton Collaboration case classification: | | | | | | |
| Level 1 | 10 (40) | 11 (61) | 0 | 7 (29) | 4 (57) | 32 (31) |
| Level 2 | 10 (40) | 3 (17) | 0 | 8 (33) | 2 (29) | 23 (22) |
| Level 3 | 3 (12) | 4 (22) | 0 | 3 (13) | 0 | 10 (10) |
| Neurologist confirmed but not level 1-3 | 2 (8) | 0 | 30 (100) | 6 (25) | 1 (14) | 39 (38) |

*UK stopped recruitment of cases and controls for case-control study on 2 Feb 2010.
†Register from which cases identified in Denmark ran until end of December 2009.
‡Based on VENICE data.
§Based on 1.5 per 100 000 person years (IR) and 5 month study period: IR*source population*5/12.

**Table 4.17** Distribution of chronic comorbidity and infections in cases and controls by country in case control study of association between influenza A(H1N1)pdm09 vaccine and Guillain-Barré syndrome. Figures are numbers (percentages).

| | Netherlands | | Sweden | | UK | | France | | Denmark | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control (n=227) | Case (n=25) | Control (n=60) | Case (n=18) | Control (n=300) | Case (n=30) | Control (n=21) | Case (n=7) | Control (n=590)* | Case (n=24) |
| **Chronic comorbidity** | | | | | | | | | | |
| Autoimmune disease | 6 (3) | 2 (8) | 4 (7) | 0 | 47 (16) | 8 (27) | 0 | 0 | NA | 0 |
| History of Guillain-Barré | 0 | 1 (4) | 0 | 0 | 0 | 1 (3) | 0 | 0 | NA | 1 (4) |
| Epstein Barr virus | 12 (5) | 2 (8) | 0 | 0 | 1 (0.3) | 1 (3) | 0 | 0 | NA | 0 |
| Malignancy | 12 (5) | 1 (4) | 4 (7) | 2 (11) | 16 (5) | 2 (7) | 3 (14) | 1 (14) | NA | 1 (4) |
| Immune compromised | 5 (2) | 1 (4) | 0 | 1 (6) | 26 (9) | 4 (13) | 2 (10) | 0 | NA | 0 |
| **Infections in 6 weeks before** | | | | | | | | | | |
| Gastrointestinal infection | 1 (0.4) | 2 (8) | 1 (2) | 4 (22) | 0 | 0 | 0 | 2 (29) | NA | 2 (8) |
| Influenza-like illness | 3 (1) | 8 (32) | 0 | 2 (11) | 1 (0.3) | 0 | 0 | 0 | NA | 4 (17) |
| Upper respiratory tract infection | 10 (4) | 8 (32) | 3 (5) | 4 (22) | 11 (4) | 5 (17) | 0 | 2 (29) | NA | 0 |
| Influenza-like illness or upper respiratory tract infection (%) | 13 (6) | 12 (48) | 3 (5) | 6 (33) | 12 (4) | 5 (17) | 0 | 2 (29) | NA | 4 (17) |

*No information collected on covariates.

**Table 4.18** Influenza vaccinations in cases and controls according to timing of vaccination (≤6 weeks or >6 weeks) before onset of symptoms and brand.

| | Netherlands | | Sweden | | UK | | France | | Denmark | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Case | Control | Case | Control | Case | Control | Case | Control | Case |
| **Pandemic influenza A (H1N1) 2009 vaccine** | | | | | | | | | | |
| None | 149 (66) | 13 (52) | 23 (38) | 7 (39) | 279 (93) | 28 (93) | 20 (95) | 5 (71) | 568 (96) | 20 (83) |
| ≤6 weeks* | 33 (15) | 6 (24) | 11 (18) | 6 (33) | 16 (5) | 2 (7) | 0 | 1 (14) | 6 (1) | 2 (8) |
| Dose: | | | | | | | | | | |
| 1 dose | 26 (12) | 2 (8) | 11 (18) | 6 (33) | 16 (5) | 2 (7) | 0 | 0 | 6 (1) | 2 (8) |
| 2 doses | 7 (3) | 4 (16) | 0 | 0 | 2 (2) | 0 | 0 | 1 (14) | 0 | 0 |
| Brand: | | | | | | | | | | |
| Pandemrix | 0 | 0 | 11 (18) | 6 (33) | 13 (4) | 2 (7) | 0 | 0 | 6 (1) | 2 (8) |
| Focetria | 33 (15) | 6 (24) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Panenza | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 (14) | 0 | 0 |
| Unknown | 0 | 0 | 0 | 0 | 3 (1) | 0 | 0 | 0 | 0 | 0 |
| >6 weeks† | 42 (19) | 6 (24) | 14 (23) | 4 (22) | 5 (2) | 0 | 0 | 0 | 16 (3) | 2 (8) |
| Unknown timing | 3 (1) | 0 | 12 (20) | 1 (6) | 0 | 0 | 1 (5) | 1 (14) | 0 | 0 |
| **Seasonal influenza vaccination** | | | | | | | | | | |
| None | 145 (64) | 13 (52) | 53 (88) | 18 (100) | 222 (74) | 19 (63) | 0 | 0 | NA | 0 |
| ≤6 weeks* | 24 (11) | 2 (8) | 2 (3) | 0 | 28 (9) | 7 (23) | 0 | 0 | NA | 0 |
| >6 weeks† | 57 (25) | 10 (40) | 3 (5) | 0 | 50 (17) | 4 (13) | 0 | 0 | NA | 0 |
| Unknown timing | 1 (0.4) | 0 | 2 (3) | 0 | 0 | 0 | 0 | 0 | NA | 0 |

*Vaccine given ≤6 weeks before index date (earliest date of first symptoms or diagnosis of Guillain-Barré syndrome).

‡Vaccine given >6 weeks before index date.

**Table 4.19** Crude and adjusted relative risk estimates (odds ratio and 95% confidence intervals) for Guillain-Barré syndrome after influenza A(H1N1)pdm09 vaccination according to timing of vaccination (≤6 weeks or >6 weeks) before onset of symptoms.

| | Unadjusted matched analysis* | ILI/URTI adjusted only | Adjusted for seasonal influenza vaccination only | Adjusted for seasonal influenza vaccination and ILI/URTI |
|---|---|---|---|---|
| Denmark: | | | | |
| None | Reference | — | — | — |
| ≤6 weeks | 9.5 (1.7 to 53) | — | — | — |
| >6 weeks | 3.4 (0.7 to 17) | — | — | — |
| Netherlands: | | | | |
| None | Reference | Reference | Reference | Reference |
| ≤6 weeks | 2.5 (0.7 to 9.3) | 1.3 (0.3 to 6.1) | 1.7 (0.3 to 8.8) | 0.6 (0.1 to 4.4) |
| 1 dose | 0.7 (0.1 to 6.0) | 0.2 (0.0 to 4.2) | 0.5 (0.1 to 5.1) | 0.2 (0.01 to 4.3) |
| 2 doses | 6.8 (1.3 to 36) | 5.3 (0.6 to 44.1) | 6.2 (1.1 to 35.4) | 6.9 (0.6 to 81.0) |
| >6 weeks | 1.7 (0.4 to 6.4) | 0.9 (0.2 to 4.2) | 0.7 (0.1 to 4.8) | 0.2 (0.02 to 1.6) |
| Missing dates | NC | NC | NC | NC |
| Sweden†: | | | | |
| None | Reference | Reference | Reference† | Reference† |
| ≤6 weeks | 2.3 (0.5 to 11.7) | 1.8 (0.3 to 10.7) | 2.4 (0.5 to 11.8) | 1.8 (0.3 to 12) |
| >6 weeks | 0.9 (0.2 to 4.9) | 1.0 (0.2 to 6.3) | 1.2 (0.2 to 6.3) | 1.3 (0.2 to 8.5) |
| Missing date | 0.3 (0.03 to 3.5) | 0.5 (0.0 to 5.5) | 0.4 (0.0 to 4.0) | 0.6 (0.1 to 6.8) |
| UK: | | | | |
| None | Reference | Reference | Reference | Reference |
| ≤6 weeks | 1.3 (0.3 to 6.4) | 1.1 (0.2 to 5.7) | 0.7 (0.1 to 4.2) | 0.7 (0.1 to 4.1) |
| >6 weeks | NC | NC | NC | NC |

ILI/URTI=influenza-like illness or upper respiratory infection; NC=not calculated because of low numbers. *Matched on age (within 1 year), sex, and index date; additionally matched on GP practice in Netherlands and UK†No cases exposed to seasonal influenza vaccination (possible under-reporting).

**Table 4.20** Crude and adjusted relative risk estimates (odds ratio and 95% confidence intervals) from pooled analyses for Guillain-Barré syndrome after influenza A(H1N1)pdm09 vaccination given ≤6 weeks before onset of symptoms.

| | Unadjusted matched analysis* | ILI/URTI adjusted only | Adjusted for seasonal influenza vaccination only | Adjusted analysis for seasonal influenza vaccination and ILI/URTI |
|---|---|---|---|---|
| **No exposure as reference** | | | | |
| Netherlands, UK, Sweden, Denmark | 2.8 (1.3 to 6.0) | — | — | — |
| Netherlands, UK, Sweden | 2.0 (0.9 to 4.8) | 1.4 (0.5 to 3.5) | 1.5 (0.6 to 3.9) | 1.0 (0.3 to 2.7) |
| Netherlands, UK | 1.9 (0.7 to 5.3) | 1.2 (0.4 to 3.7) | 1.2 (0.4 to 3.8) | 0.7 (0.2 to 2.5) |
| **Restricted to people without ILI/URTI; no exposure as reference** | | | | |
| Netherlands, UK, Sweden | 1.9 (0.7 to 5.6) | — | 1.2 (0.4 to 4.0) | — |
| Netherlands, UK | 2.5 (0.6 to 10.7) | — | 1.2 (0.3 to 5.8) | — |

ILI/URTI=influenza-like illness or upper respiratory infection.
*Matched on age (within 1 year), sex, and index date; additionally matched on GP practice in Netherlands and UK

*Sensitivity analyses*

We carried out a number of sensitivity analyses to assess the impact of misclassification of the outcome and exposure as well as residual confounding. Restricting the cases to Brighton Collaboration case classification levels 1 to 3 did not materially alter the risk estimates (pooled random effects adjusted odds ratio 0.9, 0.2 to 4.6). Extending the risk window for pandemic influenza A (H1N1) 2009 vaccine to any time before the index date reduced this to 0.7 (0.3 to 1.9). Considering people with missing dates of pandemic influenza vaccination as exposed in the risk window reduced the estimate to 0.8 (0.3 to 2.3) as data were missing mostly in controls. Considering them as unexposed had no effect on the estimate. Excluding Sweden (the only country with interview based assessment of exposure and covariates) from the pooled analyses changed the adjusted pooled random effects estimate from 1.0 (0.3 to 2.7) to 0.7 (0.2 to 2.5) (table 4.20).

**Discussion**

*Principal findings*

In a source population of around 50 million people in Europe we could not find any association between adjuvanted pandemic influenza A (H1N1) 2009 vaccine and Guillain-Barré syndrome (adjusted odds ratio 1.0, 95% confidence interval 0.3 to 2.7). The increased risk in the unadjusted analyses disappeared when we adjusted for the apparent strong confounding of influenza-like illness/upper respiratory tract infections and seasonal influenza vaccination. Based on the 95% confidence interval for the adjusted odds ratio it is unlikely that the relative risk is above 2.7. Thus it is unlikely that there would be more than one excess case of Guillain-Barré syndrome per 340,000 vaccinated people (or three per million) given a risk window of six weeks and a background incidence rate of 1.5 per 100,000 person years.

The effects of adjustment for seasonal influenza vaccination were strong but differed between countries, which could be explained by differences in vaccination strategies. In the Netherlands the population targeted for pandemic influenza A (H1N1) 2009 vaccine overlapped largely with the population targeted for seasonal influenza vaccination, whereas in the UK it only partially overlapped as not all older people were targeted for pandemic influenza A (H1N1) 2009 vaccination. In Sweden, pandemic influenza A (H1N1) 2009 vaccine was made available to the entire population, but

there was under-reporting of seasonal influenza vaccination so that we could not appropriately adjust for it.

*Relation to other studies*

The VAESCO consortium is one of the first groups to provide data on the association between pandemic influenza A (H1N1) 2009 vaccines and Guillain-Barré syndrome with substantial power and mostly adjuvanted vaccines. Our results are comparable with those of a study investigating the risk of Guillain-Barré syndrome with non-adjuvanted pandemic influenza A (H1N1) 2009 vaccine in the US, which showed an age adjusted rate ratio of 1.77 (1.12 to 2.56) [29]. In the US Vaccine Safety Datalink no increased risk of adverse events was identified after administration of 1,195,552 doses of non-adjuvanted vaccine to people aged under 18 and 4,773,956 doses to adults [30]. Those studies made no statistical adjustment for influenza-like illness/upper respiratory tract infections and seasonal influenza vaccination.

Influenza-like illness/upper respiratory tract infections are a recognised risk factor for Guillain-Barré syndrome [16], as confirmed in our study. The association with influenza-like illness shown previously in the UK General Practice Research Database was stronger (18.0 (7.5 to 46.4) for influenza-like illness and 5.2 (3.5 to 7.6) for acute respiratory tract infections) than in our study (4.9 (1.6 to 15.5) for influenza-like illness/upper respiratory tract infections and predominantly comprising upper respiratory tract infections) [21].

Several vaccines have been associated with Guillain-Barré syndrome [31-33], but controversy remains for the influenza vaccines [9;12;13;20;34;35]. A recent study found no association between seasonal influenza vaccination and Guillain-Barré syndrome [24], whereas our study showed an increased risk. Different circumstances and differences in study design could explain this discrepancy. The previous study was a self controlled case series, had differential case verification, and used data up to 2005. In 2009, during the study period of the present study, seasonal influenza vaccinations were supplied while the pandemic was coming to its peak. As in most countries pandemic influenza vaccines became available only after the seasonal vaccination campaign, people with influenza symptoms might have had a higher uptake of seasonal influenza vaccination. If there was under-reporting of influenza-like illness in the General Practice Research Database, because patients were discouraged to visit the general practitioner for such symptoms in the UK in 2009, seasonal influenza vaccination could therefore be a proxy for influenza-like illness. This could

explain why the effect of seasonal influenza vaccination was higher than expected in the General Practice Research Database.

*Strengths and weaknesses*

By combining data from several European countries we showed consistency of the risk estimate across countries and we could increase the sample size by pooling data that were collected, transferred, and analysed in a standardised way, reducing heterogeneity between study sites. By pooling through meta-analysis we accounted for population size and differences in exposure prevalence [28]. Moreover, the differences in data collection between countries allowed us to establish the impact of potential biases.

Because this study was conducted in a pandemic situation it also has limitations, especially given the increased awareness of a potential increase in the risk of Guillain-Barré syndrome associated with pandemic influenza vaccination. As a consequence, people at increased baseline risk (such as those with a history of the syndrome) might be less likely to have received the vaccine and there could have been over-reporting or selective inclusion of exposed people with Guillain-Barré syndrome in the participating countries.

In the Netherlands there was under-reporting of cases, but verification against objective claims data suggested this was non-differential with regards to exposure. In Sweden and France, there were substantial delays in inclusion of cases, and selectiveness could not be fully assessed as data on non-included patients were not available. In the UK and Denmark, patient consent was not required, which should reduce the likelihood of differential under-reporting. This assumption, however, could not be verified with the available data. A priori we had assumed that any selection would work in the direction of including more exposed cases as many physicians were aware of the potential risk. The latter would have resulted in an overestimated risk, which does not seem to have affected our study as we did not find an increased risk.

Misclassification of the timing of pandemic influenza A (H1N1) 2009 vaccine, as reflected by the amount of missing information on vaccination, occurred mostly in controls, suggesting more accurate collection of data for cases, especially in Sweden. Sweden was the only country in which exposure was collected by interview rather than a registry, which could have introduced recall bias. Sensitivity analyses addressing this

particular issue showed that complete information on all dates would have resulted in even lower risk estimates.

We addressed important confounders by matching (age, sex, calendar time, and country) and by adjusting in a multivariate analysis. Adjustment for influenza-like illness/upper respiratory tract infection and seasonal influenza vaccination had strong effects on the risk estimates and caused the pooled estimate to reduce from 2.8 to 1.0. Both factors were positively associated with pandemic influenza vaccination and also with Guillain-Barré syndrome. In particular seasonal influenza vaccination and pandemic influenza vaccination were strongly associated with each other and adjustment for seasonal vaccination had the most pronounced effect on the effect estimate, as shown in table 4.19, both in the UK and the Netherlands. As argued above, seasonal influenza vaccination could be a proxy for being at high risk for complications associated with influenza or for having influenza symptoms as the seasonal vaccination was supplied at the beginning of the pandemic when there was fear of the consequences and the pandemic influenza vaccination was not yet supplied.

Residual confounding will exist for the countries where information on influenza-like illness/upper respiratory tract infection or seasonal influenza vaccination was (partly) unavailable, such as in Denmark, Sweden (seasonal vaccination), and France. Differential recording of risk factors for Guillain-Barré syndrome cannot be ruled out and hence more information regarding these risk factors might have been available for cases than for controls, especially if cases were recruited through neurologists. This would have resulted in an underestimated risk. Recall bias in the Swedish data cannot be ruled out as information was gathered from cases and controls by interview. In the UK information on covariates was obtained similarly for cases and controls, showing slightly less impact of influenza-like illness/upper respiratory tract infection, and the adjusted risk estimate showed no association. The relatively low impact of influenza-like illness/upper respiratory tract infection on Guillain-Barré syndrome in the UK could also be the consequence of non-differential false negative misclassification of infections: patients were advised not to visit their general practitioner for influenza-like illness.

*Meaning of the study*

In our opinion the study contributes at least four pieces of important information. The quantification of the association between Guillain-Barré syndrome and adjuvanted pandemic influenza vaccines allows for subsequent assessment of benefit to risk. Our point estimate shows no association between pandemic influenza vaccination and Guillain-Barré syndrome, although the upper confidence limit is 2.7. In terms of absolute risk, on the basis of the upper confidence limit the absolute risk would be less than three excess cases after one million vaccinations. This is well below the observed increase in risk with the 1976 swine origin influenza A (H1N1) subtype A/NJ/76 vaccine applied in the US, which was reported to be sevenfold. The consistent pattern across countries provides reassurance about the findings. The study also highlights the added value of an international data linkage study with a single protocol, a common data model, and a uniform analysis plan for the assessment of vaccine safety.

*Unanswered questions and future research*

Residual confounding by unmeasured patients' characteristics that are not time dependent (such as the underlying reason for being eligible for vaccination) can be studied with a self controlled case series design. VAESCO is finalising such a study of the association between pandemic influenza A (H1N1) 2009 vaccination and Guillain-Barré syndrome in seven countries. The series will include the cases from the study presented here supplemented with unmatched cases and cases from additional countries over a longer period. It will also eliminate any differential recording of confounders between cases and controls.

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[1] Girard MP, Katz J, Pervikov Y, Palkonyay L, Kieny M-P. Report of the 6th meeting on the evaluation of pandemic influenza vaccines in clinical trials World Health Organisation Geneva, Switzerland, 17-18 February 2010. *Vaccine* 2010;28:6811-20.

[2] Plennevaux E, Sheldon E, Blatter M, Reeves-Hoche MK, Denis M. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. *Lancet* 2010;375:41-8.

[3] Vajo Z, Tamas F, Sinka L, Jankovics I. Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009-10 influenza season: a multicentre, randomised controlled trial. *Lancet* 2010;375:49-55.

[4] Roman F, Vaman T, Gerlach B, Markendorf A, Gillard P, Devaster JM. Immunogenicity and safety in adults of one dose of influenza A H1N1v 2009 vaccine formulated with and without AS03A-adjuvant: preliminary report of an observer-blind, randomised trial. *Vaccine* 2010;28:1740-5.

[5] Nolan T, McVernon J, Skeljo M, Richmond P, Wadia U, Lambert S, et al. Immunogenicity of a monovalent 2009 influenza A(H1N1) vaccine in infants and children: a randomized trial. *JAMA* 2010;303:37-46.

[6] Oh CE, Lee J, Kang JH, Hong YJ, Kim YK, Cheong HJ, et al. Safety and immunogenicity of an inactivated split-virus influenza A/H1N1 vaccine in healthy children from 6 months to <18 years of age: a prospective, open-label, multi-center trial. *Vaccine* 2010;28:5857-63.

[7] Lu W, Tambyah PA. Safety and immunogenicity of influenza A H1N1 vaccines. *Expert Rev Vaccines* 2010;9:365-9.

[8] Lu CY, Shao PL, Chang LY, Huang YC, Chiu CH, Hsieh YC, et al. Immunogenicity and safety of a monovalent vaccine for the 2009 pandemic influenza virus A (H1N1) in children and adolescents. *Vaccine* 2010;28:5864-70.

[9] Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977. *Am J Epidemiol* 1979;110:105-23.

[10] Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981. Lack of an association with influenza vaccination. *JAMA* 1982;248:698-700.

[11] Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barré syndrome and the 1978-1979 influenza vaccine. *N Engl J Med* 1981;304:1557-61.

[12] Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *N Engl J Med* 1998;339:1797-802.

[13] Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, et al. Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. *Arch Intern Med* 2006;166:2217-21.

[14] Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2010;29:599-612.

[15] Vucic S, Kiernan MC, Cornblath DR. Guillain-Barré syndrome: an update. *J Clin Neurosci* 2009;16:733-41.

[16] Jacobs BC, Rothbarth PH, van der Meche FG, Herbrink P, Schmitz PI, de Klerk MA, et al. The spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. *Neurology* 1998;51:1110-5.

[17] Van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome. *Lancet Neurol* 2008;7:939-50.

[18] McGrogan A, Madle G, Seaman H, de Vries C. The epidemiology of Guillain-Barré syndrome worldwide. A systematic literature review. *Neuroepidemiology* 2009;32:150-63.

[19] Rees J, Thompson R, Smeeton N, Hughes R. Epidemiological study of Guillain-Barré syndrome in south east England. *J Neurol Neurosurg Psychiatry*. 1998;64:74-7.

[20] Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barré syndrome. *J Infect Dis* 1997;176(suppl 2):S92-8.

[21] Tam CC, O'Brien SJ, Petersen I, Islam A, Hayward A, Rodrigues LC. Guillain-Barré syndrome and preceding infection with campylobacter, influenza and Epstein-Barr virus in the general practice research database. *PLoS One* 2007;2:e344.

[22] Weise MJ, Carnegie PR. An approach to searching protein sequences for superfamily relationships or chance similarities relevant to the molecular mimicry hypothesis: application to the basic proteins of myelin. *J Neurochem* 1988;51:1267-73.

[23] Nachamkin I, Shadomy SV, Moran AP, Cox N, Fitzgerald C, Ung H, et al. Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barré syndrome. *J Infect Dis* 2008;198:226-33.

[24] Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barré syndrome with influenza vaccine and influenza-like illness using the United Kingdom General Practice Research Database. *Am J Epidemiol* 2009;169:382-8.

[25] Lehmann HC, Hartung HP, Kieseier BC, Hughes RA. Guillain-Barré syndrome after exposure to influenza virus. *Lancet Infect Dis* 2010;10:643-51.

[26] Coloma P, Schuemie M, Trifirò G, Gini R, Herings R, Hippisley-Cox J, et al. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project. *Pharmacoepidemiol Drug Saf* 2011;20:1-11.

[27] Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Pub Health* 1989;70:340-9.

[28] Fleis J. The statistical basis of meta-analysis. *Stat Methods in Med Res* 1993;2:121-45.

[29] Preliminary results: surveillance for Guillain-Barré syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine—United States, 2009-2010. *MMWR Morb Mortal Wkly Rep* 2010;59:657-61.

[30] Greene SK, Kulldorff M, Lewis EM, Li R, Yin R, Weintraub ES, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *Am J Epidemiol* 2010;171:177-88.

[31] Hemachudha T, Griffin DE, Chen WW, Johnson RT. Immunologic studies of rabies vaccination-induced Guillain-Barré syndrome. *Neurology* 1988;38:375-8.

[32] Piyasirisilp S, Hemachudha T. Neurological adverse events associated with vaccination. *Curr Opin Neurol* 2002;15:333-8.

[33] Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barré syndrome. *Drug Saf* 2009;32:309-23.

[34] Haber P, DeStefano F, Angulo FJ, Iskander J, Shadomy SV, Weintraub E, et al. Guillain-Barré syndrome following influenza vaccination. *JAMA* 2004;292:2478-81.

[35] Roscelli JD, Bass JW, Pang L. Guillain-Barré syndrome and influenza vaccination in the US Army, 1980-1988. *Am J Epidemiol* 1991;133:952-5.

## 4.6 Guillain-Barré syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccines: a multinational self-controlled case series in Europe

**The work presented in this section is based on work published in:**

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**Abstract**

***Background:*** Based on a-priori concerns about the risk of Guillain-Barré syndrome (GBS) following the 1976 swine flu vaccination campaign in the USA, active surveillance programs were enhanced during the pandemic influenza A(H1N1)pdm09 mass immunization campaigns. The objective of this study was to estimate the risk of developing GBS following influenza A(H1N1)pdm09 vaccination.

***Methods:*** A self-controlled case series (SCCS) analysis was performed in Denmark, Finland, France, Netherlands, Norway, Sweden, and the United Kingdom. Information was collected using a common protocol and standardised data collection procedures. Cases were classified according to the Brighton Collaboration case classification system. A 42 day post vaccination risk window was used. We adjusted for calendar month and if possible for gastrointestinal (GI) infections, influenza-like illness (ILI), and upper respiratory tract infections (URTI). Conditional Poisson regression was used for estimation of the risk ratio (RR) and pooling was done using a random effects approach.

***Findings:*** 303 GBS cases were included in the study. The unadjusted pooled RR for all countries was 3.5 (95% Confidence Interval (CI): 2.3-5.3). After adjustment for calendar month, the pooled RR was 2.0 (95% CI: 1.2-3.1). Accounting for contra-indication to vaccination reduced the pooled RR to 1.9 (95% CI: 1.1-3.2). In countries where further adjustment for infections (GI, ILI, and URTI) was possible (Netherlands, Norway, United Kingdom) the pooled RR decreased from 1.7 (adjusted for calendar month) to 1.3 (95% CI: 0.6-2.7).

***Interpretation:*** This study illustrates the potential of collaborative European vaccine safety studies. The effect of adjustments for infections and vaccinations in a subset of the countries suggests the pooled estimates for all countries suffer from residual confounding. Based on the upper limits of the partially and fully adjusted pooled estimates, we can rule out with 95% certainty that the number of excess GBS cases after influenza A(H1N1)pdm09 vaccination would be more than 3 per million vaccinated.

## Introduction

During the influenza A (H1N1) 2009 pandemic, new monovalent adjuvanted and non-adjuvanted influenza A(H1N1)pdm09 vaccines were introduced in Europe. Documented immunogenicity and safety was in line with the Committee for Medicinal Products for Human use (CHMP) Note for Guidance, but safety data were limited [1-3]. Vaccination campaigns started in the autumn of 2009 at the peak of the pandemic in Europe.

The primary safety concern with the influenza A(H1N1)pdm09 vaccines was the possible occurrence of neuroimmunologic adverse events including Guillain-Barré syndrome (GBS). An increased risk of GBS was observed in the 6 weeks following receipt of the swine-origin influenza subtype A/NJ/76 vaccine introduced in the USA in 1976, resulting in the abrupt discontinuation of the vaccination campaign [4]. All subsequent prospective surveillance studies and retrospective epidemiological studies on seasonal influenza (SI) vaccines used in 1978, 1992, 1993 and beyond showed no or modest increases in the risk of GBS [5-8]. Despite this, based on the 1976 experience, the US Food and Drug Administration (FDA), the World Health Organization (WHO) and the European Medicines Agency (EMA) all recommended to actively monitor a potential association between the influenza A(H1N1)pdm09 vaccine and the occurrence of GBS.

GBS is an acute inflammatory demyelinating polyradiculoneuropathy (AIDP) in the majority of cases [9]. Three to ten per cent of patients with GBS die and an estimated 20% experience continued disability for more than six months [10]. Prospective studies in developed countries have estimated an incidence rate of 2 per 100,000 population per year with an increased risk with age and in males [11]. GBS is thought to be primarily triggered by a preceding respiratory or gastrointestinal infection [12]. It has been suggested that the association between GBS and influenza A(H1N1)pdm09 vaccine is considered biologically plausible through the cross-production of anti-ganglioside antibodies during the immunization process [13] however Yuki et al recently reported no anti-ganglioside antibody production following influenza A(H1N1)pdm09 vaccination of both mice and men [14].

The European Centre for Disease prevention and Control (ECDC) requested the VAESCO (Vaccine Adverse Events Surveillance and Communication) consortium to conduct hypothesis testing studies on the potential association between influenza A(H1N1)pdm09 vaccine and GBS. Two designs were used: a case control design for a rapid initial assessment of an association, and a large-scale prospective self-controlled

case series (SCCS) study. The VAESCO consortium case control study was based on 104 cases in five European countries and showed no association between A(H1N1)pdm09 vaccine and GBS [15]. In this paper we present the results from the SCCS study.

## Methods

*Setting and design*

To investigate the association between influenza A(H1N1)pdm09 vaccination and GBS a prospective self-controlled case series (SCCS) study was conducted in the VAESCO consortium. The SCCS is a case-only design which compares the incidence of disease during risk and non-risk periods within the same person, thereby inherently controlling for measured and unmeasured confounding factors that remain stable over time [16]. The VAESCO consortium aims to improve post licensure vaccine safety surveillance in Europe. The project was initiated and core funded by the European Centre for Disease Prevention and Control (ECDC) and partners are a mixture of public health organizations, regulatory authorities and academic research institutions in Europe. The project was coordinated by the Brighton Collaboration Foundation. Sites from the United Kingdom (UK), France, Norway, Sweden, Finland, Netherlands and Denmark contributed to the study. All participating centres worked according to a common protocol with a standardised Brighton Collaboration case definition. Implementation of the common protocol and data collection differed per country based on ethical requirements and the healthcare structure. Data harmonization, transformation and pooling were done based on methods and infrastructure that were derived from the EU-ADR project [17]. In short, centers were asked to create harmonized input files according to well-defined instructions. Data could be obtained directly from automated resources or by manual data entry through an electronic case report form. Subsequently at each centre transformations of input data were done by a standardized JAVA-based program (Jerboa® version 2.6.0, September 2010, Erasmus University Medical Center, Rotterdam, the Netherlands). Only completely anonymous and de-identified information with no individual dates of disease or exposure were shared for individual patient level data pooling and centralised analysis. Consent forms, original data and Jerboa input files were retained at the local sites. Secondary quality control and verification of transmitted data was done at the central data management and analysis center (Erasmus University) in close collaboration with all the sites and the VAESCO consortium. Each of the study sites received the data and had the opportunity to comment on the data prior to release.

*Source and study population*

The source populations from which the cases were recruited exceeded 50 million (M) subjects with most countries recruiting cases on a national level (Norway (4.8 M), Sweden (9 M), Finland (5.5 M), Denmark (5 M), Netherlands (16 M)). In the UK the General Practice Research Database (GPRD) (3.5 M) was used and in France specialised hospitals with a large but undefined catchment area participated. Case recruitment started on 1st November 2009 and lasted a maximum of 365 days.

The study population encompassed all cases with GBS or its variant Miller Fisher syndrome with onset of disease during the study period.

Detailed descriptions of case recruitment are provided in Table 4.21. Completeness of case recruitment was verified retrospectively at the end of the study period by comparing recruited and diagnosed case lists; additional cases identified in this way were included retrospectively where possible. For each subject, follow-up started at the beginning of the study period or date of birth, if born after the start of the study period. Follow up ended at the end of the study period or death, if occurring prior to the end of the study period.

The earliest available date of onset of first neurological symptoms was used as the index date. If the date of first symptoms could not be retrieved the date of diagnosis or hospitalization was used as the index date. Informed consent was required for cases in Sweden and France. Information about case characteristics were obtained from neurologists, or discharge letters and used to classify the case according to the Brighton Case Classification using the Automated Brigton Classsification (ABC) tool (www.brightoncollaboration.org).

*Vaccine Exposure*

The primary exposure of interest was vaccination with A(H1N1)pdm09 vaccine which was assessed from vaccination registries (France, Denmark, Finland, Norway), General Practitioners' (GP) records (Netherlands, UK) or patient interview (Sweden). The risk window of interest (risk period) began the day after vaccination and ended 42 days later, reflecting the 6 week risk period observed in 1976. If two doses of the vaccine were administered, the risk window of the first dose ended when the second dose was administered. Brand specific information was collected for each influenza A(H1N1)pdm09 vaccination.

**Table 4.21** Sources of cases, exposure and covariate information per country

| | Cases recruitment | Exposure Information | Covariates during follow-up | Potential bias |
|---|---|---|---|---|
| **DK** | Cases were identified from the National Patient Register using primary discharge diagnoses only (ICD-10: G61.0). Case validation based on retrospective chart review. | Vaccination registry | None (only from case hospital charts) | Cases: not all charts available<br>No ability to control for time varying confounders |
| **FI** | From hospital Discharge and hospital outpatient records, primary diagnoses (ICD-10 G61.0). Case validation based on retrospective chart review | Vaccination registry | None (only from case hospital charts) | Cases: not all charts available<br>No ability to control for time varying confounders |
| **FR** | Cases were identified prospectively through neurologists in 7 reference hospitals in FR. Patients needed to provide informed consent. Completeness was verified against pharmacy data (immunoglobulin prescriptions) and showed incomplete reporting (<50%), Vaccination status of non-reported cases could not be verified since linkage to vaccination registry required consent. | Ad hoc A(H1N1)pdm09 vaccination registry | Hospital charts and interview, only for period prior to GBS | Incompleteness and potential selection bias cannot be excluded.<br>No ability to control for time varying confounders |
| **NL** | Cases were identified prospectively through neurologists. Completeness was verified retrospectively by checking against the claims codes in each of the reporting hospitals. Missing patients were included retrospectively in hospitals that were reporting at least one case prospectively. | GP medical record | GP medical record | Small potential for misclassification of exposure since A(H1N1)pdm09 vaccination could also be provided through public health agency for parents of young children |
| **NO** | Nationwide neurologist reporting network, group of neurologists. Case validation based on review of GBS experts | Vaccination registry | Neurologists, Hospitals, and GPs | Potential selection due to incompleteness?<br>Information on co-variates collected differently for period prior to GBS. |
| **SE** | Cases of GBS were identified through seven neurology assessment labs where GBS cases are laboratory confirmed for a population of 9.4 million. Informed consent needed to be obtained from all cases. Completeness of cases was checked in the National Patient Registry for part of the country. Recruitment was incomplete because of delays in consent and non-consent. It was not possible to assess whether this non-response differed by vaccination status and hence selection bias cannot be excluded. | By interview at end of follow-up, recall bias cannot be excluded. | By interview for cases at the end of follow up. Change in region over time. Should not be used for adjustment | Consent required, potential selection bias.<br>Recall bias (differential recall over time) |
| **UK** | Each case identified from GPRD by using appropriate READ codes (F370.00, F370000, F370100, F370200, F370z00). Case verification done with free text, scanned hospital letters as well as GPs' notes regarding diagnostic procedures. | GP medical record | GP medical record | Potential for misclassification of exposure since A(H1N1)pdm09 vaccination could also be provided outside GP setting. |

Abbreviations:, DK, Denmark; FI, Finland; FR, France; NL, Netherlands; NO, Norway; SE, Sweden; UK, United Kingdom.

*Covariates*

Information on several time varying risk factors for GBS were collected during follow-up. The impact of seasonal influenza vaccination, influenza-like illness (ILI), upper respiratory tract infections (URTI), and gastrointestinal infections (GI) were assessed over a 42 day risk period. The risk period began on the day of onset of ILI, URTI, or GI or the date of seasonal influenza vaccine receipt and ended 42 days later. Covariate information was not collected in Denmark and Finland. In France, covariate data were collected from neurologists at case occurrence for the period prior to GBS whereas in Sweden information was collected at the end of follow-up by interview. In the UK, Netherlands and Norway, general practitioner records were used and data from these records were collected similarly over the entire period; Norway also assessed covariate information received from neurologists at the time of case data collection, potentially leading to a slight differential in data collection over time. To adjust for seasonal effects and changes in circulation of the wild type influenza A(H1N1)pdm09 virus and differences in case inclusion over the observation period we considered calendar month as a time varying covariate.

*Statistical analysis*

The incidence rate ratio (RR) for the association between vaccination and GBS was estimated by using a conditional Poisson regression analysis. This was done for each country separately. Adjustment for calendar month was possible in all countries, whereas further adjustment for ILI, URTI, GI and seasonal influenza vaccination was only possible in NL, UK and NO. Sensitivity analyses were conducted to assess the effects of confounding and misclassification of exposure.

To explore confounding by contra-indication to influenza A(H1N1)pdm09 vaccination in cases with GBS, two approaches were applied: an analysis including vaccinated cases only and an analysis using a pseudo-likelihood approach. In the analysis including vaccinated cases only the observation period began on the vaccination date and continued until the end of the observation period. Dropping unexposed case-time has an adverse effect on the statistical power of the study and can introduce selection bias therefore a pseudo-likelihood approach was also applied. This approach includes all observation time for all cases but only includes the first exposure in the RR calculation and redefines any post event exposed time as baseline time, adjusting the number of events observed in this time period to that which would be expected had there been no exposures [16, 26].

To assess the impact of residual confounding by ILI, URTI, seasonal influenza vaccination and GI infections, a subset analysis was conducted in the countries where this was possible. To study misclassification of the risk period sensitivity analyses were done looking at smaller risk periods within the 42 days. In order to study effect modification by infections just prior to GBS onset, stratified analyses were done for age, sex, history of GBS and prior infections (ILI, URTI, GI), for the countries that collected this information around case occurrence. The country specific estimates were pooled using a random effects model. SAS v9.1 (Cary, North Carolina) was used for all analyses.

**Results**

During the study period, which varied across the seven participating countries, a total of 730 potential GBS cases were identified. From these 730 cases, 427 cases were excluded: 13 did not provide consent, for 160 the diagnosis could not be confirmed after validation, 5 cases were duplicates, 99 cases had onset of GBS prior to start of the study period and 150 cases were excluded since they had no available information to assess onset of disease or vaccination exposure. Finally, we included 303 GBS cases in the study (Figure 4.7). Case inclusion declined with time from 133 cases in the first three months of the study period to 18 in the last three months. Despite this decline, the percentage of influenza A(H1N1)pdm09 vaccinated cases (including those vaccinated outside the 6 week risk window) did not appear to change significantly over time.

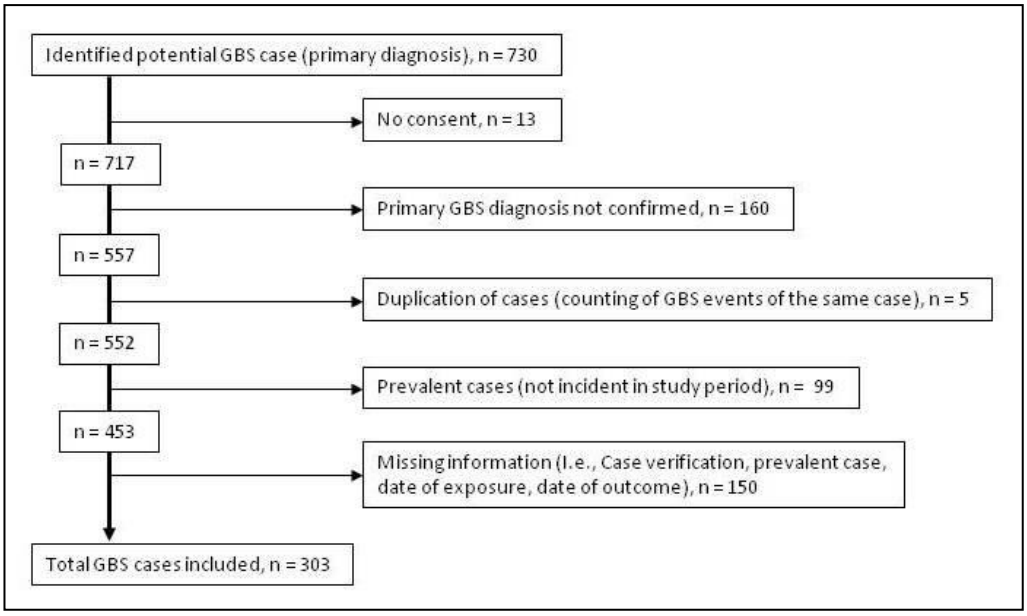


**Figure 4.7:** Flowchart of SCCS case inclusion

Cases had a mean age of 50 years (SD: 4.1) ranging from 45 years (SD: 20.8) in the Netherlands to 56 (SD: 19.5) years in Norway, and less than 10% of the cases were younger than 20. On average the follow-up period for the cases was 321 days. The case certainty classification differed by country depending on the type of data source that was used for case recruitment. From the total number of cases, 36% were classified as Brighton Collaboration classification level 1, 26% as level 2, 13% as level 3 and 25% as level 4a. In 69 cases electrophysiology either had not been performed for diagnosis or it was not explicitly recorded. When electrophysiology was performed, most cases were classified as AIDP. On a scale of 0 to 6, with 0 meaning complete physical fitness and 6 meaning death, the disability score was most frequently 4 (30.6 %), with few extreme values (Table 4.22).

99 cases (33%) were administered an influenza A(H1N1)pdm09 vaccine before symptom onset, most of which were adjuvanted with AS03 (Table 4.23). Among the 99 vaccinated cases 36 (37%) had an index date within 42 days of a first dose of influenza A(H1N1)pdm09 vaccination whereas 7 had an index date within the risk window after a second dose of influenza A(H1N1)pdm09 vaccination.

Few countries could collect data on time-varying covariates over the entire follow-up period. Most countries assessed covariates at the time of case collection, but not afterwards, and therefore these data cannot be utilized for adjustments but only for stratification. Based on the information collected at case occurrence, 15 cases developed GBS within 42 days after seasonal influenza vaccination and 79 cases developed GBS within 42 days after onset of ILI or URTI (Table 4.23).

**Table 4.22** Distribution of patient characteristics in GBS cases included in the SCCS study of the association between influenza A(H1N1)pdm09 vaccine and Guillain-Barré syndrome.

| Characteristic | UK | | NL | | FR | | SE | | FI | | NO | | DK | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | N | % | n | % | n | % | N | % | n | % | N | % | n | % |
| Cases in study period | 40 | 13.2 | 80 | 26.4 | 41 | 13.5 | 32 | 10.6 | 29 | 9.6 | 50 | 16.5 | 31 | 10.2 | 303 | 100 |
| Females | 17 | 42.5 | 32 | 40.0 | 20 | 48.8 | 12 | 37.5 | 12 | 41.4 | 25 | 50.0 | 14 | 45.2 | 132 | 43.6 |
| **\|Age** | | | | | | | | | | | | | | | | |
| Mean (SD)[1] [years] | 45.4 (20.4) | | 45.0 (20.8) | | 50.0 (21.9) | | 51.5 (20.2) | | 54.4 (20.8) | | 55.5 (19.5) | | 49.2 (20.2) | | 50.1 (4.1) | |
| Age ≤ 4 | 2 | 5.0 | 2 | 2.5 | 1 | 2.4 | 0 | 0.0 | 0 | 0.0 | 1 | 2.0 | 0 | 0.0 | 6 | 2.0 |
| Age 5 - 19 years | 3 | 7.5 | 10 | 12.5 | 4 | 9.8 | 2 | 6.3 | 3 | 10.3 | 0 | 0.0 | 3 | 9.7 | 25 | 8.3 |
| Age 20 - 59 years | 24 | 60.0 | 44 | 55.0 | 18 | 43.9 | 15 | 46.9 | 10 | 34.5 | 21 | 42.0 | 18 | 58.1 | 15 | 49.5 |
| Age ≥ 60 | 11 | 27.5 | 24 | 30.0 | 18 | 43.9 | 15 | 46.9 | 16 | 55.2 | 28 | 56.0 | 10 | 32.3 | 122 | 40.3 |
| **Brighton** | | | | | | | | | | | | | | | | |
| 1 | 0 | 0.0 | 28 | 35.0 | 13 | 31.7 | 19 | 59.4 | 17 | 58.6 | 21 | 42.0 | 10 | 32.3 | 108 | 35.6 |
| 2 | 0 | 0.0 | 30 | 37.5 | 16 | 39.0 | 8 | 25.0 | 3 | 10.3 | 14 | 28.0 | 8 | 25.8 | 79 | 26.1 |
| 3 | 0 | 0.0 | 11 | 13.8 | 7 | 17.1 | 5 | 15.6 | 7 | 24.1 | 5 | 10.0 | 4 | 12.9 | 39 | 12.9 |
| 4a | 40 | 100.0 | 10 | 12.5 | 5 | 12.2 | 0 | 0.0 | 2 | 6.9 | 10 | 20.0 | 9 | 29.0 | 76 | 25.1 |
| Unknown | 0 | 0.0 | 1 | 1.3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 0.3 |
| **Electrophysiology** | | | | | | | | | | | | | | | | |
| AIDP[2] | 0 | 0.0 | 36 | 45.0 | 15 | 36.6 | 23 | 71.9 | 16 | 55.2 | 29 | 58.0 | 23 | 74.2 | 142 | 46.9 |
| AMAN[3] | 0 | 0.0 | 6 | 7.5 | 1 | 2.4 | 0 | 0.0 | 0 | 0.0 | 3 | 6.0 | 0 | 0.0 | 10 | 3.3 |
| AMSAN[4] | 2 | 5.0 | 4 | 5.0 | 0 | 0.0 | 6 | 18.8 | 2 | 6.9 | 1 | 2.0 | 1 | 3.2 | 16 | 5.3 |
| Equivocal | 0 | 0.0 | 9 | 11.3 | 6 | 14.6 | 1 | 3.1 | 0 | 0.0 | 7 | 14.0 | 0 | 0.0 | 23 | 7.6 |
| Normal | 0 | 0.0 | 3 | 3.8 | 2 | 4.9 | 0 | 0.0 | 0 | 0.0 | 6 | 12.0 | 2 | 6.5 | 13 | 4.3 |
| Not performed | 0 | 0.0 | 20 | 25.0 | 12 | 29.3 | 2 | 6.3 | 11 | 37.9 | 3 | 6.0 | 5 | 16.1 | 53 | 17.5 |
| Unresponsive nerves | 0 | 0.0 | 1 | 1.3 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 2.0 | 0 | 0.0 | 2 | 0.7 |
| Unknown | 38 | 95.0 | 1 | 1.3 | 5 | 12.2 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 44 | 14.5 |
| **Disability score** | | | | | | | | | | | | | | | | |
| 0 | 0 | 0 | 0 | 0.0 | 6 | 14.6 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0 | 6 | 2.0 |
| 1 | 0 | 0 | 5 | 6.3 | 0 | 0.0 | 1 | 3.1 | 0 | 0.0 | 7 | 14.0 | 0 | 0 | 13 | 4.3 |
| 2 | 0 | 0 | 19 | 23.8 | 2 | 4.9 | 6 | 18.6 | 9 | 31.0 | 11 | 22.0 | 0 | 0 | 47 | 15.5 |
| 3 | 0 | 0 | 21 | 26.3 | 10 | 24.4 | 7 | 21.9 | 4 | 13.8 | 6 | 12.0 | 0 | 0 | 48 | 15.8 |
| 4 | 0 | 0 | 20 | 25.0 | 11 | 26.8 | 10 | 31.3 | 13 | 44.8 | 17 | 34.0 | 0 | 0 | 71 | 23.4 |
| 5 | 0 | 0 | 13 | 16.3 | 2 | 4.9 | 7 | 21.9 | 2 | 6.9 | 8 | 16.0 | 0 | 0 | 32 | 10.6 |
| 6 | 0 | 0 | 1 | 1.3 | 0 | 0.0 | 1 | 3.1 | 1 | 3.4 | 1 | 2.0 | 0 | 0 | 4 | 1.3 |
| Unknown | 40 | 100.0 | 1 | 1.3 | 10 | 24.4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 31 | 100.0 | 82 | 27.1 |

| *.....continued from previous page* | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Index month** | | | | | | | | | | | | | | | | |
| Nov 2009 | 6 | 15.0 | 5 | 6.3 | 9 | 22.0 | 8 | 25.0 | 4 | 13.8 | 5 | 10.0 | 9 | 29.0 | 46 | 15.2 |
| Dec 2009 | 4 | 10.0 | 22 | 27.5 | 8 | 19.5 | 6 | 18.8 | 5 | 17.2 | 12 | 24.0 | 1 | 3.2 | 58 | 19.1 |
| Jan 2010 | 5 | 12.5 | 8 | 10.0 | 9 | 22.0 | 3 | 9.4 | 5 | 17.2 | 8 | 16.0 | 6 | 19.4 | 44 | 14.5 |
| Feb 2010 | 8 | 20.0 | 9 | 11.3 | 6 | 14.6 | 5 | 15.6 | 6 | 20.7 | 1 | 2.0 | 5 | 16.1 | 40 | 13.2 |
| Mar 2010 | 6 | 15.0 | 5 | 6.3 | 3 | 7.3 | 3 | 9.4 | 3 | 10.3 | 4 | 8.0 | 4 | 12.9 | 28 | 9.2 |
| Apr 2010 | 3 | 7.5 | 7 | 8.8 | 4 | 9.8 | 2 | 6.3 | 5 | 17.2 | 4 | 8.0 | 3 | 9.7 | 28 | 9.2 |
| May 2010 | 1 | 2.5 | 8 | 10.0 | 1 | 2.4 | 2 | 6.3 | 1 | 3.4 | 3 | 6.0 | 3 | 9.7 | 19 | 6.3 |
| Jun 2010 | 3 | 7.5 | 2 | 2.5 | 1 | 2.4 | 3 | 9.4 | 0 | 0.0 | 3 | 6.0 | 0 | 0.0 | 12 | 4.0 |
| Jul 2010 | 1 | 2.5 | 3 | 3.8 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 3 | 6.0 | 0 | 0.0 | 7 | 2.3 |
| Aug 2010 | 2 | 5.0 | 4 | 5.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 2 | 4.0 | 0 | 0.0 | 8 | 2.6 |
| Sep 2010 | 0 | 0.0 | 4 | 5.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 4 | 8.0 | 0 | 0.0 | 8 | 2.6 |
| Oct 2010 | 1 | 2.5 | 3 | 3.8 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 2.0 | 0 | 0.0 | 5 | 1.7 |
| TOTAL | 40 | | 80 | | 41 | | 32 | | 29 | | 50 | | 31 | | 303 | |

[1] Standard Deviation
[2] AIDP: acute inflammatory demyelinating polyradiculoneuropathy
[3] AMAN: acute motor axonal neuropathy
[4] AMSAN: acute motor and sensory axonal neuropathy
Abbreviations: UK, United Kingdom; NL, Netherlands; FR, France; SE, Sweden; FI, Finland, NO, Norway, DK, Denmark.

*Risk ratio of GBS*

The crude RR of GBS during the influenza A(H1N1)pdm09 vaccination risk period varied from 1.6 in Finland to 7.7 in Denmark, with an overall pooled estimate of 3.5 (95% CI: 2.3-5.3). Adjustment for calendar month had a significant impact on the pooled estimate (RR 2.0, 95% CI: 1.2-3.1). Sensitivity analyses accounting for the fact that vaccination may be contra-indicated after GBS onset produced minor changes. The RR changed from 2.0 to 1.9 when the pseudolikelihood method was used (95% CI: 1.1-3.2), and to 1.8 (95% CI: 0.7-4.7) when considering vaccinated cases only (Table 4.24).

In countries where further adjustment for infections, seasonal influenza vaccination and other time dependent covariates were possible (Netherlands, Norway, UK) the RR decreased from the unadjusted RR of 3.2 (95% CI: 1.8-5.6) to 1.7 (95% CI: 0.9-3.2) after adjustment for calendar month and to 1.3 (95% CI: 0.6-2.7) upon further adjustment for ILI and URTI.

Sensitivity analyses in which we varied the risk period showed that restriction of the risk period to the first four weeks yielded a month-adjusted pooled RR of 2.3 (95% CI: 1.4-3.8) for the association between influenza A(H1N1)pdm09 vaccination and GBS. The RR was 2.3 (95% CI: 1.2-4.4) in the first two weeks and 2.6 (95% CI 1.4-4.9) during weeks three to four.

The RR of GBS following influenza A(H1N1)pdm09 vaccination adjusted for calendar month was higher in persons aged 60 or higher (RR 3.2, 95% CI 1.5-6.9) than in people who were younger than 60 (RR 1.3, 95% CI: 0.5-3.6). We did not observe statistically significant interactions between infections or seasonal influenza vaccination and the risk associated with the influenza A(H1N1)pdm09 vaccine (Table 4.25).

**Table 4.23** GBS occurrence during follow-up and during the 6-week (42 days) risk period following influenza A(H1N1)pdm09 vaccination and infection.

| Exposure | UK | | NL | | FR | | SE | | FI | | NO | | DK | | TOTAL | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Cases in study period** | 40 | 13.2 | 80 | 26.4 | 41 | 13.5 | 32 | 10.6 | 29 | 9.6 | 50 | 16.5 | 31 | 10.2 | 303 | 100 |
| **Follow-up total (mean) in days** | 12,666 (316) | | 26,322 (329) | | 11,421 (278) | | 11,471 (358) | | 6,127 (211) | | 17,845 (356) | | 11,286 (364) | | 97,138 (320) | |
| **Cases exposed to A(H1N1)pdm09 vaccine anytime during follow-up period** | 3 | 7.5 | 29 | 36.3 | 5 | 12.2 | 22 | 68.8 | 13 | 44.8 | 23 | 46.0 | 4 | 12.9 | 99 | 32.7 |
| **GBS in A(H1N1)pdm09 vaccination risk period** | | | | | | | | | | | | | | | | |
| 1st dose [1)] | 1 | 2.5 | 10 | 12.5 | 2 | 4.9 | 9 | 28.1 | 4 | 13.8 | 8 | 16.0 | 2 | 6.5 | 36 | 11.9 |
| 2nd dose [1)] | 0 | 0 | 5 | 6.3 | 2 | 4.9 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 7 | 2.3 |
| **Cases during risk period following SI vaccination** | 5 | 12.5 | 4 | 5 | 1 | 2.4 | 0 | 0 | 1 | 3.4 | 4 | 8 | 0 | 0 | 15 | 0.05 |
| **Cases during risk period following infections (ILI, URTI) risk period** | 3 | 7.5 | 16 | 20 | 10 | 24.4 | 8 | 25.0 | 6 | 20.7 | 30 | 60.0 | 6 | 19.4 | 79 | 26.11 |
| ILI [1)] | 1 | 2.5 | 6 | 7.5 | 2 | 4.9 | 1 | 3.1 | 1 | 3.4 | 13 | 26.0 | 5 | 16.1 | 29 | 9.6 |
| URTI [1)] | 2 | 5 | 10 | 12.5 | 8 | 19.5 | 7 | 21.9 | 5 | 17.2 | 17 | 34.0 | 1 | 3.2 | 50 | 16.5 |

[1)] % per number of cases included per country
Abbreviations: SI, seasonal influenza; ILI, influenza like illness; URI, Upper respiratory tract infection; UK, United Kingdom; NL, Netherlands; FR, France; SE, Sweden; FI, Finland, NO, Norway, DK, Denmark.

**Table 4.24** Rate ratios for the association between ILI/URTI, influenza A(H1N1)pdm09 vaccination, seasonal influenza vaccination and GBS.

| RR | UK | | NL | | FR | | SE | | FI | | NO | | DK | | Pooled | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| **ILI (Pooled UK, NL, NO)** | 1.8 | 0.2-16.0 | 5.5 | 1.3-23.5 | | | | | | | 8.6 | 2.0-37.8 | | | 3.4 | 1.2-9.8 |
| **URTI** | 2.2 | 0.4-10.6 | 9.1 | 2.8-29.2 | | | | | | | 6.1 | 2.1-17.7 | | | 9.9 | 4.5-21.7 |
| **Seasonal influenza vaccination** | 6.0 | 1.8-19.7 | 1.2 | 0.4-4.0 | | | | | | | 3.3 | 0.8-13.0 | | | 2.3 | 1.1-5.0 |
| **Influenza A(H1N1)pdm09 vaccination** | 3.3 | 0.3-36.5 | 2.7 | 1.3-5.9 | 6.4 | 1.0-40.4 | 4.8 | 2.1-11.1 | 1.6 | 0.5-5.4 | 3.9 | 1.6-9.3 | 7.7 | 1.1-54.4 | 3.5 | 2.3-5.3 |
| **Adjusted for calendar month** | 2.3 | 0.2-27.7 | 1.4 | 0.6-3.4 | 2.9 | 0.4-19.6 | 2.7 | 1.0-7.8 | 1.6 | 0.5-5.4 | 1.9 | 0.7-5.2 | 3.9 | 0.5-32.2 | 2.0 | 1.2-3.1 |
| Pooled UK, NL, NO month adjusted[1] | | | | | | | | | | | | | | | 1.7 | 0.9-3.2 |
| **Fully adjusted (month, ILI/URTI)** [2) 3)] | 1.5 | 0.1-23.1 | 1.2 | 0.5-3.3 | NA | | NA | | NA | | 1.5 | 0.5-4.6 | NA | | 1.3 | 0.6-2.7 |
| **Pseudo likelihood** | | | | | | | | | | | | | | | | |
| 1st dose | 4.8 | 0.3-83.9 | 1.3 | 0.4-4.0 | 0.6 | 0.1-6.7 | 2.4 | 0.8-6.9 | 3.2 | 0.7-14.6 | 1.6 | 0.6-4.3 | 3.6 | 0.4-29.5 | 1.9 | 1.1-3.2 |
| 2nd dose (Pooled NL and FR) | NA | | 1.2 | 0.4-3.4 | 2.2 | 0.2-26.3 | NE | | NA | | NA | | NA | | 1.3 | 0.5-3.4 |
| **Vaccinated cases only** [4)] | NA | | 1.2 | 0.2-8.3 | NA | | 2.5 | 0.4-16.0 | 2.6 | 0.2-32.5 | 1.6 | 0.3-7.9 | NA | | 1.8 | 0.7-4.7 |

[1)] Pooled estimate of the RR for UK-NL-NO adjusting only for calendar month
[2)] NA= no adjustment possible since information not available
[3)] Based on 1st episode of ILI/URTI if multiple episodes occurred
[4)] NA= Vaccinated-cases-only calculation applied only if enough vaccinated cases available
[5)] NE= Not estimable due to small numbers
Abbreviations: RR: relative incidence rate; ILI, influenza like illness; URTI, upper respiratory tract infection; SI, seasonal influenza; UK, United Kingdom; NL, Netherlands; FR, France; SE, Sweden; FI, Finland, NO, Norway, DK, Denmark.

**Table 4.25** Stratified analyses for the association between ILI/URTI, influenza A(H1N1)pdm09 vaccination, seasonal influenza vaccination and GBS

| | UK | | NL | | FR | | SE | | FI | | NO | | DK | | Pooled [1] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| **Risk windows** | | | | | | | | | | | | | | | | |
| 1-28 days | 4.2 | (0.4-50.2) | 2.5 | (1.0-6.4) | 1.3 | (0.1-12.6) | 2.7 | (0.9-7.8) | 1.0 | (0.2-4.6) | 2.2 | (0.8-6.1) | 4.4 | (0.5-35.6) | 2.3[4] | (1.4-3.8) |
| 1-14 days | 10.8 | (0.9-133.2) | 2.5 | (0.7-9.3) | 3.4 | (0.3-33.3) | 1.0 | (0.2-4.7) | 2.3 | (0.5-10.6) | 1.3 | (0.3-5.9) | 7.6 | (0.9-61.7) | 2.3[5] | (1.2-4.4) |
| 15-28 days | 0.0 | - | 1.9 | (0.7-5.5) | 0.0 | - | 3.7 | (1.2-11.1) | 0.0 | - | 2.5 | (0.8-7.8) | NE[3] | - | 2.6 | (1.4-4.9) |
| **42 day risk window** | | | | | | | | | | | | | | | | |
| Cases 19 – 59 years old | 0.0 | - | 1.0 | (0.1-10.7) | - | - | 1.0 | (0.2-6.6) | 3.3 | (0.5-19.3) | 0.6 | (0.1-5.5) | 0.0 | - | 1.3 | (0.5-3.6) |
| Cases older than 59 years | 11.9 | (0.4-365.5) | 1.1 | (0.3-4.9) | 0.0 | - | 7.6 | (1.6-35.8) | 0.0 | - | 3.5 | (1.0-12.6) | 2.3 | (0.1-38.0) | 3.2 | (1.5-6.9) |
| Cases with co-morbidities [2] | 0.0 | - | 0.0 | | 0.24 | - | 0.0 | - | 2.5 | (0.2-35.5) | 3.2 | (0.6-17.0) | 0.0 | - | 3 | (0.7-12.3) |
| Cases without co-morbidities [2] | 0.0 | - | 1.9 | (0.6-6.6) | 1.7 | (0.1-19.6) | 0.0 | - | 1.7 | (0.4-6.7) | 1.4 | (0.4-5.3) | 0.0 | - | 1.7 | (0.8-3.4) |
| Cases with SI vacvination | 0.0 | - | 0.5 | (0.1-3.6) | 0.2 | - | 0.0 | - | 3.0 | (0.2-50.4) | 2.1 | (0.2-19.0) | 0.0 | - | 1.2 | (0.3-4.5) |
| Cases without seas. vaccination | 0.0 | - | 2.2 | (0.4-11.2) | 4.8 | (0.3-83.6) | 0.0 | - | 1.6 | (0.4-6.4) | 1.7 | (0.6-5.4) | 0.0 | - | 1.9 | (0.9-4) |
| Cases with ILI, URTI infection | 0.0 | - | 1.1 | (0.1-11.4) | 2.9 | (0.2-51.9) | 3.2 | (0.8-14.0) | 1.1 | (0.1-10.6) | 1.4 | (0.4-4.8) | NE | - | 1.8 | (0.8-3.9) |
| Cases without ILI, URTI infection | NE | - | 1.5 | (0.4-5.8) | 0.0 | - | 2.7 | (0.6-13.2) | 2.2 | (0.5-10.3) | 3.6 | (0.5-24.3) | 2.5 | (0.2-34.4) | 2.2 | (1.1-4.7) |

[1] Meta analysis with random effects
[2] Malignancy, immune suppression, or autoimmune disorder
[3] NE= Not estimable due to small numbers
Abbreviations: RR, relative incidence rate?; SI, seasonal influenza; ILI, influenza like illness; URI, Upper respiratory tract infection; UK, United Kingdom; NL, Netherlands; FR, France; SE, Sweden; FI, Finland, NO, Norway, DK, Denmark
[4] 2.28 (1.39-3.77)
[5] 2.34 (1.24-4.44)

**Discussion**

Based on a source population of more than 25 million subjects from the Netherlands, the UK, and Norway, and adjusting for ILI, URTI, calendar month and a number of other potential confounders, we found no association between immunization with an adjuvanted influenza A(H1N1)pdm09 vaccine (mostly AS03 adjuvanted) and the onset of GBS (RR 1.3, 95% CI: 0.6-2.7). These data therefore confirm the results from the previous VAESCO case control study published elsewhere [15], which captured only one third of the cases in a subset of the countries. The slightly higher pooled RI estimate for all countries (RI 2.0, 95% CI 1.2-3.1) should be interpreted with caution as it is likely to result from residual confounding due to a lack of adjustment for ILI and URTI.

The direct pooling of data from seven countries using a common protocol, common case definitions, a common infrastructure and common data elaboration scripts is a unique approach to vaccine safety assessment in Europe. This innovative method goes beyond the traditional approach of meta-analysis, where estimates resulting from different designs, methods and settings are often pooled. It should be noted that, while the implementation of common methods standardized the study design and some of the methods, the common protocol approach did not remove all heterogeneity between sources; as specified in Table 4.21, identification of cases, exposures and covariates varied between sources included in the study. As a result, the results from each individual source may be subject to different biases.

In France, Netherlands, and Sweden, claims records indicated that case identification through reporting networks was incomplete, in the Netherlands such cases were included retrospectively while in Sweden and France no further information on such cases could be obtained. If reporting networks were more likely to report vaccinated cases, risk estimates from Sweden and France may overestimate the association between vaccination and GBS. In order to investigate whether the changes in case inclusion over time that were observed were related to exposure we assessed the distribution of vaccinated cases (including those vaccinated outside the 6 week risk period) over time; no significant trend was observed, suggesting that time trends in non-inclusion are unlikely to have introduced selection bias.

Data sources recruiting cases directly from neurologists (i.e., France, Netherlands, Norway, and Sweden) were able to collect data for case verification prospectively, as a result case certainty in these sources was high. In Denmark, where retrospective chart

review was used for case verification, the detailed diagnostic information required to assign high levels of case certainty was sometimes missing from the chart. Details of specialist test results are not routinely recorded in GP records in the UK, therefore all UK cases were classified at the lowest Brighton Collaboration case certainty level. Any non-differential misclassification of outcome status will have resulted in bias towards the null whereas differential misclassification, which may have occurred if vaccinated individuals without GBS were more likely to receive a working diagnosis of GBS based on the purported association with vaccination than non-vaccinated individuals, would have resulted in an overestimate of the RI. While non-differential misclassification may therefore explain the lack of association observed in the UK, the consistency of the estimates with those in the Netherlands are reassuring. In addition, despite the lack of test details, all UK cases required a record of diagnosis by a specialist in order to be included.

Sweden was the only country in which case data was obtained through interviews and may therefore have suffered from recall bias. This would be expected to result in an overestimation of any association. In the Netherlands, exposure may have been misclassified in young children (<5) who were participating in mass vaccination campaigns, however as there were very few paediatric cases this is unlikely to impact results. Misclassification of exposure among individuals vaccinated outside a GP setting (e.g. in secondary care) may have occurred in the UK, however as the pandemic vaccination campaign was primarily administered in GP practices and as vaccinations outside the GP setting should be reported back to the GP we expect such misclassification to be minimal.

Misclassification of exposure may also occur due to misspecification of the risk period. The sensitivity analysis regarding the definition of the risk period showed no difference in the RR when the risk window was restricted to 15 and 28 days after vaccination (RR 2.6, 95% CI: 1.4-4.9); compared to the first two weeks (RR 2.3, 95% CI: 1.2-4.4) and the risk in a risk window 4 weeks (RR 2.3, 95% CI: 1.4-3.8).

The sensitivity analysis investigating whether GBS could be a contra-indication for influenza A(H1N1)pdm09 vaccine showed that the pooled RR reduced slightly from 2 to 1.9 for the pseudo likelihood method and 1.8 if only vaccinated cases were included, indicating that contra-indications were not an important issue.

While the SCCS design controls for all time-constant confounders, adjustment for time-varying confounders remains necessary. Adjustment for calendar month was

possible in all countries, and was found to be important; most likely because it acts as a proxy for infection with influenza A(H1N1)pdm09 and other respiratory pathogens, which were highly time dependent and co-occurring with the mass vaccination campaigns. Adjustment for additional time-varying confounders, such as ILI and URTI, lowered the RR in the countries where this was possible (Netherlands, Norway, UK) from 3.2 (95 % CI: 1.8-5.6) to 1.3 (95 % CI: 0.6-2.7). These findings suggest that residual confounding by influenza status in the overall pooled estimate is very likely.

There is a possibility that ILI and URTI lie in the causal pathway between vaccination and GBS. If this is the case adjusting for them would result in overadjustment bias [27]. Overadjustment will have results in bias towards the null and the extent of the bias would be dependent on the nature of the causal relationship between the three variables, if the only causal pathway from influenza A(H1N1)pdm09 vaccine to GBS is through ILI/URTI then, in the absence of other biases, adjustment would completely remove any true association. The potential role of ILI/URTI in the causal pathway between vaccination and GBS warrants further investigation.

Our estimates, and those from the previous VAESCO study [15], compare well with those in the literature. In studies where little or no adjustment for ILI, URTI or calendar time have been made, moderate increases in risk have been observed in both the United States( RI 2.1, 95% CI: 1.2-3.5 [18]; RI 4.4, 95% CI: 1.3-14.2 [19]; RI 2.5, 95% CI: 0.4-15.0 [20]) and Germany (RI 4.7, 95% CI: 2.2-10.0 [21]). However, where adjustment for calendar month has been possible, increases in risk have not been observed in the UK (RI 1.05, 95% CI: 0.37–2.24 [22]), France (RI 0.9, 95% CI: 0.1-7.6 [23]), Sweden (RI 1.1 95% CI: 0.6-1.9 [24]) and Canada (1.9. 95% CI 1.0-3.5 [25]).

**Conclusion**

This large, multinational self-controlled case series study confirms the results from the initial, smaller VAESCO case control study [15]. In each country, the unadjusted association between influenza A(H1N1)pdm09 vaccine and GBS suggests a possible increase in risk, and adjustment for confounders consistently lowered this risk. Full adjustment could only be carried out in a subset of countries and demonstrated the effect of confounding by influenza like illness and upper respiratory tract infections, which themselves are strong risk factors for GBS. Potential biases associated with each individual data source should be taken into account in interpreting both the country-specific and also the pooled results. Based on the upper limit of the

confidence interval of the partially and fully adjusted RR estimates we can rule out with 95% certainty that adjuvanted influenza A(H1N1)pdm09 vaccines (mainly AS03 adjuvanted) would have resulted in more than 2 or 3 excess cases of GBS per 1 million vaccinated persons.

*Acknowledgments*
This study is based in part on data from the Full Feature General Practice Research Database obtained under licence from the UK Medicines and Healthcare products Regulatory Agency and covers the data collection time period up to February 2011. However, the interpretation and conclusions contained in this report are those of the authors alone.

[1] Lu CY, Shao PL, Chang LY, Huang YC, Chiu CH, Hsieh YC, et al. Immunogenicity and safety of a monovalent vaccine for the 2009 pandemic influenza virus A (H1N1) in children and adolescents. Vaccine 2010;28(36):5864-70.

[2] Lu W, Tambyah PA. Safety and immunogenicity of influenza A H1N1 vaccines. Expert Rev Vaccines 2010;9(4):365-9.

[3] Wijnans L, de Bie S, Dieleman J, Bonhoeffer J, Sturkenboom M. Safety of pandemic H1N1 vaccines in children and adolescents. Vaccine 2011;29(43):7559-71.

[4] Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, Keenlyside RA, Ziegler DW, Retailliau HF, et al. Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976--1977. Am J Epidemiol 1979;110(2):105-23.

[5] Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barre syndrome and the 1978-1979 influenza vaccine. N Engl J Med 1981;304(26):1557-61.

[6] Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, et al. Guillain-Barre syndrome after influenza vaccination in adults: a population-based study. Arch Intern Med 2006;166(20):2217-21.

[7] Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981. Lack of an association with influenza vaccination. JAMA 1982;248(6):698-700.

[8] Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N Engl J Med 1998;339(25):1797-802.

[9] Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine 2011;29(3):599-612.

[10] van Doorn PA, Ruts L, Jacobs BC. Clinical features, pathogenesis, and treatment of Guillain-Barre syndrome. Lancet Neurol 2008;7(10):939-50.

[11] McGrogan A, Madle GC, Seaman HE, de Vries CS. The epidemiology of Guillain-Barre syndrome worldwide. A systematic literature review. Neuroepidemiology 2009;32(2):150-63.

[12] Govoni V, Granieri E. Epidemiology of the Guillain-Barre syndrome. Curr Opin Neurol 2001;14(5):605-13.

[13] Nachamkin I, Shadomy SV, Moran AP, Cox N, Fitzgerald C, Ung H, et al. Anti-ganglioside antibody induction by swine (A/NJ/1976/H1N1) and other influenza vaccines: insights into vaccine-associated Guillain-Barre syndrome. J Infect Dis 2008;198(2):226-33.

[14] Yuki N, Takahashi Y, Ihara T, Ito S, Nakajima T, Funakoshi K, et al. Lack of antibody response to Guillain-Barre syndrome-related gangliosides in mice and men after novel flu vaccination. J Neurol Neurosurg Psychiatry 2012;83(1):116-7.

[15] Dieleman J, Romio S, Johansen K, Weibel D, Bonhoeffer J, Sturkenboom M. Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe. BMJ 2011;343:d3908.

[16] Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. Biostatistics 2009;10(1):3-16.

[17] Coloma PM, Schuemie MJ, Trifiro G, Gini R, Herings R, Hippisley-Cox J, et al. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EU-ADR Project. Pharmacoepidemiol Drug Saf 2011;20(1):1-11

[18] Tokars JI, Lewis P, DeStefano F, Wise M, Viray M, Morgan O, et al. The risk of Guillain-Barre syndrome associated with influenza A (H1N1) 2009 monovalent vaccine and 2009-2010 seasonal influenza vaccines: results from self-controlled analyses. Pharmacoepidemiol Drug Saf 2012;21(5):546-52.

[19] Greene SK, Rett M, Weintraub ES, Li L, Yin R, Amato AA, et al. Risk of Confirmed Guillain-Barre Syndrome Following Receipt of Monovalent Inactivated Influenza A (H1N1) and Seasonal Influenza Vaccines in the Vaccine Safety Datalink Project, 2009-2010. Am J Epidemiol 2012;175(11):1100-9.

[20] Yih WK, Lee GM, Lieu TA, Ball R, Kulldorff M, Rett M, et al. Surveillance for adverse events following receipt of pandemic 2009 H1N1 vaccine in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System, 2009-2010. Am J Epidemiol 2012;175(11):1120-8.

[21] Paul-Ehrlich-Institut. Zusammenhang zwischen pandemischer Influenza A/H1N1v-Impfung und Guillain-Barre-Syndrome / Miller-Fisher-Syndrome in Deutschland; 2012.

[22] Andrews N, Stowe J, Al-Shahi Salman R, Miller E. Guillain-Barre syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. Vaccine 2011;29(45):7878-82.

[23] Grimaldi-Bensouda L, Alperovitch A, Besson G, Vial C, Cuisset JM, Papeix C, et al. Guillain-Barre syndrome, influenzalike illnesses, and influenza vaccination during seasons with and without circulating A/H1N1 viruses. Am J Epidemiol 2011;174(3):326-35.

[24] Bardage C, Persson I, Ortqvist A, Bergman U, Ludvigsson JF, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. BMJ 2011;343:d5956.

[25] De Wals P, Deceuninck G, Toth E, Boulianne N, Brunet D, Boucher RM, et al. Risk of Guillain-Barre syndrome following H1N1 influenza vaccination in Quebec. JAMA 2012;308(2):175-81.

[26] Hua W, Sun G, Dodd CN, Romio SA, Whitaker HJ, Izurieta HS, et al. A simulation study to compare three self-controlled case series approaches: correction for violation of assumption and evaluation of bias. Pharmacoepidemiol Drug Saf. 2013;22(8):819-25

[27] Schisterman EF, Cole SR, and Platt RW. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiology. 2009; 20(4): 488–95.

## *4.7 Evaluating the Hazard of Foetal Death Following H1N1 Influenza Vaccination: a Population Based Cohort Study in the UK GPRD*

**The work presented in this section is based on work published in:**

*Sammon, C. J., McGrogan, A., Snowball, J. and De Vries, C. Evaluating the Hazard of Foetal Death Following H1N1 Influenza Vaccination; a Population Based Cohort Study in the UK GPRD. PLoS ONE. 2012 Dec;7(12):e51734.*

**The version presented herein has been edited for inclusion in this thesis therefore the views expressed may not represent those of authors who collaborated on the published manuscript.**

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|---|---|
| Word Count (Abstract): | 294 |
| Word Count (Full text): | 3,189 |
| Number of tables: | 5 |
| Number of figures: | 2 |

**Abstract**

**Objectives** – To evaluate the risk of foetal loss associated with pandemic influenza vaccination in pregnancy.

**Design** - Retrospective cohort study.

**Setting** – UK General Practice Research Database

**Participants** Pregnancies ending in delivery or spontaneous foetal death after 21 October 2009 and starting before 01 January 2010.

**Main outcome measures** – Hazard ratios of foetal death for vaccinated compared to unvaccinated pregnancies were estimated for gestational weeks 9 to 12, 13 to 24 and 25 to 43 using discrete-time survival analysis. Separate models were specified to evaluate whether the potential effect of vaccination on foetal loss might be transient (for ~4 weeks post vaccination only) or permanent (for the duration of the pregnancy).

**Results** – 39,863 pregnancies meeting our inclusion criteria contributed a total of 969,322 gestational weeks during the study period. 9,445 of the women were vaccinated before or during pregnancy. When the potential effect of vaccination was assumed to be transient, the hazard of foetal death during gestational weeks 9 through 12 ($HR_{unadj}$ 0.56; $CI_{95}$ 0.43 to 0.73) and 13 through 24 ($HR_{unadj}$ 0.45; $CI_{95}$ 0.28 to 0.73) was lower in the 4 weeks after vaccination than in other weeks. Where the more permanent exposure definition was specified, vaccinated pregnancies had a lower hazard of foetal loss than unvaccinated pregnancies in gestational weeks 9 through 12 ($HR_{unadj}$ 0.74; $CI_{95}$ 0.62 to 0.88) and 13 through 24 ($HR_{unadj}$ 0.59; $CI_{95}$ 0.45 to 0.77). There was no significant difference in the hazard of foetal loss during weeks 25 to 43 in either model. Sensitivity analyses suggest the strong protective associations observed may be due in part to unmeasured confounding.

**Conclusions** – Influenza vaccination during pregnancy does not appear to increase the risk of foetal death. This study therefore supports the continued recommendation of influenza vaccination of pregnant women.

## Introduction

Current evidence suggests the risk/benefit profile of influenza vaccination in pregnancy is favourable for both the mother and her newborn. The benefits of vaccination to the mother are particularly evident in the second and third trimester and during pandemics [1, 2]. This is reflected in national immunisation policies implemented in countries throughout the world [3]. Despite this, little is known about the effects of influenza and influenza vaccination on the developing foetus. A small number of studies have linked influenza infection to an increased rate of foetal death [4-7], babies born small for their gestational age [8] and prematurity [8]. If influenza infection does increase the risk of these adverse pregnancy outcomes, vaccination might prove beneficial in mitigating this risk. However, given the paucity of evidence available, few public health authorities currently cite influenza-related adverse pregnancy outcomes as their rationale for recommending influenza vaccination of pregnant women.

With regard to foetal risks, little is known about the potential adverse effect that influenza vaccination may have. While maternal safety can be extrapolated to a certain extent from the general population, it is not possible to extrapolate risks to the foetus from other populations. Given ethical issues concerning the inclusion of pregnant women in randomised controlled trials, most studies that have considered influenza vaccine safety in pregnancy have been observational in nature. Those that have evaluated the vaccine-associated risk of adverse pregnancy outcomes have focused on outcomes such as preterm birth [9, 10], malformations [10-12] and caesarean section [9]. Few studies have investigated the risk of pregnancy loss (miscarriages/stillbirths) following influenza vaccination [12] as there are a number of methodological challenges inherent in studying such associations. Bias introduced by the incomplete ascertainment of implantation failures and early embryonic deaths is the primary problem; ~60% of conceptions are lost prior to clinical recognition [13], while variation in both exposure and outcome [14] incidence over gestational time may also create challenges. If these issues are not accounted for appropriately in study design and analysis they can result in profoundly biased risk estimates.

While influenza vaccination in pregnancy is recommended in the UK and many other countries, uptake of influenza vaccines by pregnant women is low [15-20]. Perceptions that influenza infection is not dangerous, and vaccine safety concerns have been identified as major barriers to uptake of both pandemic [21-25] and seasonal [24, 26, 27] influenza vaccine in pregnant women. Without insight into the

risk of pregnancy loss associated with vaccination it will be difficult to achieve a meaningful increase in vaccination uptake. In this study we have investigated whether the hazard of foetal death is altered in pregnancies vaccinated against influenza A(H1N1)pdm09.

**Methods**

We designed a cohort study in which we used discrete-time survival analysis to compare the hazard of foetal death occurring after 8 weeks gestation between vaccinated and unvaccinated pregnant women. Using survival analysis allowed us to account for the changing incidence of pregnancy losses and pandemic vaccination with increasing gestational age, while using a discrete parameterization of time acknowledged potential uncertainties in estimated last menstrual period (LMP) dates. Delaying study entry until the 9th week of gestation means we focus solely on pregnancy losses occurring after 8 weeks and therefore exclude the selection bias that would be introduced by the incomplete ascertainment of embryonic deaths. However, this also means any risk estimates reported in the study are conditional on the pregnancy surviving through at least the first 8 weeks gestation.

This study was carried out using the UK General Practice Research Database (GPRD). The GPRD is a primary care database containing the anonymised records of ~8.4% of the UK population [28]. Patient data routinely available in the database include demographic details, diagnoses and symptoms leading to hospital admissions, immunisations, pregnancies, laboratory tests, referrals to specialists, prescriptions issued by the GP, contraception, hospital discharge and clinic summaries and deaths [29]. The GPRD operates a continuous quality control procedure and check that all data submitted by practices meet a specific set of quality criteria; those meeting the criteria are considered of a standard sufficient for research purposes.

The study population consisted of all women with a pregnancy ending after the start of the vaccination campaign on 21 October 2009 and starting before 1 January 2010, for whom at least 6 months of data was available before their LMP date (Figure 4.7). Pregnancies were identified using an algorithm similar to those described elsewhere [30, 31]. In summary this algorithm identifies individual pregnancies based on records of pregnancy outcomes and estimates each pregnancy's start and end date using all pregnancy related events in a woman's record. Where a pregnancy outcome was identified but the pregnancy start date remained unclear the pregnancy was assigned

a default start date of 280 days before the date of delivery/stillbirth or 70 days before the date of foetal death.

This algorithmic approach to pregnancy identification on the GPRD has been verified using manual review of electronic and paper medical records [32]. Ectopic pregnancies and pregnancies resulting in hydatidiform mole or induced abortions were excluded from the study population and where a woman had multiple eligible pregnancies only the first pregnancy was included. Previous work suggested pandemic vaccinations may be misclassified in Northern Irish GPRD practices therefore pregnancies in women registered with Northern Irish practices were excluded.

The main outcome in this study was foetal death, defined as a pregnancy loss at any time between the 9$^{th}$ gestational week and the onset of labour/delivery. Foetal death includes first trimester miscarriages (gestational weeks 9-12), second trimester miscarriages (gestational weeks 13-24) and second or third trimester stillbirths (gestational weeks 25+).

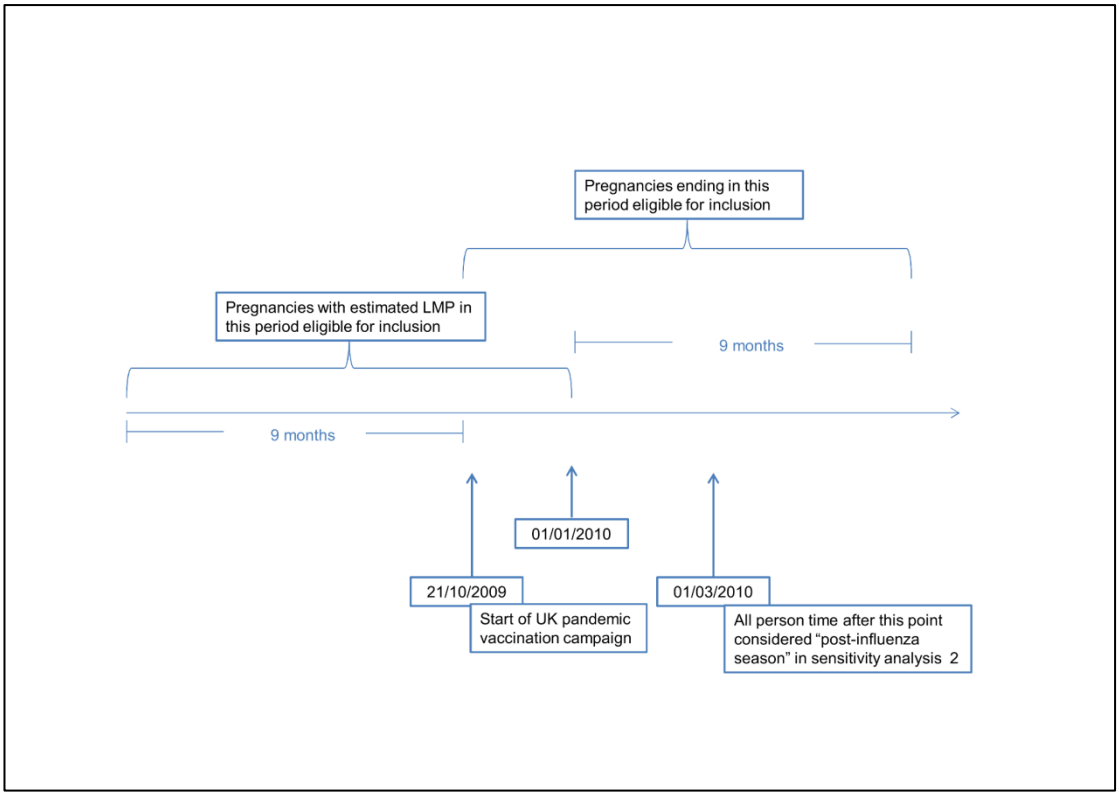


**Figure 4.7** Time periods for inclusion of pregnancies in the study.

Pandemic influenza vaccinations were identified using influenza A(H1N1)pdm09 vaccine specific medical and product codes; codes which had been created to allow differential recording of seasonal and pandemic vaccinations on GP systems [33]. Where a woman had more than one pandemic vaccination recorded the first record of vaccination was considered to be on the vaccination date.

Potential confounders and effect modifiers identified *a priori* and investigated in the analysis included: maternal age, history of spontaneous loss, diabetes, pre-pregnancy smoking status, pre-pregnancy alcohol use, pre-pregnancy body mass index, indices of multiple deprivation score of the area in which a patients practice was located, the number of consultations in the 6 months before the LMP date and being in an influenza A(H1N1)pdm09 clinical risk group (i.e. recommended for pandemic influenza vaccination due to a chronic medical condition). A separate category was created for all those with missing data on pre-pregnancy smoking status, alcohol use or BMI.

In the discrete survival model, weekly intervals were used to define exposure and event occurrence and separate hazard ratios were estimated for weeks 9-12, weeks 13-24 and weeks 25-42. Delayed entry was used to account for left truncation of pregnancies beginning before the start of the study period. Influenza A(H1N1)pdm09 vaccination status was coded as a time varying covariate. We used two influenza A(H1N1)pdm09 vaccine exposure definitions to represent the two separate hypotheses under investigation:

a) To assess whether vaccination had an acute adverse effect on pregnancy outcome we assumed exposure to be transient and investigated whether there was an association between influenza A(H1N1)pdm09 vaccination and foetal death in the week of vaccination or the three weeks immediately thereafter.
b) To assess whether immunisation protected against foetal death by conferring immunity against influenza and its related morbidity, we assumed exposure to be permanent and investigated whether there was an association between influenza A(H1N1)pdm09 vaccination and foetal death in any subsequent week of pregnancy.

Henceforth these two models shall be referred to as the 'toxicity model' (a) and the 'immunity model' (b). Effect modification was identified through stratification and introduction of interaction terms into the models. Confounders were defined as variables whose inclusion in the model changed the point estimate of the HR for vaccination by >10%. The proportionality assumption was investigated within each

gestational period under investigation through the introduction of interaction terms between each variable and gestational age. All statistical analyses were carried out using STATA 12.

Previous work identifying pregnancies on the GPRD suggested that it would not be possible to ascertain the exact pregnancy start date for a large proportion of the first trimester spontaneous losses. In the main analysis a default pregnancy start date of 70 days before foetal death was assigned to any such pregnancies; as a result in the main analysis all such foetal deaths were defined as occurring in the $10^{th}$ week. To investigate the sensitivity of our estimates to this defaulting of first trimester pregnancy losses we estimated models in which we changed the default pregnancy start date to 42, 56 and 84 days before loss, defining foetal deaths as occurring in the $6^{th}$, $8^{th}$ or $12^{th}$ week respectively.

Vaccination does not confer immediate immunity on an individual; there is approximately a 1-2 week delay between influenza vaccination and the onset of immunity. As a sensitivity analysis for the immunity model we therefore coded both one- and two-week periods after vaccination as unexposed with "exposure" only beginning after immunity could plausibly have developed.

In order to investigate whether the associations observed in the 'immunity' model were due to underlying differences between individuals who were vaccinated and those who were not (a "healthy user effect") we performed an additional analysis stratifying gestational weeks as <1 March 2010 or >28 February 2010. As influenza was not circulating widely after February 2010 [34] little or no protective association should be observed in this period; any association that was observed could therefore be considered an estimate of the level of confounding present in our main model estimates.

A fourth sensitivity analysis modelled the effect of a hypothetical confounder on our results [35]. It investigated whether some unmeasured factor, such as a healthy lifestyle, might be both associated with a decreased risk of foetal death and more prevalent among vaccinated than unvaccinated pregnancies.

**Results**

39,863 pregnancies meeting our inclusion criteria contributed a total of 969,322 gestational weeks during the study period. 36,438 of these pregnancies ended in a delivery and 3,425 ended in foetal death. 9,445 of the women had been immunised with an influenza vaccination before the end of their pregnancy and 9,161 of the vaccinations occurred during pregnancy. Patient characteristics are given in Table 4.26. The proportion of pregnancies vaccinated and the proportion of foetal deaths occurring over gestational time are shown in Figure 4.8.

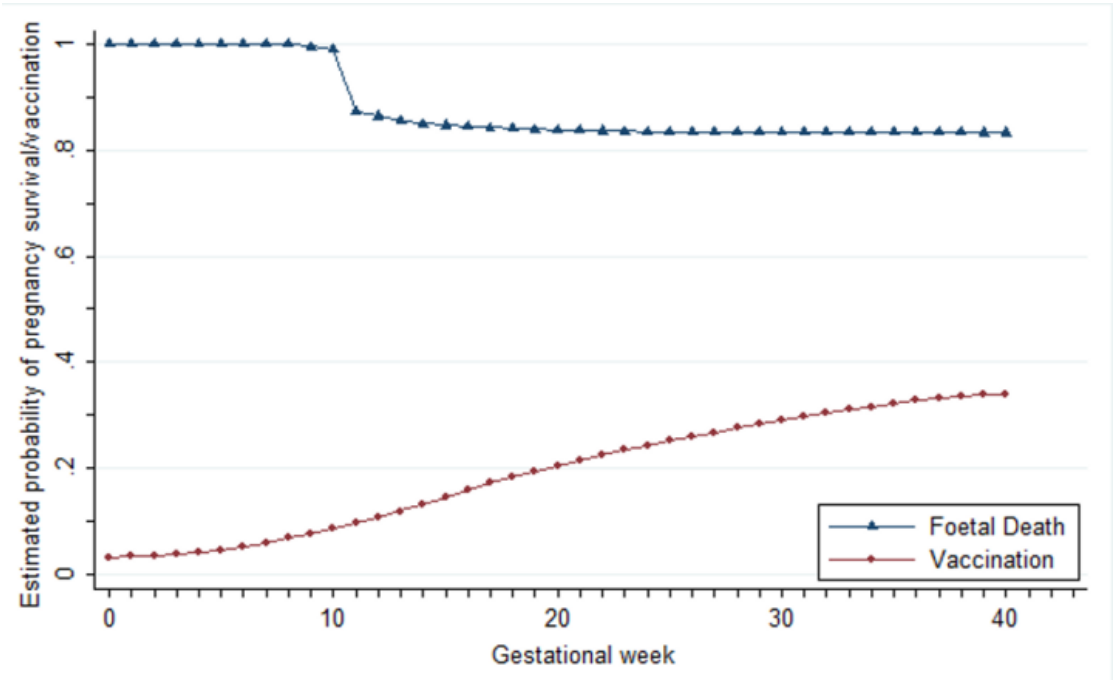


**Figure 4.8** Percentage of pregnancies surviving (blue) and vaccinated (red) by each gestational week. The drop in survival at 10 weeks is an artefact of the defaulting process. In reality the losses contributing to this curve would be more evenly distributed across weeks 9-12 resulting in a more gradual drop in survival.

**Table 4.26** Population characteristics of pregnant women eligible for influenza vaccination during the influenza A(H1N1)pdm09 pandemic.

| | | Delivery | Foetal death | | |
|---|---|---|---|---|---|
| | | | Week 9-12 | Week 13-24 | Week 25-41 |
| **Total (n)** | | 36,438 | 2,543 | 711 | 171 |
| **Mean pregnancy length, weeks (SD)** | | 40.8 (1.4) | 10.2 (0.6) | 16.6 (3.5) | 36 (6.0) |
| **Unvaccinated weeks** | | | | | |
| | **weeks 1-12** | 59,425 | 4,912 | 2,081 | 298 |
| | **weeks 13-24** | 215,195 | - | 2,614 | 1,182 |
| | **weeks 25-43** | 388,192 | - | - | 1,416 |
| **Vaccinated (weeks)** | | | | | |
| | **weeks 1-12** | 4,897 | 269 | 142 | 12 |
| | **weeks 13-24** | 41,554 | - | 253 | 141 |
| | **weeks 25-43** | 123,658 | - | - | 288 |
| **Maternal age (years)** | | | | | |
| | **Mean (SD)** | 29.9 (6.0) | 32.2 (7.2) | 31.6 (6.7) | 30.0 (6.4) |
| | **11-19** | 1,194 | 93 | 21 | 8 |
| | **20-34** | 25,350 | 1,371 | 422 | 117 |
| | **35-40** | 7,594 | 619 | 156 | 33 |
| | **40-44** | 2,151 | 393 | 102 | 12 |
| | **45-49** | 149 | 67 | 10 | 1 |
| **Number of previous spontaneous abortions** | | | | | |
| | **0** | 30,089 | 376 | 522 | 136 |
| | **1** | 5,175 | 1,624 | 160 | 25 |
| | **2** | 929 | 379 | 22 | 7 |
| | **>2** | 245 | 164 | 7 | 3 |
| **In clinical risk group for influenza vaccination** | | | | | |
| | **No** | 34,304 | 2,359 | 669 | 164 |
| | **Yes** | 2,134 | 184 | 42 | 7 |
| **Diabetes** | | | | | |
| | **No** | 36,136 | 2,501 | 700 | 168 |
| | **Yes** | 302 | 42 | 11 | 3 |
| **Number of consultations in 6 months before LMP** | | | | | |
| | **0-1** | 8,664 | 554 | 158 | 47 |
| | **2-3** | 8,199 | 534 | 177 | 43 |
| | **4-5** | 6,095 | 404 | 101 | 28 |
| | **6-9** | 7,258 | 506 | 133 | 36 |
| | **10+** | 6,222 | 545 | 142 | 17 |
| **Pre-pregnancy smoking status** | | | | | |
| | **Smoker** | 8,973 | 658 | 185 | 53 |
| | **Non-smoker** | 19,751 | 1,327 | 383 | 82 |
| | **Ex-smoker** | 7,491 | 534 | 141 | 36 |
| | **Unknown** | 223 | 24 | 2 | 0 |

The results of the main analyses are shown in Table 4.27. Both in the toxicity model and in the immunity model, the hazard of foetal death was reduced after A/H1N1pdm09 vaccinations in each of weeks 9 to 24 of gestation. This association appeared to be strongest in the toxicity model. After gestational week 24, no statistically significant associations were observed.

As anticipated, maternal age, number of previous spontaneous losses, being in a influenza clinical risk group and having diabetes were all associated with the hazard of foetal death. However, no variables were observed to confound the association between vaccination and foetal death. Hazard ratios and confidence intervals for the missing categories did not suggest they masked a confounding association (data not shown). Fitting interactions between the vaccination and gestational age suggested that the hazards across vaccination groups were proportional within each gestational period reported (data not shown).

**Table 4.27** Hazard ratios and 95% confidence intervals for association between pandemic influenza vaccination and foetal death in different gestational periods

| | "Immunity model" | | "Toxicity model" | |
|---|---|---|---|---|
| | **$HR_{unadj}$** | **$CI_{95}$** | **$HR_{unadj}$** | **$CI_{95}$** |
| Foetal death in weeks 9-12 | 0.74 | (0.62 - 0.88) | 0.56 | (0.43 - 0.73) |
| Foetal death in weeks 13-24 | 0.59 | (0.45 - 0.77) | 0.45 | (0.28 - 0.73) |
| Foetal death in weeks 25 - 43 | 0.70 | (0.47 - 1.03) | 1.56 | (0.73 – 3.34) |

For 2,025 of 2,543 first trimester foetal deaths, no information was available regarding the LMP date or the expected date of delivery. These pregnancies were assigned a default pregnancy start date of 63 to 70 days before the date of loss (i.e. foetal death occurred in the $10^{th}$ gestational week). In a sensitivity analysis, as we moved the default start date forward, and therefore decreased the estimated gestational age of many of the first trimester foetal deaths, our risk estimates moved towards, and then greater than, 1. (Table 4.28).

**Table 4.28** Sensitivity analysis 1: effect of varying the default length of first trimester spontaneous losses*.

| | "Immunity model" | | "Toxicity model" | |
|---|---|---|---|---|
| | **$HR_{unadj}$** | **$CI_{95}$** | **$HR_{unadj}$** | **$CI_{95}$** |
| default 6th week | 1.24 | (1.04 - 1.48) | 1.06 | (0.82 - 1.38) |
| default 8th week | 0.98 | (0.83 - 1.17) | 0.78 | (0.60 - 1.00) |
| default 10th week** | 0.74 | (0.62 - 0.88) | 0.56 | (0.43 - 0.73) |
| default 12th week | 0.59 | (0.49 - 0.70) | 0.44 | (0.35 – 0.58) |

*All hazard ratios are for gestational weeks 9-12 only. **same as effect estimates in table 4.27

When we changed exposure status in the first two weeks following vaccination to unexposed (to allow for delay between vaccination and onset of immunity) we observed a decrease in the protective association observed. This was most notable in the 9-12 week gestational period when the rates of vaccination and loss were changing rapidly (Table 4.29). Associations between influenza A(H1N1)pdm09 vaccine and foetal death were not found to be statistically significant during periods of little/no influenza circulation, however point estimates were of a similar magnitude during periods of high influenza circulation and during periods of little/no influenza circulation (Table 4.30).

**Table 4.29** Sensitivity analysis 2: one and two week post vaccination time periods coded as unexposed to account for a delay between vaccination and onset of immunity.

| | | "Immunity model" | |
|---|---|---|---|
| | | **$HR_{unadj}$** | **$CI_{95}$** |
| **week of vaccination** coded as unexposed | loss in weeks 9-12 | 0.80 | (0.66 – 0.96) |
| | loss in weeks 13-24 | 0.63 | (0.48 - 0.83) |
| | loss in weeks 25 - 43 | 0.69 | (0.47 – 1.02) |
| week of vaccination **and week following vaccination** coded as unexposed | loss in weeks 9-12 | 0.84 | (0.69 – 1.03) |
| | loss in weeks 13-24 | 0.64 | (0.48 – 0.85) |
| | loss in weeks 25 - 43 | 0.69 | (0.46 – 1.02) |

**Table 4.30** Sensitivity analysis 3: pregnancy weeks stratified as being either during influenza season or post-influenza season; no causal protective associations are expected in the post-influenza season period.

| | | "Immunity model" | |
|---|---|---|---|
| | | ***$HR_{unadj}$** | **$CI_{95}$** |
| | loss in weeks 9-12 | 0.76 | (0.63 - 0.92) |
| Influenza season | loss in weeks 13-24 | 0.55 | (0.40 - 0.75) |
| | loss in weeks 25 - 43 | 0.70 | (0.38 – 1.29) |
| | loss in weeks 9-12 | 0.63 | (0.39 – 1.05) |
| Post-influenza season | loss in weeks 13-24 | 0.68 | (0.42 – 1.10) |
| | loss in weeks 25 - 43 | 0.71 | (0.43 – 1.18) |

The sensitivity analysis modelling the effect of a hypothetical confounder suggested that in order for a confounder to completely account for the protective associations observed in the immunity model or to mask an adverse association in the toxicity model it would have to be both considerably more prevalent among the vaccinated than unvaccinated and strongly associated with a decreased risk of foetal death (Appendix 3). Taking healthy lifestyle as an example, if 90% of vaccinated women followed this healthy lifestyle and only 20% of unvaccinated women did, the healthy lifestyle factor would have to be associated with a 40% reduced risk of foetal death to produce the protective associations observed in weeks 9-12 or a 50% reduced risk to produce the protective association in weeks 13-24. A similarly distributed healthy lifestyle would have to be associated with a reduction in the risk of foetal death of 70%-80% to hide an acute adverse effect in weeks 9-12 or 13-24.

**Discussion**

Vaccination against influenza A(H1N1)pdm09 was associated with a lower risk of foetal death. While this may be explained in part or completely by residual uncontrolled confounding, this study provides reassurance that vaccination is unlikely to be associated with an increased risk of pregnancy loss.

To our knowledge this is one of the first large population based studies of the association between influenza A(H1N1)pdm09 vaccination and foetal death [36, 37]. As the influenza A(H1N1)pdm09 vaccine most commonly used in the UK was the AS03 adjuvanted vaccine, Pandemrix®, this is also one of the first studies to investigate the association between an adjuvanted vaccine and foetal loss. The rates of foetal death and vaccine uptake observed in the GPRD are in line with rates observed elsewhere [16, 38, 39]. As the A(H1N1)pdm09 vaccine was primarily administered in GP surgeries, the accuracy of vaccination information in the GPRD should be high. However, misclassification of vaccination status may have occurred where pandemic vaccinations were recorded using non-specific influenza vaccination codes or obtained from outside the GP practice. The use of a discrete-time survival analysis enabled us to account for the opposing trends in the incidence of vaccine uptake and foetal death during pregnancy, while acknowledging uncertainties in the estimated gestational age of event occurrence. We were able to examine a number of potential confounders in this study; sensitivity analyses suggested residual confounding, for instance by lifestyle or dietary factors or folic acid intake, remained present.

The observation of a protective association immediately after vaccination and the similar magnitude of (statistically non-significant) point estimates observed during periods of little/no influenza circulation to those observed during periods of high influenza circulation is suggestive of unmeasured confounding as the vaccine can provide little or no true protective effect in these periods. There is a possibility that women may begin to feel ill or be admitted to hospital in the days preceding foetal death, if this were the case they would be unlikely to be vaccinated in such a period. This could explain the protective associations observed in both models and the stronger association observed in the toxicity model. The weakening of the protective associations when changing the exposure definition may result from the partial removal of such bias (Table 4.29). While the potential influence of residual confounding on our estimates needs to be carefully considered, it is reassuring that the risk estimates were reasonably precise and no statistically significant increases in

the hazard of foetal death were observed in any of the sensitivity analyses evaluating this.

The sharp drop in survival at 10 weeks in Figure 4.8 results from the defaulting of LMP dates of first trimester foetal deaths to 10 weeks before the date of loss; the results were sensitive to misclassification resulting from such defaulting. However, sensitivity analysis results suggest it is unlikely that any such misclassification would be substantial enough to hide an increased hazard of foetal death among vaccinated pregnancies (Table 4.28) as a significantly increased hazard was only observed when the default LMP date of first trimester foetal deaths was set to 6 weeks before the foetal death: an unlikely situation. In view of missing information on early pregnancy loss on the GPRD we excluded pregnancy losses occurring before 9 weeks gestation from our analysis; this study therefore provides no insight into the risk of embryonic death following vaccination. However, most pregnant women do not contact their GP for their pregnancy until close to the end of the embryonic period; exposure to influenza vaccine is therefore low, and mainly limited to those in clinical risk groups, early in pregnancy.

A number of recent studies have investigated the risk of foetal death following H1N1 vaccination. Pasternak *et al* reported non- or marginally-significant differences in the propensity score adjusted hazard of overall foetal death (HR 0.79; $CI_{95}$ 0.53 to 1.16), spontaneous loss (HR 1.11; $CI_{95}$ 0.71 to 1.73) and stillbirth (HR 0.44; $CI_{95}$ 0.20 to 0.94) between vaccinated and unvaccinated women; these point estimates and those from their sensitivity analyses generally suggest a lower hazard of foetal death among vaccinated women [36]. Recently, Fell *et al.* evaluated the risk of a range of pregnancy outcomes following influenza A(H1N1)pdm09 vaccination, reporting an adjusted RR of foetal death after 20 weeks of 0.66 ($CI_{95}$ 0.47 to 0.91)[37]. Restricting our analysis to foetal deaths occurring after 20 weeks for comparison, we observed a HR of a similar magnitude (HR 0.62; $CI_{95}$ 0.46 to 0.84). In a primarily methodological paper, Xu *et al* compared the rate of spontaneous loss in H1N1 vaccinated women contacting North American teratology information services with unvaccinated women contacting the same service [40]. While study power was low, spontaneous loss rates among the vaccinated were similar to those in the unvaccinated. Tavares *et al* and Moro *et al* have reported rates of spontaneous loss among vaccinated pregnant women with both finding rates to be within the range expected [41, 42].

Reassuringly, while the protective associations reported in some of these studies may be completely explained by underlying differences between women who choose to be

vaccinated and those who do not, none found any evidence to suggest an increase in the risk of foetal death following vaccination. Indeed, sensitivity analyses suggested that a confounder would have to be both strongly protective against foetal death and highly prevalent among vaccinated women for it to hide an adverse association between vaccination and foetal death.

As methodological difficulties and low exposure prevalence complicate the evaluation of the risk of embryonic death, future study may be better directed at further evaluating the risk of adverse pregnancy outcomes such as foetal death, malformations, preterm birth and growth retardation. Developing methods to account for, or evaluate, residual confounding will be vital in any such studies. While this study does not provide any definitive evidence that influenza vaccination in pregnancy is completely safe or effective, its results provide some reassurance to patients that vaccination is unlikely to increase the risk of foetal death. Taken alongside current evidence, this study supports a favourable risk-benefit profile of influenza vaccines and the continued recommendation of influenza vaccination of pregnant women.

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[1] Skowronski DM, De SG. Is routine influenza immunization warranted in early pregnancy? Vaccine 2009;27(35):4754-70.

[2] Mak TK, Mangtani P, Leese J, Watson JM, Pfeifer D. Influenza vaccination in pregnancy: current evidence and selected national policies. Lancet Infect Dis 2008;8(1):44-52.

[3] Ng S, Wu P, Nishiura H, Ip DK, Lee ES, 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 Infect Dis 2011;11:230.

[4] Bloom-Feshbach K, Simonsen L, Viboud C, Molbak K, Miller MA, Gottfredsson M, et al. Natality decline and miscarriages associated with the 1918 influenza pandemic: the Scandinavian and United States experiences. J Infect Dis 2011;204(8):1157-64.

[5] Stanwell-Smith R, Parker AM, Chakraverty P, Soltanpoor N, Simpson CN. Possible association of influenza A with fetal loss: investigation of a cluster of spontaneous abortions and stillbirths. Commun Dis Rep CDR Rev 1994;4(3):R28-32.

[6] Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. BMJ 2011;342:d3214.

[7] Lieberman RW, Bagdasarian N, Thomas D, Van De Ven C. Seasonal influenza A (H1N1) infection in early pregnancy and second trimester fetal demise. Emerg Infect Dis 2011;17(1):107-9.

[8] Omer SB, Goodman D, Steinhoff MC, Rochat R, Klugman KP, Stoll BJ, et al. Maternal influenza immunization and reduced likelihood of prematurity and small for gestational age births: a retrospective cohort study. PLoS Med 2011;8(5):e1000441.

[9] 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. Am J Perinatol 2004;21(6):333-9.

[10] Sumaya CV, Gibbs RS. Immunization of pregnant women with influenza A/New Jersey/76 virus vaccine: reactogenicity and immunogenicity in mother and infant. J Infect Dis 1979;140(2):141-6.

[11] Heinonen OP, Shapiro S, Monson RR, Hartz SC, Rosenberg L, Slone D. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. IntJ Epidemiol 1973;2(3):229-35.

[12] Deinard AS, Ogburn P, Jr. A/NJ/8/76 influenza vaccination program: effects on maternal health and pregnancy outcome. Am J Obstet Gynecol 1981;140(3):240-5.

[13] Macklon NS, Geraedts JP, Fauser BC. Conception to ongoing pregnancy: the 'black box' of early pregnancy loss. Hum Reprod Update 2002;8(4):333-43.

[14] Hoesli IM, Walter-Gobel I, Tercanli S, Holzgreve W. Spontaneous fetal loss rates in a non-selected population. Am J Med Genet 2001;100(2):106-9.

[15] Department of Health website. Begum F, Pebody R. (2011) Seasonal influenza vaccine uptake amongst GP patient groups in England. Winter season 2010-11. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_129856.pdf. Accessed 15/08/2012.

[16] Department of Health website. Begum F, Pebody R. (2010) Pandemic H1N1 (Swine) Influenza Vaccine Uptake amongst Patient Groups in Primary Care in England 2009/10. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_121014.pdf. Accessed 15/08/2012.

[17] Mereckiene J, Cotter S, Weber J, Nicoll A, D'Ancona F, Lopalco P, et al. Influenza A(H1N1)pdm09 vaccination policies and coverage in Europe. Euro Surveill 2012;17(4).

[18] Influenza vaccination coverage among pregnant women --- United States, 2010-11 influenza season. MMWR Morb Mortal Wkly Rep 2011;60(32):1078-82.

[19] Ropero-Alvarez AM, Whittembury A, Kurtis HJ, dos Santos T, Danovaro-Holliday MC, Ruiz-Matus C. Pandemic influenza vaccination: lessons learned from Latin America and the Caribbean. Vaccine 2012;30(5):916-21.

[20] Department of Health website. The Immunisation Team Newsletter - Issue 187 - March 2012. Available:https://www.wp.dh.gov.uk/immunisation/files/2012/03/VaccineUpdate_I187_Mar12_acc.pdf. Accessed 31/03/2012.

[21] Fabry P, Gagneur A, Pasquier JC. Determinants of A (H1N1) vaccination: cross-sectional study in a population of pregnant women in Quebec. Vaccine 2011;29(9):1824-9.

[22] van Lier A, Steens A, Ferreira JA, van der Maas NA, de Melker HE. Acceptance of vaccination during pregnancy: Experience with 2009 influenza A (H1N1) in the Netherlands. Vaccine 2012;[epub ahead of print].

[23] Steelfisher GK, Blendon RJ, Bekheit MM, Mitchell EW, Williams J, Lubell K, et al. Novel pandemic A (H1N1) influenza vaccination among pregnant women: motivators and barriers. Am J Obstet Gynecol 2011;204(6 Suppl 1):S116-23.

[24] Goldfarb I, Panda B, Wylie B, Riley L. Uptake of influenza vaccine in pregnant women during the 2009 H1N1 influenza pandemic. Am J Obstet Gynecol 2011;204(6 Suppl 1):S112-5.

[25] Ding H, Santibanez TA, Jamieson DJ, Weinbaum CM, Euler GL, Grohskopf LA, et al. Influenza vaccination coverage among pregnant women--National 2009 H1N1 Flu Survey (NHFS). Am J Obstet Gynecol 2011;204(6 Suppl 1):S96-106.

[26] Naleway AL, Smith WJ, Mullooly JP. Delivering influenza vaccine to pregnant women. Epidemiol Rev 2006;28:47-53.

[27] Yudin MH, Salaripour M, Sgro MD. Pregnant women's knowledge of influenza and the use and safety of the influenza vaccine during pregnancy. J Obstet Gynaecol Can 2009;31(2):120-5.

[28] General Practice Research Database website. (2011) Facts and Figures. Available:http://www.gprd.com/gprd/factsandfigures.asp. Accessed 18/10/2011.

[29] Wood L, Martinez C. The general practice research database: role in pharmacovigilance. Drug Saf 2004;27(12):871-81.

[30] Hardy JR, Holford TR, Hall GC, Bracken MB. Strategies for identifying pregnancies in the automated medical records of the General Practice Research Database. Pharmacoepidemiol Drug Saf 2004;13(11):749-59.

[31] Devine S, West S, Andrews E, Tennis P, Hammad TA, Eaton S, et al. The identification of pregnancies within the general practice research database. Pharmacoepidemiol Drug Saf 2010;19(1):45-50.

[32] 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;33(9):741-50.

[33] Department of Health. PRIMIS+. (2010) Influenza A (H1N1)v Uptake Survey 2009/10, ImmForm, Read Codes Version 1.0. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_107347.pdf. Accessed 15/08/2012.

[34] Department of Health website. McClean E, Pebody R. (2010) Epidemiological report of pandemic (H1N1) 2009 in the UK. Available:http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1284475321350. Accessed 15/08/2012.

[35] Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 2006;15(5):291-303.

[36] Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. BMJ 2012;344:e2794.

[37] Fell DB, Sprague AE, Liu N, Yasseen AS, 3rd, Wen SW, Smith G, et al. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. Am J Public Health 2012;102(6):e33-40.

[38] French FE, Bierman JM. Probabilities of fetal mortality. Public Health Rep 1962;77:835-47.

[39] Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. N Engl J Med 1988;319(4):189-94.

[40] Xu R, Luo Y, Chambers C. Assessing the effect of vaccine on spontaneous abortion using time-dependent covariates Cox models. Pharmacoepidemiol Drug Saf 2012;21(8):844-50.

[41] Tavares F, Nazareth I, Monegal JS, Kolte I, Verstraeten T, Bauchau V. Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: a prospective cohort study. Vaccine 2011;29(37):6358-65.

[42] Moro PL, Broder K, Zheteyeva Y, Revzina N, Tepper N, Kissin D, et al. Adverse events following administration to pregnant women of influenza A (H1N1) 2009 monovalent vaccine reported to the Vaccine Adverse Event Reporting System. Am J Obstet Gynecol 2011;205(5):473 e1-9.

# 5. Discussion

## 5.1 Influenza pdm09 vaccine: contribution to post-marketing surveillance

The 2009/10 influenza pandemic and the resultant vaccination campaign prompted the initiation of a huge number of studies on influenza vaccine: a Pubmed search for articles published between 01-01-2009 and the 01-01-2012 containing the MeSH term "Influenza Vaccines" returns 3352 results: over 1500 more articles than in the 3 years immediately preceding this period. The six studies presented in this thesis represent a small proportion of all evidence on the risks and benefits of the pandemic influenza vaccine. Despite this, the findings can play a key role in answering a number of important questions regarding the influenza A(H1N1)pdm09 vaccine. The results may also be extrapolated to seasonal influenza vaccines and other adjuvanted vaccines.

At 40.1% and 21.6%, uptake of influenza A(H1N1)pdm09 vaccine by those in clinical risk groups and pregnant women was low. Age was the demographic characteristic most strongly associated with uptake. As described in section 4.2, this is likely to reflect the immunisation policies implemented in different age groups. Therefore an age-based policy may increase vaccination uptake in clinical risk groups. The immunisation of those not in risk groups may also provide protection to those in clinical risk groups through *herd immunity*. The UK government recently proposed intranasal influenza vaccination of all children aged 2 to 17 years[1]: our results suggest such a policy would improve uptake of the vaccine among children in clinical risk groups. Country of residence was the other key determinant of uptake: uptake in Wales, Scotland and Northern Ireland was higher than that in England. This suggests sharing of knowledge between public health authorities in each of the devolved countries might facilitate improvement of influenza vaccination rates in risk groups during vaccination campaigns. For example, while we couldn't estimate uptake among pregnant women in Northern Ireland it appears the decision to organise vaccination of pregnant women in Northern Ireland through acute trusts, as opposed to through GPs, may have resulted in higher vaccine uptake. In future, the use of multi-level regression modelling might allow more in depth investigation of the relationship between patient, practice and regional level variation in vaccine uptake.

The age standardised 10 year incidence rate of facial nerve palsy estimated in 8 data sources ranged from 5.33/100,000 PY in Sweden to 41.82/100,000 PY in Spain. These rates, and the rates of the other neurological and autoimmune diseases investigated in the VAESCO background rate study, varied across age categories, calendar time and data sources. Despite delays in providing the background rates to regulators limiting the contribution of these results to post-marketing safety surveillance of the pandemic vaccine, the results have been used to support OE analyses of the influenza

A(H1N1)pdm09 vaccine [2] and can be used to support such analyses in future vaccination campaigns. The results also demonstrate the importance of selecting an appropriate data source and population sub-group to provide the expected rates in OE analyses. Future work might seek to produce rates for other conditions and further validate the existing rates.

Risk estimates for the association between GBS and influenza A(H1N1)pdm09 vaccination in the different sources varied, however point estimates consistently showed increased risks which were reduced, or disappeared entirely, following adjustment for ILI, URTI or calendar month (CC: $IRR_{adj}$ 1.0; $CI_{95}$ [0.3 to 2.7], SCCS: $OR_{adj}$ 1.3; $CI_{95}$ [0.6 to 2.7]). These results add to the growing body of evidence suggesting that influenza A(H1N1)pdm09 vaccination was associated with little or no increased risk of GBS [3-6] and provide evidence supporting an association between respiratory infection and GBS. A potential role of ILI/URTI in the causal pathway between vaccination and GBS needs to be considered as an alternative explanation for the associations observed on adjustment. Closer investigation of the temporal relationship and clinical characteristics of vaccinated cases that developed ILI/URTI between vaccination and GBS onset may provide such information. The association between seasonal influenza vaccination and GBS observed in the GPRD data and the association between two doses of pandemic influenza vaccination and GBS observed in the Dutch (IPCI) data may warrant further investigation, however as both were based on a small number of exposed cases and as other studies have not observed similar findings these associations do not warrant great concern. The GBS issue has now been well studied using traditional epidemiological methods and, if there is a small increase in the risk of GBS following vaccination, future work might seek to identify the risk factors that render certain individuals susceptible to developing GBS post-immunisation. To this end, a number of studies currently underway in the USA are seeking to identify genetic determinants of post immunisation events such as GBS [7].

Vaccination against influenza A(H1N1)pdm09 was associated with a significantly lower risk of first ($HR_{unadj}$ 0.74; $CI_{95}$ 0.62 to 0.88) and second ($HR_{unadj}$ 0.59; $CI_{95}$ 0.45 to 0.77) trimester foetal death and a non-significantly lower risk of third trimester foetal death ($HR_{unadj}$ 0.70; $CI_{95}$ 0.47 to 1.03). While this may be explained by residual confounding, sensitivity analyses provide reassurance that vaccination is unlikely to be associated with an increased risk of pregnancy loss. These results agree with the results of other published studies [8-11], all of which report no increase in the risk of foetal death among women vaccinated against influenza A(H1N1)pdm09 during pregnancy. Further work to investigate risks associated with first trimester

vaccination, such as congenital malformations and embryonic or foetal death is needed. Given the low exposure prevalence and rarity of such outcomes, large populations will be required to study such associations. As seasonal influenza vaccination has now been universally recommended for pregnant women in the UK since the 2010/11 influenza season, the GPRD might be able to provide such a population, however methods to deal with missing and inaccurate pregnancy data need to be further explored. Most of the studies investigating the safety of pandemic vaccination in pregnancy suffer from confounding, mostly through a healthy-vaccinee effect. As a result they suggest that influenza vaccination is associated with protection against foetal death, a finding which sensitivity analyses did not support. While sensitivity analyses can be used to show that it is unlikely such confounding hid an increased risk, the protective effect cannot be quantified. Future studies investigating the safety or effectiveness of vaccination in pregnancy must therefore seek to identify ways to minimise or quantify such confounding. Specific examples of potential methods that might be used are considered in section 5.2.

Taken together, these results represent a meaningful contribution to the post-marketing surveillance of the influenza A(H1N1)pdm09vaccination campaign. Despite the interesting population level uptake findings, surveys suggest that the low uptake of pandemic influenza vaccines, like seasonal influenza vaccines, was primarily driven by two key factors: patient and healthcare practitioner perceptions of the risk of influenza infection and patient and healthcare practitioner perceptions of vaccine safety [12-17]. Therefore if influenza vaccination uptake is to be improved, public health authorities need to focus energy and funding on developing interventions to address these barriers to uptake. Any such interventions will need to be based on strong evidence, clearly illustrating that influenza infection is responsible for significant morbidity and mortality and that influenza vaccination is both safe and effective. The safety studies presented in this thesis suggest that the GPRD can play a role in generating such evidence.

## 5.2 GPRD: performance as a vaccine surveillance tool

Vaccine surveillance requires the production of accurate, precise results in a timely manner, therefore a complete assessment of the potential of the GPRD as a vaccine surveillance tool must consider its performance on all of these factors.

A key strength of the GPRD is the availability of routinely collected clinical information on a historic population of more than 10 million individuals, more than 5 million of whom were actively followed during the pandemic vaccination campaign. Therefore while the GPRD covered only 8.4% of the UK population during the study periods, its study population was comparable in size to national registries in countries such as Denmark, Finland and Norway. The size of the GPRD population permitted the calculation of precise estimates of predictors of influenza A(H1N1)pdm09 vaccine uptake, the incidence of several AESI and the hazard of foetal death. Vaccine uptake rates were comparable to those reported in national GP surveys [18, 19] while background rates of disease and foetal death were as, or more, precise than estimates in many other VAESCO countries and in the literature. The precision of estimates of the risk of GBS in the GPRD were limited by the low incidence of GBS and the low exposure prevalence in the UK in the age group at highest risk of GBS. However it should be noted that any UK data source would have suffered from this limitation, in fact it is likely that many smaller data sources may not have captured a single case of GBS following pandemic influenza vaccination. The GPRD have recently announced an expansion plan which will seek to rapidly increase the number of registered practices, this will serve to increase the precision of estimates in future studies.

While this illustrates the potential external validity that can be achieved using the GPRD the extrapolation of results is not valuable unless internal validity exists. In assessing internal validity one must consider all potential sources of bias and confounding, in this regard the accuracy and availability of exposure, outcome and confounder data is vital. The internal validity of each study in this thesis has already been discussed however a number of general observations can be made about the accuracy and availability of vaccine surveillance related data on the GPRD.

As vaccination is an acute exposure, vaccine safety studies generally assess the incidence of outcome events in biologically plausible post vaccination time windows; inaccuracy in the date of vaccination diminishes the biological plausibility of such windows. Possible scenarios in which vaccination dates on the GPRD may be inaccurately entered include recording of vaccinations administered outside a GP practice and recording of vaccination administrative procedures, such as the sending of invitations, using influenza vaccination codes. We did not carry out a formal validation to quantify the amount and magnitude of inaccuracy in vaccination records however no suggestion of inaccurate recording was observed in any of the GBS cases that were validated. As the pandemic influenza vaccine was primarily given in GP practices and specific codes exist for vaccine administration procedures, we expect

such inaccuracies to have had little impact on any of the results presented in this thesis.

In section 3.1 we described potential ways in which inaccuracy could be introduced into outcome data on the GPRD and described ways to validate outcomes. A number of these methods were applied in this thesis. The information in the free text allowed the validation of the occurrence and dates of diagnosis of most GBS cases. Cases did not meet high levels of the Brighton Collaboration GBS criteria however this is likely to reflect the poor suitability of the criteria to GP data sources rather than misclassification of outcome status or date. A Read code algorithm was used to identify pregnancies and pregnancy outcomes in the pregnancy uptake and foetal death studies. Validation has shown this algorithm to perform well. The lack of data on LMP dates limited the accuracy of gestational age at pregnancy outcome and necessitated many to be set to a default value. The sensitivity analysis showed that the results of foetal death studies on the GRPD may be sensitive to the choice of default gestational age at loss. Validation of facial nerve palsy cases was not carried out, however such an event is very likely to present and be diagnosed in general practice therefore outcome status and dates should be accurate. The variation in the rates of some of the other VAESCO outcomes such as convulsions, anaphylaxis and thrombocytopenia suggests validation would be useful, particularly where events are diagnosed or first present outside the GP setting. Routinely collected secondary care data or prospectively collected specialist data might be better placed to accurately identify these and other vaccine related outcomes; however each of these sources suffer from their own limitations. Linkage of the GPRD with such data sources would combine the strengths of each source while mitigating many of their weaknesses. The GPRD expansion plan includes plans to increase the number of linkages available therefore such an approach may become increasingly feasible.

As GPRD data is collected for general patient care, a large number of potential confounders such as comorbidities, drug prescribing and lifestyle factors can be identified and used in GPRD studies. In the GBS studies the GPRD was one of the few sources capable of partially controlling for influenza like illness and upper respiratory infection while in the foetal death and uptake studies a range of potential confounders could be controlled for. Despite this, important variables will not be recorded in the GPRD if they are not considered clinically relevant or are not reported to the GP. Linkage of the GPRD with other data sources may provide extra information on such variables. For example, linkage with other routinely collected data sources such as the NHS Number for Babies and birth registries databases would add up to 99% complete

data on pregnancy variables such as gestational age at pregnancy outcome and birth weight to that already available in the GPRD. However in vaccine safety studies confounders may exist that cannot be accurately measured in any routinely collected data source. An example of such a confounder is the healthy vaccinee effect, the vaccine equivalent of confounding by indication, whereby individuals who choose to be vaccinated are generally healthier and therefore less likely to suffer an outcome than unvaccinated individuals. In such cases special study designs and statistical analyses must be used to reduce confounding. The SCCS, applied in section 4.6 is an example of a study design which has been designed for this purpose. However, current SCCS methods are not suitable for application in all situations, such as in pregnancy safety studies. Propensity scores and instrumental variables have both been proposed as methods to deal with unmeasured confounding, however the ability of propensity scores to adjust for unmeasured confounding is dependent on the ability of the measured confounders used in the propensity score to act as proxies for unmeasured confounders while the identification of suitable instruments has also proven difficult. The potential of these two methods to improve such studies has therefore yet to be fully realised. Where suitable methods have not yet been developed, sensitivity analyses can be used to estimate what the true results might be if the observed results are subject to different levels of confounding; such an analysis was carried out in the foetal death study. The main problem with this approach is that it relies on a number of subjective assumptions about the relationships between exposure, unmeasured confounder and outcome. If detailed information on difficult to measure confounders can be collected in smaller samples of the population using patient questionnaires or interviews this information can be used to better inform the assumptions of sensitivity analyses applied in larger data sources such as the GPRD.

The timeliness with which vaccine surveillance results can be produced is of great importance as problems with a vaccination campaign can only be rectified within a limited time frame. This is particularly important in vaccine safety as uncertainty can lead to a loss of confidence in vaccination campaigns and, in the face of true adverse associations, in avoidable harm to patients. Near real time surveillance of vaccine safety using routinely collected clinical data has been pursued in sources such as the US Vaccine Safety Datalink. The GPRD could potentially be used in a similar fashion based on its monthly updates however its use as a passive signal detection tool is not currently warranted as this would limit its use in hypothesis testing. Further to this, the experience gained carrying out the studies in this thesis highlight a number of delays which may be encountered in conducting vaccine safety studies on the GPRD. Most notable were the delays in specialist diagnoses being communicated to a GP and

delays in obtaining additional validation data from the GPRD. Also, while the GPRD receives monthly updates, individual practices may only update their data up to every 3 months. Despite these findings the GPRD can be considered a relatively rapid data source.

Despite its size, where outcome events are rare, exposure prevalence is low or effect sizes are small, as was the case with GBS and pandemic influenza vaccination, years of data collection may be required for the GPRD to provide precise estimates of an association. In such cases the use of collaborative studies might facilitate more rapid investigation of associations.

### 5.3 VAESCO: potential as a platform for collaborative vaccine safety studies

*Can the VAESCO approach provide answers more rapidly?*

The belief that the large population available in a collaborative study could provide meaningful answers to important vaccine safety questions more rapidly than individual studies carried out in sources like the GPRD was one of the main premises upon which the VAESCO studies were initiated. It is well known that the size of a study population, or more accurately, the amount of person follow-up available in an analysis, plays a key role in determining the statistical power of that analysis (and therefore its ability to investigate rare outcomes) [20]. In theory, it is therefore true that a VAESCO-sized study would produce precise results much more rapidly than a GPRD-sized study, were it conducted in the same population.

In practice, however, the GPRD and VAESCO study populations are not based on the same underlying populations; drop-out rates, vaccine uptake rates and outcome incidence rates varied widely across VAESCO data sources. As a result, VAESCO data could not be simply combined into a single large dataset and analysed as if it came from a single population as it has been shown that in the presence of heterogeneous exposure prevalence this can produce biased results; in some extreme cases even changing the direction of associations [21].

Instead, a meta-analytical approach was taken. That is, datasets supplied from each individual collaborating data source were analysed individually and an average estimate of the effect observed across all sources was calculated. The average effects

were estimated using a random effects model, which assumes that the effect estimates in each individual study had been sampled from a population of true effect estimates (in contrast to a fixed effects model, which assumes there is a single true population effect and any variability observed in individual study results is solely due to chance) [22]. Generally the pooled estimates obtained from a random effects meta-analysis will be more precise than those of the individual studies contributing to it. However, heterogeneity between effect estimates from individual studies decreases the precision of a random effects pooled estimate, therefore the ability of the VAESCO model to provide precise estimates in a short time frame was largely dependent on its ability to remove unnecessary heterogeneity between contributing data sources [23].

Can the VAESCO approach remove unnecessary heterogeneity?

The VAESCO approach involved substantial efforts to reduce heterogeneity between data sources. Two common protocols were developed prior to the 2009 pandemic, one for the background incidence rate study and one for the case control and SCCS investigations of the pandemic vaccination GBS association. These protocols standardised the collection of information on observation periods, vaccinations, AESI (using Brighton Collaboration case definitions) and a range of additional covariates. The use of Jerboa, the Java-based data processing software developed by the informatics team at Erasmus University Medical Centre Rotterdam for use in collaborative studies, standardised the processing and anonymisation of data collected across all sites, creating a common analysis file for each. The analysis of these Jerboa output files at a single site by a single analysis team served to standardise the analysis process and also allowed for a central data quality check to be carried out.

Despite these efforts, in all three VAESCO studies in this thesis heterogeneity can still be observed between the results from each VAESCO source. While this may be due to natural variation in the association between vaccination and GBS (i.e. in line with a random effects model) it is likely that it is at least partly a result of residual heterogeneity. The major reason for residual heterogeneity is the underlying qualitative differences in the data sources included in the study, most notably those related to data collection as different data collection methods are associated with potentially differential biases which can be of unpredictable direction and magnitude. For example, false negative misclassification of exposures and covariates in sources of routinely collected data due to missing information, recall bias in sources which rely on interview data and biased case ascertainment in countries with incomplete case identification. Somewhat counter-intuitively, this residual heterogeneity has been put

forward as a potential strength of the VAESCO model, the argument being that it provides insight into the different biases at work in each data source. While this is true to a certain extent, accurately determining how much of the heterogeneity between results is due to chance and how much is due to bias or a lack of standardisation was not possible.

Given this residual heterogeneity, in assessing the working model it would be useful to obtain a measure of how much heterogeneity the VAESCO approach actually removed. However in the absence of information on the alternative to the VAESCO approach, that is, a set of independent studies carried out in each VAESCO data source, it is not possible to directly obtain such a measure. Investigating heterogeneity in the methods applied across non-VAESCO studies of the association between influenza A(H1N1)pdm09 vaccine and GBS can provide some insight into the amount of heterogeneity that can arise between independent studies, and therefore the relative success of VAESCO. In table 5.1 I compare some key design features of VAESCO studies and independent, non-VAESCO studies. While the harmonisation of overall study design is the most obvious advantage of the VAESCO approach, the majority of independent studies also used an SCCS approach. In addition most independent studies used a 0-42 day post vaccination exposure window (the exceptions being the German study which used 5-42 days and the Canadian study which used 0-56 days) and while some of the non-VAESCO studies did not use Brighton Collaboration case definitions for verification of cases it could be argued that in some VAESCO sources, such as the GPRD, the use of Brighton Collaboration case definition added little. Overall the table shows that the non-VAESCO studies do not appear to be much more heterogeneous than the VAESCO studies. Despite this, it should also be noted that the level of homogeneity between these studies is aided by the characteristics of the specific research question: the acute nature of vaccination, the wide agreement on the 6 week post-vaccination risk period, the specificity of diagnoses and diagnostic codes used to identify GBS and the availability of a standardised case definition for confirmation of GBS. An investigation of the association between exposure to a chronic treatment (such as blood glucose lowering agents) and a complex outcome (such as cancer) would be likely to result in much greater heterogeneity between exposure and outcome definitions used in independent studies; in such situations the amount of heterogeneity removed through the VAESCO approach would be more substantial.

**Table 5.1** Comparison of study characteristics across VAESCO and non-VAESCO studies of association between A(H1N1)pdm09 vaccine and GBS

| | Study design | exposure identification | Exposure window | Case identification | Case validation | control source |
|---|---|---|---|---|---|---|
| **VAESCO** | | | | | | |
| Netherlands | SCCS and case control | GP database | 0-42 days | neurologist network and claims | Yes, BC | Case GP |
| UK | SCCS and case control | GP database | 0-42 days | Read codes F370* | Yes, BC | Case GP |
| Sweden | SCCS and case control | interview | 0-42 days | neurologist network | Yes, BC | Population registry |
| Denmark | SCCS and case control | registry | 0-42 days | ICD10 G610 | Yes, BC | Population registry |
| Norway | SCCS and case control | registry | 0-42 days | neurologist network | Yes, BC | NA |
| France | SCCS and case control | registry | 0-42 days | neurologist network | Yes, BC | Hospital |
| Finland | SCCS and case control | registry | 0-42 days | ICD10 G610 | Yes, BC | NA |
| **Non-VAESCO** | | | | | | |
| Grimaldi-Bensouda *et al* [24] | case control | Interview and registry | 0-42 days | neurologist network | yes, BC | GP |
| Bardage *et al* [25] | cohort | registry | 0-42 days | ICD10 G610 | No | NA |
| Andrews *et al* [26] | SCCS | Hospital database | 0-42 days | ICD10 G610 | No | NA |
| Greene *et al* [27] | SCCS and case-centred | registry | 0-42 days | ICD9 357.0 | Yes, BC | NA |
| Tokars *et al* [28] | SCCS | interview and registry | 0-42 days | neurologist network and ICD G610 | Yes, BC | NA |
| Paul Ehrlich Institute [29] | SCCS | neurologist network | 5-42 days | neurologist network and ICD G610 | Yes, BC | NA |
| De Wals *et al* [30] | SCCS and cohort | registry | 0-56 days | neurologist network and ICD G610 | Yes, BC | NA |

SCCS, self-controlled case series; BC, Brighton Collaboration; GP, General Practitioner; ICD; International Classification of Disease.

One might argue that despite the residual heterogeneity observed in VAESCO, and the apparent homogeneity of the independent non-VAESCO study characteristics, the removal of any heterogeneity that would otherwise have existed rendered the use of the VAESCO working model worthwhile in this, and future scenarios. However, the advantages of any increases in homogeneity must be balanced against the potentially detrimental effect the VAESCO approach can have on other aspect of the study such as the speed with which results are obtained and the interpretation of results by external stakeholders.

*Pitfalls of the VAESCO working model*

As VAESCO discussions involved experts from a range of subject areas (e.g. public health, epidemiology, medicine) and cultures, differences in opinion were to be expected. The VAESCO background incidence rate and GBS protocols did not suffer any substantial delays due to differences in opinion however the subsequent VAESCO study investigating the association between narcolepsy and pandemic vaccination encountered considerable delays in protocol development due to the contrasting views of internal stakeholders. Collaborative studies such as this require well-defined mediation procedures in order to ensure any conflicts that arise are handled in a timely and satisfactory manner. Procedures to establish an independent arbitration committee might prove useful in dealing with situations in which mediation proves unsuccessful. Notably, independent studies carried out by investigators with differences of opinion are less likely to suffer such delays.

In the absence of strong differences in opinion, discussion and agreement on standardised study definitions can still be a laborious process. For example, in the VAESCO studies the code lists used to define outcomes, exposures and covariates at each source had to be harmonised across the different coding dictionaries. For some of the complex, less well characterised events, such as generalised convulsive seizure or vasculitis, this proved to be a time consuming process, and was the major factor responsible for the delay in providing regulatory authorities with background incidence rates for use in real time OE analyses. In future, the protocol for defining, drafting, reviewing and finalising clinical and operational study definitions needs to be clearly defined during protocol development in order to avoid such unnecessary delays.

It has been suggested that the use of Jerboa was a key strength of the VAESCO studies. However, anecdotal evidence suggests some external experts were uncertain about the role of Jerboa in the study, viewing it as a "black-box" into which study data

was entered. Similar concerns were also initially voiced by some internal VAESCO collaborators, however once it was explained that Jerboa carried out relatively simple data processing, that it was written in Java so that it could be run at all sites without the need for expensive software licences to be purchased and that all code had been cross validated in SAS, internal concerns dissipated. This same information needs to be clearly communicated to external stakeholders in order to ensure confidence in results is maintained. A contrasting problem might also arise if the functions of Jerboa are not clearly described to external stakeholders: casual readers might be led to believe that Jerboa is better than it is, for example that it is capable of removing heterogeneity in data collected from different sources. Such a belief might lead to a false sense of confidence in the comparability of results.

The collaborative approach implemented in VAESCO resulted in the analysis of all study data at a single site, Erasmus University Medical Centre. Collaborating partners interested in providing input in the analysis were afforded the opportunity to contribute to the analysis both remotely and at in person analysis meetings. Despite this, the use of Jerboa and the sending of data to an external study site may have created a psychological divide between individual collaborators and their data. Such a situation might leave collaborators feeling like data providers rather than investigators. This disconnect may have had knock-on effects on participation in the discussion of results and the review of any draft manuscripts or reports.

A practical problem with developing a common protocol is that any error in the design or analysis of the study will be implemented in all data sources. If a large proportion of the best epidemiological data sources available are recruited to a collaborative study like this, few sources of valid estimates may remain.

Publication of data from all sources in a single manuscript allows for external stakeholders to compare results across sources and develop an overall picture of the research question however it can also result in important information that might normally be included in a manuscript being left out. In addition, publication of data from all sources as a single "study" may provide the reader with a false sense of the comparability of sources, and therefore an incorrect interpretation of the results. The single publication approach can also affect the speed of result dissemination, whereby delays in one source lead to a delay in the publication as a whole, even if some sources have data ready on time. A way around this problem is to report no results, or interim results, for the delayed sources; however this might not be well accepted by individuals working on the delayed source

*Suggestions for the future*

In closing it should be emphasized that while the VAESCO studies provided useful information to inform the surveillance of the pandemic vaccination campaign, the VAESCO project was primarily a proof of principle endeavour. As a result it is important that the difficulties described above are viewed not as failings, but as challenges to be addressed in future implementations of the working model.

Indeed an adapted version of the VAESCO working model has now been implemented in a collaborative multinational project investigating the safety of drugs used in the treatment of type 2 diabetes [31]. Changes made to the model for this project include: recruitment of more comparable data sources, distribution of the responsibility for study efforts across all collaborators in a clear and open manner, creating a "remote research environment" (a remote desktop located within the firewalls of Erasmus UMC Rotterdam) which collaborators log into using a password in order to contribute to analyses, pre-specification of a publication plan which involves contribution from as many partners as possible and a strong effort to clearly describe the role of Jerboa to a wider audience. These changes should serve to address some of the aforementioned limitations of the VAESCO working model. As the remote research environment removes the need to transmit data by email, data is uploaded to it through a secure file transfer protocol client, data protection has also been improved.

In another collaborative drug safety initiative [32] a less collaborative working model has been implemented. Within this model a common protocol is drafted and implemented across all sources but all data processing and analysis is conducted locally using local scripts. Local results are then meta-analysed across sites and data disseminated in a single manuscript.

As the associations under investigation in both of these new studies require more complex definitions of study populations, exposures, outcomes and covariates it will be interesting to see if the collaborative approach implemented in these studies improves comparability over previous non-collaborative studies of the same associations, and over the VAESCO studies. In future, a simple method to obtain a formal measure of the heterogeneity removed through these collaborations might be to ask individual partners to first draft local, data source specific protocols and then compare these with the final common protocol. Given the relative infancy of large collaborative European drug and vaccine safety projects, the financial support they

require and their uncertain effectiveness in harmonising data and results in the VAESCO project, it is vital that such comparisons are made in order to ensure that the theoretical advantages of collaboration are realised operationally and outweigh any possible disadvantages.

## 5.4 Conclusions

- At 40.3% and 21.6%, uptake of influenza A(H1N1)pdm09 vaccine by those in clinical risk groups and pregnant women was low. Age was the demographic characteristic most strongly associated with uptake among those in clinical risk groups. Being in a clinical risk group was the strongest predictor of uptake in pregnant women.

- The age standardised 10 year incidence rate of facial nerve palsy estimated in 8 data sources ranged from 5.33/100,000 PY in Sweden to 41.82/100,000 PY in Spain with the rate in the UK estimated as 27.22/100,000 PY. Variation observed across age categories, calendar time and data sources suggest it is important that such factors are considered when carrying out comparisons between observed and expected rates of facial nerve palsy.

- Risk estimates for the association between GBS and influenza A(H1N1)pdm09 vaccination in the different sources varied, however point estimates consistently showed increased risks which were reduced, or disappeared entirely, following adjustment for ILI, URTI or calendar month ([CC: $IRR_{adj}$ 1.0, $CI_{95}$ 0.3 to 2.7]; [SCCS: $OR_{adj}$ 1.3, $CI_{95}$ 0.6 to 2.7]).

- Vaccination against influenza A(H1N1)pdm09 was associated with a lower risk of first ($HR_{unadj}$ 0.74, $CI_{95}$ 0.62 to 0.88), second ($HR_{unadj}$ 0.59, $CI_{95}$ 0.45 to 0.77) and third ($HR_{unadj}$ 0.70, $CI_{95}$ 0.47 to 1.03) trimester foetal death. While this may be explained by residual confounding, sensitivity analyses provide reassurance that vaccination is unlikely to be associated with an increased risk of pregnancy loss.

- Taken together, these results represent a meaningful contribution to the post-marketing surveillance of the influenza A(H1N1)pdm09vaccination campaign and suggest that the campaign was characterised by the low uptake of a generally safe vaccine against a relatively mild pandemic strain of influenza.

- The findings also show that the GPRD performed well as a vaccine surveillance tool, providing accurate data on influenza A(H1N1) pdm09 vaccination and disease incidence. We highlight a number of possible developments which might serve to improve the GPRD's ability to contribute meaningfully to vaccine surveillance during future vaccination campaigns.

- The collaborative VAESCO studies illustrate the potential advantages and difficulties of international collaboration in vaccine safety. The VAESCO working model served to reduce heterogeneity across data sources however further investigation is needed to determine whether the reduction in heterogeneity is worthwhile given the potential limitations the model can impose on the speed, quality and interpretation of study results.

[1] Department of Health. (2012) Flu vaccination programme extended to all children. Available:http://mediacentre.dh.gov.uk/2012/07/25/flu-vaccination-programme-extended-to-all-children/. Accessed 04/12/2012.

[2] Kurz X, Domergue F, Slattery J, Segec A, Szmigiel A, Hidalgo-Simon A. Safety monitoring of Influenza A/H1N1 pandemic vaccines in EudraVigilance. Vaccine 2011;29(26):4378-87.

[3] Grimaldi-Bensouda L, Alperovitch A, Besson G, Vial C, Cuisset JM, Papeix C, et al. Guillain-Barre syndrome, influenzalike illnesses, and influenza vaccination during seasons with and without circulating A/H1N1 viruses. Am J Epidemiol 2011;174(3):326-35.

[4] Andrews N, Stowe J, Al-Shahi Salman R, Miller E. Guillain-Barre syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. Vaccine 2011;29(45):7878-82.

[5] Bardage C, Persson I, Ortqvist A, Bergman U, Ludvigsson JF, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. BMJ 2011;343:d5956.

[6] Paul-Ehrlich-Institut. Zusammenhang zwischen pandemischer Influenza A/H1N1v-Impfung und Guillain-Barre-Syndrome / Miller-Fisher-Syndrome in Deutschland; 2012.

[7] Centers for Disease Control and Prevention. (2012) Vaccine Safety and Human Genetic Variations. Available:http://www.cdc.gov/vaccinesafety/Activities/cisa/genomics.html. Accessed 27/03/2013.

[8] Fell DB, Sprague AE, Liu N, Yasseen AS, 3rd, Wen SW, Smith G, et al. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes. Am J Public Health 2012;102(6):e33-40.

[9] Pasternak B, Svanstrom H, Molgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. BMJ 2012;344:e2794.

[10] Tavares F, Nazareth I, Monegal JS, Kolte I, Verstraeten T, Bauchau V. Pregnancy and safety outcomes in women vaccinated with an AS03-adjuvanted split virion H1N1 (2009) pandemic influenza vaccine during pregnancy: a prospective cohort study. Vaccine 2011;29(37):6358-65.

[11] Moro PL, Broder K, Zheteyeva Y, Revzina N, Tepper N, Kissin D, et al. Adverse events following administration to pregnant women of influenza A (H1N1) 2009

monovalent vaccine reported to the Vaccine Adverse Event Reporting System. Am J Obstet Gynecol 2011;205(5):473 e1-9.

[12] Kroneman M, van Essen GA, John PW. Influenza vaccination coverage and reasons to refrain among high-risk persons in four European countries. Vaccine 2006;24(5):622-8.

[13] Muller D, Szucs TD. Influenza vaccination coverage rates in 5 European countries: a population-based cross-sectional analysis of the seasons 02/03, 03/04 and 04/05. Infection 2007;35(5):308-19.

[14] Holm MV, Blank PR, Szucs TD. Developments in influenza vaccination coverage in England, Scotland and Wales covering five consecutive seasons from 2001 to 2006. Vaccine 2007;25(46):7931-8.

[15] Steelfisher GK, Blendon RJ, Bekheit MM, Mitchell EW, Williams J, Lubell K, et al. Novel pandemic A (H1N1) influenza vaccination among pregnant women: motivators and barriers. Am J Obstet Gynecol 2011;204(6 Suppl 1):S116-23.

[16] Goldfarb I, Panda B, Wylie B, Riley L. Uptake of influenza vaccine in pregnant women during the 2009 H1N1 influenza pandemic. Am J Obstet Gynecol 2011;204(6 Suppl 1):S112-5.

[17] Ding H, Santibanez TA, Jamieson DJ, Weinbaum CM, Euler GL, Grohskopf LA, et al. Influenza vaccination coverage among pregnant women--National 2009 H1N1 Flu Survey (NHFS). Am J Obstet Gynecol 2011;204(6 Suppl 1):S96-106.

[18] Begum F, Pebody R. (2010) Pandemic H1N1 (Swine) Influenza Vaccine Uptake amongst Patient Groups in Primary Care in England 2009/10. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_121014.pdf. Accessed 12/11/2010.

[19] Begum F, Pebody R. (2010) Seasonal influenza vaccine uptake among the 65 years and over and under 65 years at risk in England - Winter season 2009-10. Available:http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_118645.pdf. Accessed 20/09/2010.

[20] Altman DG. Practical statistics for medical research. 1st ed. London ; New York: Chapman and Hall; 1991.

[21] Bravata DM, Olkin I. Simple Pooling versus Combining in Meta-Analysis. Evaluation & the Health Professions 2001;24(2):218-30.

[22] Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods. 2010;1(2):97-111.

[23] Cohn LD, Becker BJ. How meta-analysis increases statistical power. Psychol Methods. 2003;8(3):243-53.

[24] Grimaldi-Bensouda L, Alperovitch A, Besson G, Vial C, Cuisset JM, Papeix C, et al. Guillain-Barre syndrome, influenzalike illnesses, and influenza vaccination during seasons with and without circulating A/H1N1 viruses. Am J Epidemiol 2011;174(3):326-35.

[25] Bardage C, Persson I, Ortqvist A, Bergman U, Ludvigsson JF, Granath F. Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden. BMJ 2011;343:d5956.

[26] Andrews N, Stowe J, Al-Shahi Salman R, Miller E. Guillain-Barre syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series. Vaccine 2011;29(45):7878-82.

[27] Greene SK, Rett M, Weintraub ES, Li L, Yin R, Amato AA, et al. Risk of Confirmed Guillain-Barre Syndrome Following Receipt of Monovalent Inactivated Influenza A (H1N1) and Seasonal Influenza Vaccines in the Vaccine Safety Datalink Project, 2009-2010. Am J Epidemiol 2012;175(11):1100-9.

[28] Tokars JI, Lewis P, DeStefano F, Wise M, Viray M, Morgan O, et al. The risk of Guillain-Barre syndrome associated with influenza A (H1N1) 2009 monovalent vaccine and 2009-2010 seasonal influenza vaccines: results from self-controlled analyses. Pharmacoepidemiol Drug Saf 2012;21(5):546-52.

[29] Paul-Ehrlich-Institut. Zusammenhang zwischen pandemischer Influenza A/H1N1v-Impfung und Guillain-Barre-Syndrome / Miller-Fisher-Syndrome in Deutschland; 2012.

[30] De Wals P, Deceuninck G, Toth E, Boulianne N, Brunet D, Boucher RM, et al. Risk of Guillain-Barre syndrome following H1N1 influenza vaccination in Quebec. JAMA 2012;308(2):175-81.

[31] SAFEGUARD website. (2013). Available: http://www.safeguard-diabetes.org/. Accessed 01/09/2013.

[32] IMI-PROTECT website. (2013). Available: http://www.imi-protect.eu/. Accessed 01/09/2013.

# 6. Appendices

## 6.1 Appendix 1 – Comparison of GPRD and ONS data

| | GPRD* | | ONS** | |
|---|---|---|---|---|
| | N(1000s) | % | N(1000s) | % |
| Male | 2,212 | 0.50 | 30154 | 0.49 |
| Female | 2,253 | 0.50 | 31243 | 0.51 |

| | GPRD* | | ONS** | |
|---|---|---|---|---|
| | MALE | | | |
| | N(1000s) | % | N(1000s) | % |
| Under 1 | 23 | 1.06 | 403 | 1.34 |
| 1 - 4 | 105 | 4.76 | 1,492 | 4.95 |
| 5 - 9 | 125 | 5.65 | 1,735 | 5.75 |
| 10 - 14 | 136 | 6.14 | 1,872 | 6.21 |
| 15 - 19 | 141 | 6.35 | 2,049 | 6.80 |
| 20 - 29 | 278 | 12.57 | 4,236 | 14.05 |
| 30 - 44 | 492 | 22.25 | 6,450 | 21.39 |
| 45 - 59 | 453 | 20.49 | 5,814 | 19.28 |
| 60 - 64 | 139 | 6.28 | 1,780 | 5.90 |
| 65 - 74 | 183 | 8.30 | 2,449 | 8.12 |
| 75 - 84 | 106 | 4.77 | 1,452 | 4.82 |
| 85 and over | 30 | 1.38 | 422 | 1.40 |

| | GPRD* | | ONS** | |
|---|---|---|---|---|
| | FEMALE | | | |
| | N(1000s) | % | N(1000s) | % |
| Under 1 | 22 | 0.99 | 385 | 1.23 |
| 1 - 4 | 100 | 4.44 | 1,420 | 4.54 |
| 5 - 9 | 120 | 5.32 | 1,658 | 5.31 |
| 10 - 14 | 131 | 5.80 | 1,785 | 5.71 |
| 15 - 19 | 133 | 5.91 | 1,938 | 6.20 |
| 20 - 29 | 280 | 12.42 | 4,076 | 13.05 |
| 30 - 44 | 477 | 21.16 | 6,527 | 20.89 |
| 45 - 59 | 441 | 19.59 | 5,983 | 19.15 |
| 60 - 64 | 140 | 6.21 | 1,861 | 5.96 |
| 65 - 74 | 198 | 8.78 | 2,708 | 8.67 |
| 75 - 84 | 143 | 6.35 | 1,988 | 6.36 |
| 85 and over | 68 | 3.03 | 914 | 2.93 |

| | GPRD* | | ONS** | |
|---|---|---|---|---|
| **Country** | N(1000s) | **%** | N(1000s) | **%** |
| Scotland | 428 | 7.9 | 5,169 | 8.4 |
| Wales | 382 | 7.0 | 2,990 | 4.9 |
| Northern Ireland | 151 | 2.8 | 1,775 | 2.9 |
| England | 4,467 | 82.3 | 51,465 | 83.8 |
| UK | 5,429 | 100.0 | 61,399 | 100 |

*All GPRD figures are based on 'up-to-standard' population available in the GPRD on the 01/01/2009

**Office for National Statistics (ONS) figures are based on the mid-2008 population estimates published in Chapter 15 of their *Annual Abstract of Statistics - Quarter 3, 2011* available at http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-222649

## 6.2 Appendix 2 - Facial nerve palsy data

**Numbers of facial nerve palsy events and person time of follow up by calendar year, calendar month and age category.**

| IPCI - Netherlands | | women | | men | | total | |
|---|---|---|---|---|---|---|---|
| | | Events | Person years | Events | Person years | Events | Person years |
| Calendar year | 1996 | 0 | 1130 | 0 | 1146 | 0 | 2276 |
| | 1997 | 16 | 58800 | 16 | 56717 | 32 | 115518 |
| | 1998 | 18 | 80911 | 17 | 79102 | 35 | 160013 |
| | 1999 | 21 | 109742 | 24 | 108990 | 45 | 218732 |
| | 2000 | 42 | 114375 | 38 | 113398 | 80 | 227774 |
| | 2001 | 35 | 107119 | 30 | 106579 | 65 | 213698 |
| | 2002 | 20 | 109939 | 26 | 109282 | 46 | 219221 |
| | 2003 | 34 | 108741 | 25 | 108437 | 59 | 217178 |
| | 2004 | 24 | 112035 | 25 | 111597 | 49 | 223632 |
| | 2005 | 19 | 92528 | 24 | 92690 | 43 | 185218 |
| | 2006 | 9 | 42945 | 8 | 42439 | 17 | 85384 |
| | 2007 | 0 | 864 | 0 | 871 | 0 | 1734 |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 |
| Calendar month | Jan | 25 | 80545 | 20 | 79726 | 45 | 160271 |
| | Feb | 14 | 74158 | 26 | 73404 | 40 | 147562 |
| | Mar | 22 | 81401 | 20 | 80692 | 42 | 162094 |
| | Apr | 19 | 78776 | 20 | 78090 | 39 | 156866 |
| | May | 18 | 79611 | 21 | 78965 | 39 | 158576 |
| | Jun | 22 | 77317 | 21 | 76705 | 43 | 154022 |
| | Jul | 11 | 79395 | 18 | 78757 | 29 | 158152 |
| | Aug | 23 | 79703 | 20 | 79091 | 43 | 158794 |
| | Sep | 15 | 77941 | 16 | 77382 | 31 | 155324 |
| | Oct | 24 | 79016 | 24 | 78432 | 48 | 157448 |
| | Nov | 13 | 74421 | 15 | 73830 | 28 | 148250 |
| | Dec | 32 | 76844 | 12 | 76174 | 44 | 153019 |
| Age category | 0-4 | 4 | 56380 | 2 | 59141 | 6 | 115521 |
| | 5-9 | 1 | 55037 | 3 | 57576 | 4 | 112613 |
| | 10-14 | 5 | 54897 | 5 | 56996 | 10 | 111892 |
| | 15-19 | 13 | 53317 | 9 | 54982 | 22 | 108299 |
| | 20-24 | 9 | 55824 | 8 | 57712 | 17 | 113536 |
| | 25-29 | 22 | 66090 | 11 | 68835 | 33 | 134925 |
| | 30-34 | 15 | 73015 | 17 | 79182 | 32 | 152197 |
| | 35-39 | 16 | 75476 | 17 | 80214 | 33 | 155690 |
| | 40-44 | 15 | 72896 | 17 | 75714 | 32 | 148610 |
| | 45-49 | 19 | 67999 | 25 | 69176 | 44 | 137175 |
| | 50-54 | 14 | 64715 | 28 | 66796 | 42 | 131510 |
| | 55-59 | 23 | 55050 | 21 | 56155 | 44 | 111205 |
| | 60-64 | 12 | 43131 | 23 | 43192 | 35 | 86324 |
| | 65-69 | 22 | 38448 | 16 | 35108 | 38 | 73557 |
| | 70-74 | 20 | 35324 | 16 | 28871 | 36 | 64196 |
| | 75-79 | 17 | 31277 | 9 | 21495 | 26 | 52773 |
| | 80-84 | 8 | 21851 | 2 | 12542 | 10 | 34393 |
| | 85+ | 3 | 18401 | 4 | 7559 | 7 | 25960 |
| Group Total | | 238 | 939129 | 233 | 931249 | 471 | 1870377 |

**Incidence rate of facial nerve palsy per 100,000 person years by calendar year, calendar month and age category.**

| IPCI - Netherlands | | IR/100000 | | | | | |
|---|---|---|---|---|---|---|---|
| | | **women** | **95%CI** | **men** | **95%CI** | **Total** | **95%CI** |
| Calendar year | 1996 | 0.00 | - | 0.00 | - | 0.00 | - |
| | 1997 | 27.21 | (16.19-43.14) | 28.21 | (16.78-44.72) | 27.70 | (19.30-38.60) |
| | 1998 | 22.25 | (13.65-34.40) | 21.49 | (12.99-33.63) | 21.87 | (15.49-30.06) |
| | 1999 | 19.14 | (12.20-28.70) | 22.02 | (14.47-32.22) | 20.57 | (15.20-27.27) |
| | 2000 | 36.72 | (26.83-49.14) | 33.51 | (24.08-45.49) | 35.12 | (28.04-43.47) |
| | 2001 | 32.67 | (23.14-44.90) | 28.15 | (19.37-39.63) | 30.42 | (23.68-38.51) |
| | 2002 | 18.19 | (11.46-27.54) | 23.79 | (15.91-34.32) | 20.98 | (15.56-27.73) |
| | 2003 | 31.27 | (22.03-43.16) | 23.05 | (15.29-33.48) | 27.17 | (20.88-34.78) |
| | 2004 | 21.42 | (14.08-31.34) | 22.40 | (14.85-32.54) | 21.91 | (16.40-28.71) |
| | 2005 | 20.53 | (12.78-31.41) | 25.89 | (17.02-37.88) | 23.22 | (17.03-30.96) |
| | 2006 | 20.96 | (10.35-38.25) | 18.85 | (8.89-35.57) | 19.91 | (12.04-31.16) |
| | 2007 | 0.00 | - | 0.00 | - | 0.00 | - |
| | 2008 | 0.00 | - | 0.00 | - | 0.00 | - |
| Calendar month | Jan | 31.04 | (20.58-45.08) | 25.09 | (15.81-37.98) | 28.08 | (20.74-37.21) |
| | Feb | 18.88 | (10.81-30.83) | 35.42 | (23.68-51.09) | 27.11 | (19.65-36.52) |
| | Mar | 27.03 | (17.42-40.18) | 24.79 | (15.62-37.53) | 25.91 | (18.93-34.67) |
| | Apr | 24.12 | (15.01-36.89) | 25.61 | (16.14-38.78) | 24.86 | (17.95-33.62) |
| | May | 22.61 | (13.88-34.96) | 26.59 | (16.95-39.89) | 24.59 | (17.75-33.26) |
| | Jun | 28.45 | (18.34-42.30) | 27.38 | (17.45-41.06) | 27.92 | (20.48-37.23) |
| | Jul | 13.85 | (7.35-23.98) | 22.86 | (14.03-35.34) | 18.34 | (12.54-25.96) |
| | Aug | 28.86 | (18.79-42.55) | 25.29 | (15.93-38.29) | 27.08 | (19.86-36.11) |
| | Sep | 19.25 | (11.24-30.94) | 20.68 | (12.30-32.78) | 19.96 | (13.82-27.95) |
| | Oct | 30.37 | (19.96-44.44) | 30.60 | (20.11-44.77) | 30.49 | (22.75-40.06) |
| | Nov | 17.47 | (9.78-29.02) | 20.32 | (11.87-32.67) | 18.89 | (12.82-26.90) |
| | Dec | 41.64 | (29.02-58.03) | 15.75 | (8.60-26.68) | 28.75 | (21.17-38.23) |
| Age category | 0-4 | 7.09 | (2.37-16.87) | 3.38 | - | 5.19 | (2.16-10.71) |
| | 5-9 | 1.82 | - | 5.21 | (1.44-13.90) | 3.55 | (1.19-8.45) |
| | 10-14 | 9.11 | (3.45-19.96) | 8.77 | (3.33-19.23) | 8.94 | (4.59-15.86) |
| | 15-19 | 24.38 | (13.65-40.51) | 16.37 | (8.08-29.88) | 20.31 | (13.09-30.20) |
| | 20-24 | 16.12 | (7.96-29.43) | 13.86 | (6.54-26.16) | 14.97 | (9.05-23.43) |
| | 25-29 | 33.29 | (21.45-49.49) | 15.98 | (8.48-27.66) | 24.46 | (17.14-33.92) |
| | 30-34 | 20.54 | (12.00-33.03) | 21.47 | (12.98-33.60) | 21.03 | (14.65-29.30) |
| | 35-39 | 21.20 | (12.61-33.61) | 21.19 | (12.81-33.17) | 21.20 | (14.85-29.39) |
| | 40-44 | 20.58 | (12.02-33.09) | 22.45 | (13.58-35.14) | 21.53 | (15.00-30.00) |
| | 45-49 | 27.94 | (17.39-42.74) | 36.14 | (23.96-52.49) | 32.08 | (23.61-42.64) |
| | 50-54 | 21.63 | (12.39-35.33) | 41.92 | (28.46-59.70) | 31.94 | (23.34-42.73) |
| | 55-59 | 41.78 | (27.20-61.60) | 37.40 | (23.84-56.09) | 39.57 | (29.13-52.60) |
| | 60-64 | 27.82 | (15.19-47.12) | 53.25 | (34.67-78.51) | 40.55 | (28.72-55.72) |
| | 65-69 | 57.22 | (36.88-85.07) | 45.57 | (27.11-72.25) | 51.66 | (37.13-70.12) |
| | 70-74 | 56.62 | (35.68-85.73) | 55.42 | (32.96-87.85) | 56.08 | (39.92-76.73) |
| | 75-79 | 54.35 | (32.86-85.06) | 41.87 | (20.68-76.42) | 49.27 | (32.94-71.06) |
| | 80-84 | 36.61 | (17.27-69.09) | 15.95 | - | 29.08 | (14.93-51.58) |
| | 85+ | 16.30 | (4.51-43.50) | 52.91 | (17.69-125.81) | 26.96 | (12.02-52.95) |
| Group Total | | 25.34 | (22.27-28.72) | 25.02 | (21.96-28.39) | 25.18 | (22.98-27.53) |

**Numbers of facial nerve palsy events and person time of follow up by calendar year, calendar month and age category.**

| BIFAP - Spain | | women | | men | | total | |
|---|---|---|---|---|---|---|---|
| | | Events | Person years | Events | Person years | Events | Person years |
| Calendar year | 1996 | 0 | 3509 | 0 | 3547 | 0 | 7056 |
| | 1997 | 0 | 7058 | 0 | 6435 | 0 | 13493 |
| | 1998 | 6 | 17074 | 2 | 15176 | 8 | 32250 |
| | 1999 | 21 | 76623 | 13 | 62501 | 34 | 139124 |
| | 2000 | 70 | 237733 | 70 | 193887 | 140 | 431620 |
| | 2001 | 214 | 508463 | 158 | 424495 | 372 | 932959 |
| | 2002 | 317 | 669891 | 225 | 576322 | 542 | 1246214 |
| | 2003 | 410 | 810889 | 337 | 706394 | 747 | 1517283 |
| | 2004 | 501 | 942673 | 421 | 828162 | 922 | 1770835 |
| | 2005 | 456 | 966649 | 409 | 855715 | 865 | 1822365 |
| | 2006 | 503 | 921982 | 416 | 822848 | 919 | 1744829 |
| | 2007 | 441 | 862195 | 360 | 775148 | 801 | 1637343 |
| | 2008 | 287 | 573977 | 263 | 517300 | 550 | 1091277 |
| Calendar month | Jan | 284 | 541754 | 246 | 474995 | 530 | 1016749 |
| | Feb | 271 | 501254 | 196 | 439481 | 467 | 940735 |
| | Mar | 298 | 556484 | 206 | 487799 | 504 | 1044283 |
| | Apr | 271 | 542950 | 244 | 475882 | 515 | 1018832 |
| | May | 296 | 564255 | 227 | 494619 | 523 | 1058873 |
| | Jun | 240 | 548253 | 207 | 480878 | 447 | 1029132 |
| | Jul | 255 | 565372 | 203 | 495861 | 458 | 1061233 |
| | Aug | 230 | 568578 | 228 | 498884 | 458 | 1067462 |
| | Sep | 278 | 554998 | 227 | 487516 | 505 | 1042514 |
| | Oct | 269 | 565934 | 218 | 497223 | 487 | 1063157 |
| | Nov | 285 | 537703 | 243 | 471621 | 528 | 1009325 |
| | Dec | 249 | 551182 | 229 | 483171 | 478 | 1034353 |
| Age category | 0-4 | 44 | 324894 | 38 | 342268 | 82 | 667163 |
| | 5-9 | 33 | 265076 | 37 | 279445 | 70 | 544522 |
| | 10-14 | 118 | 288846 | 65 | 302988 | 183 | 591833 |
| | 15-19 | 120 | 331597 | 135 | 342980 | 255 | 674577 |
| | 20-24 | 180 | 441965 | 159 | 420594 | 339 | 862559 |
| | 25-29 | 244 | 555240 | 216 | 501332 | 460 | 1056572 |
| | 30-34 | 274 | 571909 | 276 | 496104 | 550 | 1068013 |
| | 35-39 | 253 | 539611 | 249 | 476162 | 502 | 1015773 |
| | 40-44 | 188 | 496727 | 207 | 437580 | 395 | 934307 |
| | 45-49 | 215 | 466058 | 204 | 395075 | 419 | 861133 |
| | 50-54 | 225 | 433844 | 215 | 370646 | 440 | 804490 |
| | 55-59 | 222 | 389376 | 205 | 344577 | 427 | 733953 |
| | 60-64 | 227 | 310548 | 147 | 275937 | 374 | 586485 |
| | 65-69 | 225 | 280402 | 162 | 236152 | 387 | 516554 |
| | 70-74 | 228 | 289005 | 155 | 223711 | 383 | 512716 |
| | 75-79 | 198 | 253257 | 114 | 171679 | 312 | 424937 |
| | 80-84 | 149 | 188769 | 64 | 103706 | 213 | 292474 |
| | 85+ | 83 | 171287 | 26 | 66804 | 109 | 238091 |
| Group Total | | 3226 | 6598409 | 2674 | 5787741 | 5900 | 12386151 |

**Incidence rate of facial nerve palsy per 100,000 person years by calendar year, calendar month and age category.**

| BIFAP - Spain | | IR/100000 | | | | | |
|---|---|---|---|---|---|---|---|
| | | **women** | **95%CI** | **men** | **95%CI** | **Total** | **95%CI** |
| Calendar year | 1996 | 0.00 | - | 0.00 | - | 0.00 | - |
| | 1997 | 0.00 | - | 0.00 | - | 0.00 | - |
| | 1998 | 35.14 | (14.61-72.44) | 13.18 | - | 24.81 | (11.70-46.81) |
| | 1999 | 27.41 | (17.47-41.11) | 20.80 | (11.65-34.56) | 24.44 | (17.22-33.73) |
| | 2000 | 29.44 | (23.14-36.97) | 36.10 | (28.37-45.33) | 32.44 | (27.39-38.15) |
| | 2001 | 42.09 | (36.73-48.02) | 37.22 | (31.75-43.37) | 39.87 | (35.97-44.08) |
| | 2002 | 47.32 | (42.32-52.75) | 39.04 | (34.19-44.40) | 43.49 | (39.95-47.27) |
| | 2003 | 50.56 | (45.84-55.64) | 47.71 | (42.82-53.01) | 49.23 | (45.80-52.86) |
| | 2004 | 53.15 | (48.64-57.96) | 50.84 | (46.15-55.87) | 52.07 | (48.79-55.51) |
| | 2005 | 47.17 | (42.99-51.65) | 47.80 | (43.33-52.60) | 47.47 | (44.38-50.71) |
| | 2006 | 54.56 | (49.94-59.48) | 50.56 | (45.87-55.59) | 52.67 | (49.35-56.16) |
| | 2007 | 51.15 | (46.54-56.09) | 46.44 | (41.83-51.43) | 48.92 | (45.62-52.40) |
| | 2008 | 50.00 | (44.47-56.04) | 50.84 | (44.97-57.27) | 50.40 | (46.32-54.75) |
| Calendar month | Jan | 52.42 | (46.59-58.79) | 51.79 | (45.62-58.57) | 52.13 | (47.83-56.71) |
| | Feb | 54.06 | (47.91-60.79) | 44.60 | (38.68-51.18) | 49.64 | (45.29-54.30) |
| | Mar | 53.55 | (47.73-59.89) | 42.23 | (36.76-48.30) | 48.26 | (44.19-52.62) |
| | Apr | 49.91 | (44.23-56.13) | 51.27 | (45.14-58.02) | 50.55 | (46.32-55.06) |
| | May | 52.46 | (46.74-58.69) | 45.89 | (40.21-52.16) | 49.39 | (45.29-53.76) |
| | Jun | 43.78 | (38.50-49.58) | 43.05 | (37.48-49.22) | 43.43 | (39.55-47.60) |
| | Jul | 45.10 | (39.82-50.90) | 40.94 | (35.59-46.87) | 43.16 | (39.34-47.25) |
| | Aug | 40.45 | (35.47-45.94) | 45.70 | (40.06-51.93) | 42.91 | (39.11-46.97) |
| | Sep | 50.09 | (44.46-56.24) | 46.56 | (40.80-52.92) | 48.44 | (44.35-52.81) |
| | Oct | 47.53 | (42.10-53.47) | 43.84 | (38.31-49.96) | 45.81 | (41.87-50.01) |
| | Nov | 53.00 | (47.11-59.43) | 51.52 | (45.35-58.31) | 52.31 | (47.99-56.92) |
| | Dec | 45.18 | (39.82-51.05) | 47.40 | (41.55-53.84) | 46.21 | (42.21-50.50) |
| Age category | 0-4 | 13.54 | (9.97-18.00) | 11.10 | (7.98-15.07) | 12.29 | (9.84-15.17) |
| | 5-9 | 12.45 | (8.72-17.26) | 13.24 | (9.47-18.04) | 12.86 | (10.10-16.14) |
| | 10-14 | 40.85 | (33.97-48.73) | 21.45 | (16.70-27.16) | 30.92 | (26.68-35.65) |
| | 15-19 | 36.19 | (30.14-43.11) | 39.36 | (33.13-46.43) | 37.80 | (33.37-42.66) |
| | 20-24 | 40.73 | (35.10-47.01) | 37.80 | (32.27-44.03) | 39.30 | (35.28-43.66) |
| | 25-29 | 43.94 | (38.69-49.72) | 43.09 | (37.62-49.12) | 43.54 | (39.69-47.65) |
| | 30-34 | 47.91 | (42.49-53.84) | 55.63 | (49.36-62.49) | 51.50 | (47.33-55.94) |
| | 35-39 | 46.89 | (41.37-52.94) | 52.29 | (46.10-59.10) | 49.42 | (45.24-53.89) |
| | 40-44 | 37.85 | (32.72-43.55) | 47.31 | (41.19-54.09) | 42.28 | (38.26-46.60) |
| | 45-49 | 46.13 | (40.27-52.61) | 51.64 | (44.91-59.09) | 48.66 | (44.16-53.49) |
| | 50-54 | 51.86 | (45.41-58.98) | 58.01 | (50.64-66.16) | 54.69 | (49.76-59.99) |
| | 55-59 | 57.01 | (49.88-64.89) | 59.49 | (51.76-68.06) | 58.18 | (52.85-63.90) |
| | 60-64 | 73.10 | (64.05-83.08) | 53.27 | (45.18-62.42) | 63.77 | (57.55-70.48) |
| | 65-69 | 80.24 | (70.27-91.25) | 68.60 | (58.64-79.79) | 74.92 | (67.73-82.67) |
| | 70-74 | 78.89 | (69.14-89.64) | 69.29 | (59.01-80.85) | 74.70 | (67.50-82.47) |
| | 75-79 | 78.18 | (67.85-89.65) | 66.40 | (55.04-79.45) | 73.42 | (65.61-81.91) |
| | 80-84 | 78.93 | (67.01-92.39) | 61.71 | (47.95-78.27) | 72.83 | (63.53-83.11) |
| | 85+ | 48.46 | (38.85-59.75) | 38.92 | (26.02-56.14) | 45.78 | (37.78-55.00) |

| | | | | | |
|---|---|---|---|---|---|
| Group Total | 48.89 | (47.23-50.60) | 46.20 | (44.47-47.98) | 47.63 | (46.43-48.86) |

**Numbers of facial nerve palsy events and person time of follow up by calendar year, calendar month and age category.**

| CPRD (UK) | | women | | men | | total | |
|---|---|---|---|---|---|---|---|
| | | Events | Person years | Events | Person years | Events | Person years |
| Calendar year | 1996 | 0 | 776818 | 0 | 760035 | 0 | 1536854 |
| | 1997 | 0 | 843169 | 0 | 826004 | 0 | 1669173 |
| | 1998 | 344 | 940490 | 330 | 923411 | 674 | 1863901 |
| | 1999 | 361 | 1026493 | 359 | 1009047 | 720 | 2035540 |
| | 2000 | 403 | 1149272 | 368 | 1130736 | 771 | 2280008 |
| | 2001 | 435 | 1256154 | 445 | 1236494 | 880 | 2492647 |
| | 2002 | 503 | 1373608 | 427 | 1354390 | 930 | 2727998 |
| | 2003 | 566 | 1437423 | 505 | 1422010 | 1071 | 2859434 |
| | 2004 | 538 | 1472368 | 482 | 1459639 | 1020 | 2932007 |
| | 2005 | 572 | 1504247 | 537 | 1489532 | 1109 | 2993779 |
| | 2006 | 466 | 1510198 | 499 | 1494054 | 965 | 3004252 |
| | 2007 | 503 | 1502410 | 461 | 1487209 | 964 | 2989619 |
| | 2008 | 473 | 1328247 | 467 | 1311938 | 940 | 2640185 |
| Calendar month | Jan | 502 | 1366770 | 468 | 1348101 | 970 | 2714870 |
| | Feb | 388 | 1250158 | 391 | 1233208 | 779 | 2483365 |
| | Mar | 470 | 1372197 | 428 | 1353795 | 898 | 2725992 |
| | Apr | 407 | 1329549 | 401 | 1311785 | 808 | 2641334 |
| | May | 467 | 1375773 | 403 | 1357530 | 870 | 2733304 |
| | Jun | 386 | 1331208 | 400 | 1313676 | 786 | 2644884 |
| | Jul | 419 | 1380393 | 368 | 1362121 | 787 | 2742514 |
| | Aug | 423 | 1383298 | 389 | 1364762 | 812 | 2748060 |
| | Sep | 430 | 1342942 | 401 | 1324720 | 831 | 2667661 |
| | Oct | 443 | 1381591 | 417 | 1362952 | 860 | 2744544 |
| | Nov | 445 | 1301020 | 385 | 1283241 | 830 | 2584262 |
| | Dec | 390 | 1305998 | 434 | 1288609 | 824 | 2594606 |
| Age category | 0-4 | 42 | 871607 | 48 | 916608 | 90 | 1788216 |
| | 5-9 | 74 | 922390 | 67 | 970847 | 141 | 1893237 |
| | 10-14 | 207 | 926279 | 125 | 989771 | 332 | 1916050 |
| | 15-19 | 213 | 859131 | 182 | 955721 | 395 | 1814852 |
| | 20-24 | 234 | 765818 | 195 | 845378 | 429 | 1611196 |
| | 25-29 | 256 | 931740 | 257 | 961570 | 513 | 1893311 |
| | 30-34 | 393 | 1111296 | 359 | 1137765 | 752 | 2249060 |
| | 35-39 | 398 | 1236764 | 399 | 1272528 | 797 | 2509292 |
| | 40-44 | 401 | 1209288 | 416 | 1254057 | 817 | 2463345 |
| | 45-49 | 366 | 1123234 | 424 | 1164013 | 790 | 2287247 |
| | 50-54 | 403 | 1088395 | 420 | 1120250 | 823 | 2208645 |
| | 55-59 | 394 | 1033725 | 420 | 1054243 | 814 | 2087967 |
| | 60-64 | 395 | 895662 | 418 | 897449 | 813 | 1793111 |
| | 65-69 | 398 | 778689 | 367 | 737686 | 765 | 1516375 |
| | 70-74 | 353 | 716809 | 328 | 620983 | 681 | 1337792 |
| | 75-79 | 268 | 644206 | 233 | 483387 | 501 | 1127593 |
| | 80-84 | 203 | 500060 | 145 | 309827 | 348 | 809887 |
| | 85+ | 172 | 505805 | 82 | 212413 | 254 | 718218 |
| Group Total | | 5170 | 16120897 | 4885 | 15904499 | 10055 | 32025396 |

**Incidence rate of facial nerve palsy per 100,000 person years by calendar year, calendar month and age category.**

| CPRD (UK) | | IR/100000 | | | | | |
|---|---|---|---|---|---|---|---|
| | | **women** | **95%CI** | **men** | **95%CI** | **Total** | **95%CI** |
| Calendar year | 1996 | 0.00 | - | 0.00 | - | 0.00 | - |
| | 1997 | 0.00 | - | 0.00 | - | 0.00 | - |
| | 1998 | 36.58 | (32.86-40.60) | 35.74 | (32.04-39.75) | 36.16 | (33.51-38.97) |
| | 1999 | 35.17 | (31.68-38.94) | 35.58 | (32.04-39.40) | 35.37 | (32.86-38.03) |
| | 2000 | 35.07 | (31.77-38.62) | 32.55 | (29.35-36.00) | 33.82 | (31.49-36.27) |
| | 2001 | 34.63 | (31.49-38.00) | 35.99 | (32.76-39.45) | 35.30 | (33.03-37.69) |
| | 2002 | 36.62 | (33.52-39.93) | 31.53 | (28.64-34.63) | 34.09 | (31.95-36.34) |
| | 2003 | 39.38 | (36.23-42.72) | 35.51 | (32.52-38.71) | 37.45 | (35.26-39.75) |
| | 2004 | 36.54 | (33.55-39.73) | 33.02 | (30.17-36.07) | 34.79 | (32.70-36.97) |
| | 2005 | 38.03 | (35.00-41.24) | 36.05 | (33.10-39.20) | 37.04 | (34.91-39.27) |
| | 2006 | 30.86 | (28.15-33.76) | 33.40 | (30.56-36.43) | 32.12 | (30.14-34.20) |
| | 2007 | 33.48 | (30.65-36.50) | 31.00 | (28.26-33.93) | 32.24 | (30.26-34.33) |
| | 2008 | 35.61 | (32.51-38.93) | 35.60 | (32.48-38.94) | 35.60 | (33.38-37.93) |
| Calendar month | Jan | 36.73 | (33.62-40.05) | 34.72 | (31.68-37.97) | 35.73 | (33.53-38.03) |
| | Feb | 31.04 | (28.06-34.24) | 31.71 | (28.68-34.97) | 31.37 | (29.22-33.63) |
| | Mar | 34.25 | (31.26-37.45) | 31.61 | (28.73-34.72) | 32.94 | (30.84-35.15) |
| | Apr | 30.61 | (27.75-33.70) | 30.57 | (27.69-33.67) | 30.59 | (28.54-32.76) |
| | May | 33.94 | (30.97-37.13) | 29.69 | (26.89-32.69) | 31.83 | (29.77-34.00) |
| | Jun | 29.00 | (26.21-32.00) | 30.45 | (27.57-33.54) | 29.72 | (27.69-31.85) |
| | Jul | 30.35 | (27.55-33.37) | 27.02 | (24.36-29.88) | 28.70 | (26.74-30.75) |
| | Aug | 30.58 | (27.77-33.60) | 28.50 | (25.78-31.44) | 29.55 | (27.57-31.63) |
| | Sep | 32.02 | (29.10-35.15) | 30.27 | (27.42-33.34) | 31.15 | (29.09-33.32) |
| | Oct | 32.06 | (29.18-35.16) | 30.60 | (27.76-33.64) | 31.33 | (29.29-33.48) |
| | Nov | 34.20 | (31.14-37.49) | 30.00 | (27.12-33.11) | 32.12 | (29.99-34.36) |
| | Dec | 29.86 | (27.01-32.94) | 33.68 | (30.62-36.96) | 31.76 | (29.65-33.98) |
| Age category | 0-4 | 4.82 | (3.52-6.45) | 5.24 | (3.91-6.88) | 5.03 | (4.07-6.16) |
| | 5-9 | 8.02 | (6.35-10.01) | 6.90 | (5.39-8.71) | 7.45 | (6.29-8.75) |
| | 10-14 | 22.35 | (19.46-25.55) | 12.63 | (10.56-14.99) | 17.33 | (15.54-19.27) |
| | 15-19 | 24.79 | (21.63-28.29) | 19.04 | (16.43-21.96) | 21.76 | (19.70-23.99) |
| | 20-24 | 30.56 | (26.83-34.66) | 23.07 | (20.00-26.48) | 26.63 | (24.20-29.24) |
| | 25-29 | 27.48 | (24.26-31.00) | 26.73 | (23.61-30.15) | 27.10 | (24.83-29.52) |
| | 30-34 | 35.36 | (32.00-38.99) | 31.55 | (28.41-34.95) | 33.44 | (31.11-35.89) |
| | 35-39 | 32.18 | (29.13-35.46) | 31.35 | (28.39-34.55) | 31.76 | (29.61-34.03) |
| | 40-44 | 33.16 | (30.03-36.53) | 33.17 | (30.10-36.48) | 33.17 | (30.95-35.50) |
| | 45-49 | 32.58 | (29.37-36.05) | 36.43 | (33.08-40.02) | 34.54 | (32.19-37.01) |
| | 50-54 | 37.03 | (33.54-40.78) | 37.49 | (34.03-41.21) | 37.26 | (34.78-39.87) |
| | 55-59 | 38.11 | (34.49-42.02) | 39.84 | (36.16-43.79) | 38.99 | (36.38-41.73) |
| | 60-64 | 44.10 | (39.91-48.61) | 46.58 | (42.27-51.20) | 45.34 | (42.30-48.54) |
| | 65-69 | 51.11 | (46.27-56.32) | 49.75 | (44.85-55.04) | 50.45 | (46.97-54.12) |
| | 70-74 | 49.25 | (44.31-54.59) | 52.82 | (47.33-58.77) | 50.90 | (47.19-54.84) |
| | 75-79 | 41.60 | (36.84-46.81) | 48.20 | (42.31-54.69) | 44.43 | (40.67-48.45) |
| | 80-84 | 40.60 | (35.30-46.47) | 46.80 | (39.64-54.89) | 42.97 | (38.63-47.66) |
| | 85+ | 34.01 | (29.20-39.38) | 38.60 | (30.91-47.66) | 35.37 | (31.21-39.92) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Group Total | 32.07 | (31.20-32.95) | 30.71 | (29.86-31.59) | 31.40 | (30.79-32.02) |

**Numbers of facial nerve palsy events and person time of follow up by calendar year, calendar month and age category.**

| HSD (IT) | | women | | men | | total | |
|---|---|---|---|---|---|---|---|
| | | Events | Person years | Events | Person years | Events | Person years |
| Calendar year | 1996 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1997 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2003 | 120 | 332008 | 111 | 297611 | 231 | 629619 |
| | 2004 | 124 | 344563 | 138 | 310269 | 262 | 654832 |
| | 2005 | 148 | 350376 | 131 | 316074 | 279 | 666450 |
| | 2006 | 130 | 357703 | 140 | 323370 | 270 | 681073 |
| | 2007 | 135 | 365711 | 128 | 331439 | 263 | 697150 |
| | 2008 | 127 | 372299 | 153 | 337565 | 280 | 709864 |
| Calendar month | Jan | 78 | 177811 | 103 | 160281 | 181 | 338092 |
| | Feb | 64 | 162963 | 65 | 146940 | 129 | 309903 |
| | Mar | 73 | 178763 | 72 | 161235 | 145 | 339997 |
| | Apr | 76 | 173418 | 65 | 156447 | 141 | 329865 |
| | May | 60 | 179697 | 62 | 162188 | 122 | 341885 |
| | Jun | 49 | 174455 | 73 | 157540 | 122 | 331995 |
| | Jul | 56 | 180595 | 53 | 163112 | 109 | 343707 |
| | Aug | 46 | 180896 | 66 | 163396 | 112 | 344292 |
| | Sep | 79 | 175422 | 44 | 158464 | 123 | 333886 |
| | Oct | 62 | 181565 | 70 | 164042 | 132 | 345607 |
| | Nov | 78 | 175968 | 67 | 159002 | 145 | 334970 |
| | Dec | 63 | 181107 | 61 | 163681 | 124 | 344789 |
| Age category | 0-4 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 5-9 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 10-14 | 2 | 8526 | 1 | 9303 | 3 | 17829 |
| | 15-19 | 23 | 82896 | 23 | 91133 | 46 | 174030 |
| | 20-24 | 29 | 119869 | 34 | 125142 | 63 | 245011 |
| | 25-29 | 37 | 143771 | 44 | 141309 | 81 | 285080 |
| | 30-34 | 37 | 173668 | 66 | 166162 | 103 | 339830 |
| | 35-39 | 51 | 190124 | 65 | 181480 | 116 | 371604 |
| | 40-44 | 39 | 193551 | 69 | 183253 | 108 | 376803 |
| | 45-49 | 53 | 175053 | 73 | 168000 | 126 | 343053 |
| | 50-54 | 70 | 161291 | 54 | 156149 | 124 | 317440 |
| | 55-59 | 77 | 161341 | 73 | 152869 | 150 | 314210 |
| | 60-64 | 73 | 145426 | 62 | 135028 | 135 | 280454 |
| | 65-69 | 77 | 143559 | 83 | 125552 | 160 | 269111 |
| | 70-74 | 73 | 132418 | 63 | 105302 | 136 | 237720 |
| | 75-79 | 75 | 121937 | 44 | 84824 | 119 | 206761 |
| | 80-84 | 44 | 98261 | 36 | 57607 | 80 | 155868 |
| | 85+ | 24 | 70969 | 11 | 33216 | 35 | 104185 |
| Group Total | | 784 | 2122660 | 801 | 1916329 | 1585 | 4038989 |

**Incidence rate of facial nerve palsy per 100,000 person years by calendar year, calendar month and age category**

| HSD (IT) | | IR/100000 | | | | | |
|---|---|---|---|---|---|---|---|
| | | women | 95%CI | men | 95%CI | Total | 95%CI |
| Calendar year | 1996 | NC | - | NC | - | NC | - |
| | 1997 | NC | - | NC | - | NC | - |
| | 1998 | NC | - | NC | - | NC | - |
| | 1999 | NC | - | NC | - | NC | - |
| | 2000 | NC | - | NC | - | NC | - |
| | 2001 | NC | - | NC | - | NC | - |
| | 2002 | NC | - | NC | - | NC | - |
| | 2003 | 36.14 | (30.10-43.06) | 37.30 | (30.83-44.73) | 36.69 | (32.18-41.65) |
| | 2004 | 35.99 | (30.06-42.75) | 44.48 | (37.51-52.37) | 40.01 | (35.38-45.08) |
| | 2005 | 42.24 | (35.84-49.47) | 41.45 | (34.80-49.01) | 41.86 | (37.17-47.00) |
| | 2006 | 36.34 | (30.49-43.00) | 43.29 | (36.56-50.92) | 39.64 | (35.12-44.59) |
| | 2007 | 36.91 | (31.07-43.54) | 38.62 | (32.36-45.76) | 37.73 | (33.37-42.49) |
| | 2008 | 34.11 | (28.56-40.44) | 45.32 | (38.56-52.94) | 39.44 | (35.02-44.27) |
| Calendar month | Jan | 43.87 | (34.92-54.44) | 64.26 | (52.73-77.60) | 53.54 | (46.16-61.77) |
| | Feb | 39.27 | (30.51-49.81) | 44.24 | (34.44-56.00) | 41.63 | (34.90-49.29) |
| | Mar | 40.84 | (32.26-51.03) | 44.66 | (35.21-55.89) | 42.65 | (36.12-50.02) |
| | Apr | 43.82 | (34.78-54.53) | 41.55 | (32.34-52.60) | 42.74 | (36.12-50.25) |
| | May | 33.39 | (25.72-42.67) | 38.23 | (29.58-48.66) | 35.68 | (29.77-42.45) |
| | Jun | 28.09 | (21.02-36.81) | 46.34 | (36.60-57.91) | 36.75 | (30.65-43.71) |
| | Jul | 31.01 | (23.66-39.96) | 32.49 | (24.60-42.16) | 31.71 | (26.17-38.10) |
| | Aug | 25.43 | (18.85-33.60) | 40.39 | (31.51-51.05) | 32.53 | (26.92-38.98) |
| | Sep | 45.03 | (35.91-55.81) | 27.77 | (20.44-36.91) | 36.84 | (30.75-43.79) |
| | Oct | 34.15 | (26.42-43.47) | 42.67 | (33.53-53.57) | 38.19 | (32.09-45.14) |
| | Nov | 44.33 | (35.29-55.01) | 42.14 | (32.93-53.16) | 43.29 | (36.67-50.77) |
| | Dec | 34.79 | (26.97-44.20) | 37.27 | (28.77-47.53) | 35.96 | (30.04-42.72) |
| Age category | 0-4 | NC | - | NC | - | NC | - |
| | 5-9 | NC | - | NC | - | NC | - |
| | 10-14 | 23.46 | - | 10.75 | - | 16.83 | (4.66-44.89) |
| | 15-19 | 27.75 | (18.06-40.91) | 25.24 | (16.43-37.21) | 26.43 | (19.60-34.93) |
| | 20-24 | 24.19 | (16.54-34.25) | 27.17 | (19.14-37.50) | 25.71 | (19.94-32.67) |
| | 25-29 | 25.74 | (18.41-35.07) | 31.14 | (22.92-41.40) | 28.41 | (22.72-35.12) |
| | 30-34 | 21.31 | (15.24-29.03) | 39.72 | (30.98-50.20) | 30.31 | (24.87-36.60) |
| | 35-39 | 26.82 | (20.20-34.97) | 35.82 | (27.88-45.34) | 31.22 | (25.92-37.29) |
| | 40-44 | 20.15 | (14.54-27.25) | 37.65 | (29.54-47.35) | 28.66 | (23.63-34.46) |
| | 45-49 | 30.28 | (22.92-39.28) | 43.45 | (34.32-54.30) | 36.73 | (30.73-43.57) |
| | 50-54 | 43.40 | (34.10-54.49) | 34.58 | (26.26-44.76) | 39.06 | (32.63-46.40) |
| | 55-59 | 47.72 | (37.94-59.30) | 47.75 | (37.72-59.68) | 47.74 | (40.55-55.85) |
| | 60-64 | 50.20 | (39.65-62.73) | 45.92 | (35.53-58.45) | 48.14 | (40.52-56.78) |
| | 65-69 | 53.64 | (42.64-66.65) | 66.11 | (53.01-81.51) | 59.46 | (50.77-69.22) |
| | 70-74 | 55.13 | (43.54-68.90) | 59.83 | (46.39-76.01) | 57.21 | (48.19-67.45) |
| | 75-79 | 61.51 | (48.74-76.64) | 51.87 | (38.19-68.96) | 57.55 | (47.90-68.61) |
| | 80-84 | 44.78 | (32.97-59.53) | 62.49 | (44.49-85.51) | 51.33 | (40.98-63.52) |
| | 85+ | 33.82 | (22.22-49.48) | 33.12 | (17.57-57.32) | 33.59 | (23.80-46.16) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Group Total | 36.93 | (34.42-39.59) | 41.80 | (38.98-44.77) | 39.24 | (37.35-41.21) | |

**Numbers of facial nerve palsy events and person time of follow up by calendar year, calendar month and age category.**

| SRD (IT) | | women | | men | | total | |
|---|---|---|---|---|---|---|---|
| | | Events | Person years | Events | Person years | Events | Person years |
| Calendar year | 1996 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1997 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2001 | 4 | 36443 | 0 | 38673 | 4 | 75116 |
| | 2002 | 213 | 2435368 | 217 | 2266970 | 430 | 4702338 |
| | 2003 | 191 | 2457920 | 214 | 2290669 | 405 | 4748588 |
| | 2004 | 207 | 2487774 | 194 | 2321466 | 401 | 4809240 |
| | 2005 | 197 | 2503663 | 207 | 2339349 | 404 | 4843012 |
| | 2006 | 183 | 2521237 | 172 | 2358545 | 355 | 4879782 |
| | 2007 | 161 | 2537208 | 144 | 2375430 | 305 | 4912638 |
| | 2008 | 143 | 2556765 | 135 | 2395491 | 278 | 4952256 |
| Calendar month | Jan | 140 | 1482418 | 139 | 1384421 | 279 | 2866838 |
| | Feb | 117 | 1353726 | 112 | 1264366 | 229 | 2618091 |
| | Mar | 123 | 1484621 | 129 | 1386747 | 252 | 2871368 |
| | Apr | 121 | 1437770 | 103 | 1343120 | 224 | 2780890 |
| | May | 121 | 1486851 | 103 | 1389105 | 224 | 2875956 |
| | Jun | 90 | 1440028 | 94 | 1345518 | 184 | 2785546 |
| | Jul | 79 | 1489251 | 94 | 1391684 | 173 | 2880935 |
| | Aug | 74 | 1490517 | 95 | 1393021 | 169 | 2883538 |
| | Sep | 110 | 1443677 | 110 | 1349384 | 220 | 2793061 |
| | Oct | 136 | 1493113 | 113 | 1395763 | 249 | 2888876 |
| | Nov | 109 | 1446078 | 107 | 1351926 | 216 | 2798004 |
| | Dec | 79 | 1488328 | 84 | 1391538 | 163 | 2879866 |
| Age category | 0-4 | 47 | 878284 | 35 | 928198 | 82 | 1806482 |
| | 5-9 | 51 | 893228 | 46 | 942266 | 97 | 1835494 |
| | 10-14 | 92 | 999092 | 59 | 1054599 | 151 | 2053691 |
| | 15-19 | 45 | 1043083 | 27 | 1086648 | 72 | 2129732 |
| | 20-24 | 53 | 1057397 | 39 | 1053906 | 92 | 2111303 |
| | 25-29 | 51 | 1151858 | 52 | 1113325 | 103 | 2265182 |
| | 30-34 | 52 | 1269433 | 70 | 1213238 | 122 | 2482671 |
| | 35-39 | 62 | 1324425 | 69 | 1265116 | 131 | 2589541 |
| | 40-44 | 60 | 1300393 | 82 | 1233512 | 142 | 2533905 |
| | 45-49 | 83 | 1195962 | 87 | 1126350 | 170 | 2322312 |
| | 50-54 | 85 | 1104008 | 96 | 1041094 | 181 | 2145102 |
| | 55-59 | 96 | 1052745 | 127 | 988008 | 223 | 2040753 |
| | 60-64 | 122 | 919754 | 128 | 839732 | 250 | 1759486 |
| | 65-69 | 130 | 903261 | 124 | 782316 | 254 | 1685577 |
| | 70-74 | 111 | 841727 | 116 | 680375 | 227 | 1522102 |
| | 75-79 | 98 | 717819 | 72 | 524075 | 170 | 1241894 |
| | 80-84 | 47 | 505145 | 40 | 319976 | 87 | 825121 |
| | 85+ | 14 | 378763 | 14 | 193859 | 28 | 572622 |
| Group Total | | 1299 | 17536378 | 1283 | 16386592 | 2582 | 33922970 |

**Incidence rate of facial nerve palsy per 100,000 person years by calendar year, calendar month and age category.**

| SRD (IT) | | IR/100000 | | | | | |
|---|---|---|---|---|---|---|---|
| | | **women** | **95%CI** | **men** | **95%CI** | **Total** | **95%CI** |
| Calendar year | 1996 | NC | - | NC | - | NC | - |
| | 1997 | NC | #VALUE! | NC | - | NC | - |
| | 1998 | NC | - | NC | - | NC | - |
| | 1999 | NC | - | NC | - | NC | - |
| | 2000 | NC | - | NC | - | NC | - |
| | 2001 | 10.98 | (3.67-26.10) | 0.00 | - | 5.33 | (1.78-12.66) |
| | 2002 | 8.75 | (7.63-9.98) | 9.57 | (8.36-10.91) | 9.14 | (8.31-10.04) |
| | 2003 | 7.77 | (6.73-8.93) | 9.34 | (8.15-10.66) | 8.53 | (7.73-9.39) |
| | 2004 | 8.32 | (7.24-9.51) | 8.36 | (7.24-9.60) | 8.34 | (7.55-9.18) |
| | 2005 | 7.87 | (6.83-9.03) | 8.85 | (7.70-10.12) | 8.34 | (7.56-9.19) |
| | 2006 | 7.26 | (6.26-8.37) | 7.29 | (6.26-8.44) | 7.27 | (6.55-8.06) |
| | 2007 | 6.35 | (5.42-7.38) | 6.06 | (5.13-7.11) | 6.21 | (5.54-6.94) |
| | 2008 | 5.59 | (4.73-6.57) | 5.64 | (4.74-6.65) | 5.61 | (4.98-6.30) |
| Calendar month | Jan | 9.44 | (7.98-11.11) | 10.04 | (8.47-11.82) | 9.73 | (8.64-10.93) |
| | Feb | 8.64 | (7.18-10.32) | 8.86 | (7.33-10.62) | 8.75 | (7.67-9.94) |
| | Mar | 8.28 | (6.92-9.85) | 9.30 | (7.80-11.01) | 8.78 | (7.74-9.91) |
| | Apr | 8.42 | (7.01-10.02) | 7.67 | (6.29-9.26) | 8.05 | (7.05-9.16) |
| | May | 8.14 | (6.78-9.69) | 7.41 | (6.08-8.95) | 7.79 | (6.82-8.86) |
| | Jun | 6.25 | (5.06-7.64) | 6.99 | (5.68-8.51) | 6.61 | (5.70-7.61) |
| | Jul | 5.30 | (4.23-6.57) | 6.75 | (5.49-8.23) | 6.00 | (5.16-6.95) |
| | Aug | 4.96 | (3.93-6.20) | 6.82 | (5.55-8.30) | 5.86 | (5.03-6.80) |
| | Sep | 7.62 | (6.29-9.15) | 8.15 | (6.73-9.78) | 7.88 | (6.89-8.97) |
| | Oct | 9.11 | (7.67-10.74) | 8.10 | (6.70-9.69) | 8.62 | (7.60-9.74) |
| | Nov | 7.54 | (6.22-9.05) | 7.91 | (6.52-9.52) | 7.72 | (6.74-8.80) |
| | Dec | 5.31 | (4.23-6.58) | 6.04 | (4.85-7.43) | 5.66 | (4.84-6.58) |
| Age category | 0-4 | 5.35 | (3.98-7.05) | 3.77 | (2.67-5.18) | 4.54 | (3.63-5.60) |
| | 5-9 | 5.71 | (4.30-7.44) | 4.88 | (3.62-6.45) | 5.28 | (4.31-6.42) |
| | 10-14 | 9.21 | (7.47-11.24) | 5.59 | (4.30-7.16) | 7.35 | (6.25-8.60) |
| | 15-19 | 4.31 | (3.19-5.72) | 2.48 | (1.67-3.56) | 3.38 | (2.67-4.23) |
| | 20-24 | 5.01 | (3.80-6.50) | 3.70 | (2.67-5.00) | 4.36 | (3.53-5.32) |
| | 25-29 | 4.43 | (3.33-5.77) | 4.67 | (3.53-6.07) | 4.55 | (3.73-5.49) |
| | 30-34 | 4.10 | (3.09-5.33) | 5.77 | (4.53-7.24) | 4.91 | (4.10-5.85) |
| | 35-39 | 4.68 | (3.62-5.96) | 5.45 | (4.28-6.86) | 5.06 | (4.25-5.98) |
| | 40-44 | 4.61 | (3.55-5.90) | 6.65 | (5.32-8.21) | 5.60 | (4.74-6.58) |
| | 45-49 | 6.94 | (5.56-8.56) | 7.72 | (6.23-9.48) | 7.32 | (6.28-8.48) |
| | 50-54 | 7.70 | (6.19-9.47) | 9.22 | (7.51-11.21) | 8.44 | (7.27-9.74) |
| | 55-59 | 9.12 | (7.43-11.08) | 12.85 | (10.76-15.24) | 10.93 | (9.56-12.43) |
| | 60-64 | 13.26 | (11.06-15.78) | 15.24 | (12.77-18.06) | 14.21 | (12.53-16.05) |
| | 65-69 | 14.39 | (12.08-17.03) | 15.85 | (13.24-18.83) | 15.07 | (13.30-17.01) |
| | 70-74 | 13.19 | (10.90-15.82) | 17.05 | (14.15-20.37) | 14.91 | (13.07-16.95) |
| | 75-79 | 13.65 | (11.15-16.56) | 13.74 | (10.83-17.20) | 13.69 | (11.75-15.87) |
| | 80-84 | 9.30 | (6.92-12.26) | 12.50 | (9.06-16.84) | 10.54 | (8.50-12.94) |
| | 85+ | 3.70 | (2.12-6.04) | 7.22 | (4.14-11.79) | 4.89 | (3.32-6.96) |
| Group Total | | 7.41 | (7.01-7.82) | 7.83 | (7.41-8.27) | 7.61 | (7.32-7.91) |

**Numbers of facial nerve palsy events and person time of follow up by calendar year, calendar month and age category.**

| MBR/NHR (SK) | | women | | men | | total | |
|---|---|---|---|---|---|---|---|
| | | Events | Person years | Events | Person years | Events | Person years |
| Calendar year | 1996 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1997 | 0 | 68661 | 0 | 71898 | 0 | 140559 |
| | 1998 | 245 | 4285541 | 234 | 4178972 | 479 | 8464513 |
| | 1999 | 271 | 4343184 | 238 | 4238546 | 509 | 8581730 |
| | 2000 | 314 | 4382903 | 239 | 4280064 | 553 | 8662967 |
| | 2001 | 288 | 4372287 | 249 | 4273513 | 537 | 8645800 |
| | 2002 | 319 | 4377129 | 240 | 4283241 | 559 | 8660370 |
| | 2003 | 269 | 4365697 | 251 | 4275974 | 520 | 8641671 |
| | 2004 | 306 | 4342028 | 262 | 4255039 | 568 | 8597067 |
| | 2005 | 291 | 4283064 | 226 | 4199170 | 517 | 8482233 |
| | 2006 | 333 | 4237085 | 269 | 4156038 | 602 | 8393123 |
| | 2007 | 262 | 4178624 | 238 | 4101479 | 500 | 8280103 |
| | 2008 | 0 | 0 | 0 | 0 | 0 | 0 |
| Calendar month | Jan | 0 | 0 | 0 | 0 | 0 | 0 |
| | Feb | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mar | 0 | 0 | 0 | 0 | 0 | 0 |
| | Apr | 0 | 0 | 0 | 0 | 0 | 0 |
| | May | 0 | 0 | 0 | 0 | 0 | 0 |
| | Jun | 0 | 0 | 0 | 0 | 0 | 0 |
| | Jul | 0 | 0 | 0 | 0 | 0 | 0 |
| | Aug | 0 | 0 | 0 | 0 | 0 | 0 |
| | Sep | 0 | 0 | 0 | 0 | 0 | 0 |
| | Oct | 0 | 0 | 0 | 0 | 0 | 0 |
| | Nov | 0 | 0 | 0 | 0 | 0 | 0 |
| | Dec | 0 | 0 | 0 | 0 | 0 | 0 |
| Age category | 0-4 | 116 | 1769222 | 104 | 1865517 | 220 | 3634739 |
| | 5-9 | 189 | 2562219 | 183 | 2697461 | 372 | 5259680 |
| | 10-14 | 148 | 2795867 | 124 | 2947254 | 272 | 5743120 |
| | 15-19 | 85 | 2601308 | 57 | 2751812 | 142 | 5353121 |
| | 20-24 | 82 | 2462029 | 56 | 2587914 | 138 | 5049942 |
| | 25-29 | 72 | 2645030 | 62 | 2754794 | 134 | 5399825 |
| | 30-34 | 130 | 2889738 | 81 | 3018333 | 211 | 5908071 |
| | 35-39 | 140 | 2956445 | 105 | 3096759 | 245 | 6053205 |
| | 40-44 | 140 | 2849356 | 127 | 2962606 | 267 | 5811963 |
| | 45-49 | 148 | 2793047 | 137 | 2868528 | 285 | 5661575 |
| | 50-54 | 178 | 2931912 | 160 | 2984638 | 338 | 5916550 |
| | 55-59 | 244 | 2886608 | 192 | 2923526 | 436 | 5810134 |
| | 60-64 | 186 | 2419446 | 226 | 2394087 | 412 | 4813533 |
| | 65-69 | 216 | 2024398 | 195 | 1869871 | 411 | 3894269 |
| | 70-74 | 213 | 1903043 | 211 | 1604053 | 424 | 3507096 |
| | 75-79 | 236 | 1829256 | 202 | 1378905 | 438 | 3208160 |
| | 80-84 | 189 | 1499063 | 142 | 964914 | 331 | 2463977 |
| | 85+ | 186 | 1418217 | 82 | 642961 | 268 | 2061178 |
| Group Total | | 2898 | 43236203 | 2446 | 42313934 | 5344 | 85550137 |

**Incidence rate of facial nerve palsy per 100,000 person years by calendar year, calendar month and age category.**

| MBR/NHR (SK) | | IR/100000 women | 95%CI | men | 95%CI | Total | 95%CI |
|---|---|---|---|---|---|---|---|
| Calendar year | 1996 | NC | - | NC | - | NC | - |
| | 1997 | 0.00 | - | 0.00 | - | 0.00 | - |
| | 1998 | 5.72 | (5.03-6.47) | 5.60 | (4.92-6.35) | 5.66 | (5.17-6.18) |
| | 1999 | 6.24 | (5.53-7.02) | 5.62 | (4.94-6.36) | 5.93 | (5.43-6.46) |
| | 2000 | 7.16 | (6.40-7.99) | 5.58 | (4.91-6.33) | 6.38 | (5.87-6.93) |
| | 2001 | 6.59 | (5.86-7.38) | 5.83 | (5.14-6.58) | 6.21 | (5.70-6.75) |
| | 2002 | 7.29 | (6.52-8.12) | 5.60 | (4.93-6.35) | 6.45 | (5.94-7.01) |
| | 2003 | 6.16 | (5.46-6.93) | 5.87 | (5.18-6.63) | 6.02 | (5.52-6.55) |
| | 2004 | 7.05 | (6.29-7.87) | 6.16 | (5.45-6.94) | 6.61 | (6.08-7.17) |
| | 2005 | 6.79 | (6.05-7.61) | 5.38 | (4.71-6.12) | 6.10 | (5.59-6.64) |
| | 2006 | 7.86 | (7.05-8.74) | 6.47 | (5.73-7.28) | 7.17 | (6.62-7.76) |
| | 2007 | 6.27 | (5.54-7.06) | 5.80 | (5.10-6.58) | 6.04 | (5.53-6.59) |
| | 2008 | NC | - | NC | - | NC | - |
| Calendar month | Jan | NC | - | NC | - | NC | - |
| | Feb | NC | - | NC | - | NC | - |
| | Mar | NC | - | NC | - | NC | - |
| | Apr | NC | - | NC | - | NC | - |
| | May | NC | - | NC | - | NC | - |
| | Jun | NC | - | NC | - | NC | - |
| | Jul | NC | - | NC | - | NC | - |
| | Aug | NC | - | NC | - | NC | - |
| | Sep | NC | - | NC | - | NC | - |
| | Oct | NC | - | NC | - | NC | - |
| | Nov | NC | - | NC | - | NC | - |
| | Dec | NC | - | NC | - | NC | - |
| Age category | 0-4 | 6.56 | (5.44-7.83) | 5.57 | (4.58-6.73) | 6.05 | (5.29-6.89) |
| | 5-9 | 7.38 | (6.38-8.49) | 6.78 | (5.85-7.82) | 7.07 | (6.38-7.82) |
| | 10-14 | 5.29 | (4.49-6.20) | 4.21 | (3.51-5.00) | 4.74 | (4.20-5.32) |
| | 15-19 | 3.27 | (2.63-4.02) | 2.07 | (1.58-2.66) | 2.65 | (2.24-3.12) |
| | 20-24 | 3.33 | (2.67-4.11) | 2.16 | (1.65-2.79) | 2.73 | (2.30-3.22) |
| | 25-29 | 2.72 | (2.15-3.41) | 2.25 | (1.74-2.86) | 2.48 | (2.09-2.93) |
| | 30-34 | 4.50 | (3.77-5.32) | 2.68 | (2.15-3.32) | 3.57 | (3.11-4.08) |
| | 35-39 | 4.74 | (4.00-5.57) | 3.39 | (2.79-4.09) | 4.05 | (3.56-4.58) |
| | 40-44 | 4.91 | (4.15-5.78) | 4.29 | (3.59-5.08) | 4.59 | (4.07-5.17) |
| | 45-49 | 5.30 | (4.50-6.21) | 4.78 | (4.03-5.63) | 5.03 | (4.47-5.64) |
| | 50-54 | 6.07 | (5.23-7.01) | 5.36 | (4.58-6.24) | 5.71 | (5.13-6.35) |
| | 55-59 | 8.45 | (7.44-9.56) | 6.57 | (5.69-7.55) | 7.50 | (6.82-8.23) |
| | 60-64 | 7.69 | (6.64-8.85) | 9.44 | (8.27-10.73) | 8.56 | (7.76-9.42) |
| | 65-69 | 10.67 | (9.32-12.17) | 10.43 | (9.04-11.97) | 10.55 | (9.57-11.61) |
| | 70-74 | 11.19 | (9.76-12.77) | 13.15 | (11.47-15.02) | 12.09 | (10.98-13.28) |
| | 75-79 | 12.90 | (11.33-14.63) | 14.65 | (12.73-16.78) | 13.65 | (12.42-14.98) |
| | 80-84 | 12.61 | (10.91-14.50) | 14.72 | (12.44-17.29) | 13.43 | (12.04-14.94) |
| | 85+ | 13.12 | (11.33-15.10) | 12.75 | (10.21-15.74) | 13.00 | (11.51-14.63) |

| | | | | | |
|---|---|---|---|---|---|
| Group Total | 6.70 | (6.46-6.95) | 5.78 | (5.55-6.01) | 6.25 | (6.08-6.42) |

**Numbers of facial nerve palsy events and person time of follow up by calendar year, calendar month and age category.**

| DCRS/NHDR (DK) | | women | | men | | total | |
|---|---|---|---|---|---|---|---|
| | | Events | Person years | Events | Person years | Events | Person years |
| Calendar year | 1996 | 277 | 2766394 | 301 | 2707184 | 578 | 5473578 |
| | 1997 | 311 | 2794138 | 315 | 2736893 | 626 | 5531030 |
| | 1998 | 385 | 2828504 | 349 | 2773104 | 734 | 5601608 |
| | 1999 | 424 | 2862883 | 415 | 2809020 | 839 | 5671903 |
| | 2000 | 418 | 2885146 | 426 | 2832740 | 844 | 5717886 |
| | 2001 | 420 | 2871821 | 464 | 2821248 | 884 | 5693070 |
| | 2002 | 475 | 2864313 | 491 | 2815817 | 966 | 5680129 |
| | 2003 | 483 | 2856054 | 537 | 2809280 | 1020 | 5665334 |
| | 2004 | 568 | 2856304 | 515 | 2810368 | 1083 | 5666672 |
| | 2005 | 488 | 2840646 | 543 | 2795656 | 1031 | 5636302 |
| | 2006 | 545 | 2831759 | 583 | 2787313 | 1128 | 5619073 |
| | 2007 | 594 | 2820895 | 569 | 2776647 | 1163 | 5597542 |
| | 2008 | 590 | 2815784 | 598 | 2771403 | 1188 | 5587187 |
| Calendar month | Jan | 0 | 0 | 0 | 0 | 0 | 0 |
| | Feb | 0 | 0 | 0 | 0 | 0 | 0 |
| | Mar | 0 | 0 | 0 | 0 | 0 | 0 |
| | Apr | 0 | 0 | 0 | 0 | 0 | 0 |
| | May | 0 | 0 | 0 | 0 | 0 | 0 |
| | Jun | 0 | 0 | 0 | 0 | 0 | 0 |
| | Jul | 0 | 0 | 0 | 0 | 0 | 0 |
| | Aug | 0 | 0 | 0 | 0 | 0 | 0 |
| | Sep | 0 | 0 | 0 | 0 | 0 | 0 |
| | Oct | 0 | 0 | 0 | 0 | 0 | 0 |
| | Nov | 0 | 0 | 0 | 0 | 0 | 0 |
| | Dec | 0 | 0 | 0 | 0 | 0 | 0 |
| Age category | 0-4 | 143 | 2226634 | 207 | 2337589 | 350 | 4564223 |
| | 5-9 | 199 | 2251581 | 208 | 2360061 | 407 | 4611641 |
| | 10-14 | 281 | 2260086 | 213 | 2340512 | 494 | 4600599 |
| | 15-19 | 228 | 2302087 | 229 | 2347765 | 457 | 4649851 |
| | 20-24 | 286 | 2393381 | 282 | 2450505 | 568 | 4843887 |
| | 25-29 | 432 | 2512865 | 392 | 2591988 | 824 | 5104853 |
| | 30-34 | 532 | 2668360 | 473 | 2781335 | 1005 | 5449695 |
| | 35-39 | 464 | 2659298 | 494 | 2785812 | 958 | 5445110 |
| | 40-44 | 414 | 2566343 | 459 | 2672799 | 873 | 5239142 |
| | 45-49 | 414 | 2442165 | 495 | 2515255 | 909 | 4957419 |
| | 50-54 | 435 | 2460611 | 540 | 2516113 | 975 | 4976724 |
| | 55-59 | 426 | 2295230 | 540 | 2316549 | 966 | 4611778 |
| | 60-64 | 394 | 1952864 | 419 | 1906265 | 813 | 3859129 |
| | 65-69 | 347 | 1584021 | 379 | 1450070 | 726 | 3034091 |
| | 70-74 | 292 | 1375464 | 322 | 1143124 | 614 | 2518588 |
| | 75-79 | 298 | 1190038 | 227 | 856045 | 525 | 2046083 |
| | 80-84 | 224 | 910446 | 150 | 533561 | 374 | 1444007 |
| | 85+ | 169 | 843169 | 77 | 341326 | 246 | 1184495 |
| Group Total | | 5978 | 36894642 | 6106 | 36246672 | 12084 | 73141314 |

**Incidence rate of facial nerve palsy per 100,000 person years by calendar year, calendar month and age category.**

| DCRS/NHDR (DK) | | IR/100000 | | | | | |
|---|---|---|---|---|---|---|---|
| | | women | 95%CI | men | 95%CI | Total | 95%CI |
| Calendar year | 1996 | 10.01 | (8.89-11.25) | 11.12 | (9.92-12.43) | 10.56 | (9.73-11.45) |
| | 1997 | 11.13 | (9.94-12.42) | 11.51 | (10.29-12.83) | 11.32 | (10.46-12.23) |
| | 1998 | 13.61 | (12.30-15.02) | 12.59 | (11.32-13.96) | 13.10 | (12.18-14.08) |
| | 1999 | 14.81 | (13.45-16.27) | 14.77 | (13.40-16.25) | 14.79 | (13.82-15.82) |
| | 2000 | 14.49 | (13.15-15.93) | 15.04 | (13.66-16.52) | 14.76 | (13.79-15.78) |
| | 2001 | 14.62 | (13.28-16.07) | 16.45 | (15.00-17.99) | 15.53 | (14.53-16.58) |
| | 2002 | 16.58 | (15.14-18.13) | 17.44 | (15.95-19.03) | 17.01 | (15.96-18.10) |
| | 2003 | 16.91 | (15.45-18.47) | 19.12 | (17.55-20.78) | 18.00 | (16.92-19.13) |
| | 2004 | 19.89 | (18.30-21.57) | 18.33 | (16.79-19.96) | 19.11 | (18.00-20.28) |
| | 2005 | 17.18 | (15.71-18.75) | 19.42 | (17.84-21.11) | 18.29 | (17.20-19.43) |
| | 2006 | 19.25 | (17.68-20.91) | 20.92 | (19.27-22.67) | 20.07 | (18.93-21.27) |
| | 2007 | 21.06 | (19.41-22.80) | 20.49 | (18.86-22.23) | 20.78 | (19.61-22.00) |
| | 2008 | 20.95 | (19.31-22.70) | 21.58 | (19.90-23.36) | 21.26 | (20.08-22.50) |
| Calendar month | Jan | NC | - | NC | - | NC | - |
| | Feb | NC | - | NC | - | NC | - |
| | Mar | NC | - | NC | - | NC | - |
| | Apr | NC | - | NC | - | NC | - |
| | May | NC | - | NC | - | NC | - |
| | Jun | NC | - | NC | - | NC | - |
| | Jul | NC | - | NC | - | NC | - |
| | Aug | NC | - | NC | - | NC | - |
| | Sep | NC | - | NC | - | NC | - |
| | Oct | NC | - | NC | - | NC | - |
| | Nov | NC | - | NC | - | NC | - |
| | Dec | NC | - | NC | - | NC | - |
| Age category | 0-4 | 6.42 | (5.43-7.54) | 8.86 | (7.71-10.12) | 7.67 | (6.90-8.50) |
| | 5-9 | 8.84 | (7.67-10.13) | 8.81 | (7.68-10.07) | 8.83 | (8.00-9.71) |
| | 10-14 | 12.43 | (11.04-13.95) | 9.10 | (7.94-10.39) | 10.74 | (9.82-11.72) |
| | 15-19 | 9.90 | (8.68-11.25) | 9.75 | (8.55-11.08) | 9.83 | (8.96-10.76) |
| | 20-24 | 11.95 | (10.62-13.40) | 11.51 | (10.22-12.91) | 11.73 | (10.79-12.72) |
| | 25-29 | 17.19 | (15.63-18.87) | 15.12 | (13.68-16.68) | 16.14 | (15.07-17.27) |
| | 30-34 | 19.94 | (18.30-21.69) | 17.01 | (15.53-18.59) | 18.44 | (17.33-19.61) |
| | 35-39 | 17.45 | (15.91-19.09) | 17.73 | (16.22-19.35) | 17.59 | (16.51-18.73) |
| | 40-44 | 16.13 | (14.63-17.74) | 17.17 | (15.66-18.80) | 16.66 | (15.59-17.80) |
| | 45-49 | 16.95 | (15.38-18.65) | 19.68 | (18.00-21.47) | 18.34 | (17.17-19.56) |
| | 50-54 | 17.68 | (16.08-19.40) | 21.46 | (19.71-23.33) | 19.59 | (18.39-20.85) |
| | 55-59 | 18.56 | (16.86-20.39) | 23.31 | (21.41-25.34) | 20.95 | (19.66-22.30) |
| | 60-64 | 20.18 | (18.26-22.24) | 21.98 | (19.95-24.16) | 21.07 | (19.66-22.55) |
| | 65-69 | 21.91 | (19.69-24.30) | 26.14 | (23.60-28.87) | 23.93 | (22.23-25.72) |
| | 70-74 | 21.23 | (18.90-23.77) | 28.17 | (25.22-31.37) | 24.38 | (22.51-26.37) |
| | 75-79 | 25.04 | (22.32-28.01) | 26.52 | (23.23-30.14) | 25.66 | (23.53-27.93) |
| | 80-84 | 24.60 | (21.54-27.99) | 28.11 | (23.88-32.89) | 25.90 | (23.37-28.63) |
| | 85+ | 20.04 | (17.19-23.24) | 22.56 | (17.93-28.03) | 20.77 | (18.29-23.49) |

| | | | | | |
|---|---|---|---|---|---|
| Group Total | 16.20 | (15.80-16.62) | 16.85 | (16.43-17.27) | 16.52 | (16.23-16.82) |

**Numbers of facial nerve palsy events and person time of follow up by calendar year, calendar month and age category.**

| HILMO (FI) | | women | | men | | total | |
|---|---|---|---|---|---|---|---|
| | | Events | Person years | Events | Person years | Events | Person years |
| Calendar year | 1996 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1997 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2005 | 680 | 2,567,214 | 777 | 2,678,882 | 1,457 | 5,246,096 |
| | 2006 | 702 | 2,578,046 | 795 | 2,688,222 | 1,497 | 5,266,268 |
| | 2007 | 695 | 2,590,265 | 805 | 2,698,455 | 1,500 | 5,288,720 |
| | 2008 | 731 | 2,604,220 | 848 | 2,709,179 | 1,579 | 5,313,399 |
| Calendar month | Jan | 259 | 861,645 | 289 | 897,895 | 548 | 1,759,540 |
| | Feb | 236 | 861,645 | 250 | 897,895 | 486 | 1,759,540 |
| | Mar | 267 | 861,645 | 292 | 897,895 | 559 | 1,759,540 |
| | Apr | 209 | 861,645 | 252 | 897,895 | 461 | 1,759,540 |
| | May | 239 | 861,645 | 246 | 897,895 | 485 | 1,759,540 |
| | Jun | 174 | 861,645 | 259 | 897,895 | 433 | 1,759,540 |
| | Jul | 214 | 861,645 | 252 | 897,895 | 466 | 1,759,540 |
| | Aug | 262 | 861,645 | 299 | 897,895 | 561 | 1,759,540 |
| | Sep | 238 | 861,645 | 274 | 897,895 | 512 | 1,759,540 |
| | Oct | 245 | 861,645 | 290 | 897,895 | 535 | 1,759,540 |
| | Nov | 236 | 861,645 | 284 | 897,895 | 520 | 1,759,540 |
| | Dec | 229 | 861,645 | 238 | 897,895 | 467 | 1,759,540 |
| Age category | 0-4 | 42 | 589,712 | 40 | 564,340 | 82 | 1,154,052 |
| | 5-9 | 52 | 593,727 | 55 | 568,283 | 107 | 1,162,010 |
| | 10-14 | 73 | 657,040 | 86 | 632,435 | 159 | 1,289,475 |
| | 15-19 | 90 | 665,984 | 123 | 637,867 | 213 | 1,303,850 |
| | 20-24 | 131 | 676,405 | 165 | 646,203 | 296 | 1,322,608 |
| | 25-29 | 180 | 682,161 | 180 | 650,297 | 360 | 1,332,458 |
| | 30-34 | 154 | 650,972 | 220 | 617,772 | 374 | 1,268,744 |
| | 35-39 | 196 | 684,209 | 179 | 658,689 | 375 | 1,342,897 |
| | 40-44 | 240 | 762,120 | 222 | 739,060 | 462 | 1,501,180 |
| | 45-49 | 222 | 761,155 | 218 | 747,975 | 440 | 1,509,130 |
| | 50-54 | 260 | 781,584 | 257 | 780,421 | 517 | 1,562,004 |
| | 55-59 | 273 | 814,501 | 269 | 819,648 | 542 | 1,634,149 |
| | 60-64 | 250 | 628,742 | 248 | 656,570 | 498 | 1,285,311 |
| | 65-69 | 204 | 471,128 | 258 | 533,360 | 462 | 1,004,487 |
| | 70-74 | 188 | 369,711 | 211 | 463,351 | 399 | 833,062 |
| | 75-79 | 142 | 288,991 | 226 | 436,791 | 368 | 725,781 |
| | 80-84 | 78 | 169,256 | 166 | 339,970 | 244 | 509,226 |
| | 85+ | 33 | 92,351 | 102 | 281,711 | 135 | 374,061 |
| Group Total | | 2,808 | 10,339,744 | 3,225 | 10,774,738 | 6,033 | 21,114,482 |

**Incidence rate of facial nerve palsy per 100,000 person years by calendar year, calendar month and age category.**

| HILMO (FI) | | IR/100000 | | | | | |
|---|---|---|---|---|---|---|---|
| | | **women** | **95%CI** | **men** | **95%CI** | **Total** | **95%CI** |
| Calendar year | 1996 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1997 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1998 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 1999 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2000 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2001 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2002 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2003 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2004 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 2005 | 26.49 | (24.55-28.54) | 29.00 | (27.02-31.10) | 27.77 | (26.37-29.23) |
| | 2006 | 27.23 | (25.27-29.30) | 29.57 | (27.57-31.68) | 28.43 | (27.01-29.89) |
| | 2007 | 26.83 | (24.89-28.88) | 29.83 | (27.82-31.95) | 28.36 | (26.95-29.83) |
| | 2008 | 28.07 | (26.09-30.16) | 31.30 | (29.25-33.46) | 29.72 | (28.28-31.21) |
| Calendar month | Jan | 30.06 | (26.56-33.89) | 32.19 | (28.63-36.06) | 31.14 | (28.62-33.84) |
| | Feb | 27.39 | (24.06-31.05) | 27.84 | (24.55-31.46) | 27.62 | (25.25-30.16) |
| | Mar | 30.99 | (27.44-34.87) | 32.52 | (28.95-36.41) | 31.77 | (29.22-34.49) |
| | Apr | 24.26 | (21.13-27.72) | 28.07 | (24.76-31.69) | 26.20 | (23.89-28.67) |
| | May | 27.74 | (24.39-31.42) | 27.40 | (24.13-30.98) | 27.56 | (25.19-30.10) |
| | Jun | 20.19 | (17.36-23.37) | 28.85 | (25.49-32.52) | 24.61 | (22.37-27.01) |
| | Jul | 24.84 | (21.67-28.33) | 28.07 | (24.76-31.69) | 26.48 | (24.16-28.97) |
| | Aug | 30.41 | (26.89-34.26) | 33.30 | (29.68-37.24) | 31.88 | (29.33-34.60) |
| | Sep | 27.62 | (24.28-31.30) | 30.52 | (27.06-34.29) | 29.10 | (26.66-31.70) |
| | Oct | 28.43 | (25.04-32.16) | 32.30 | (28.74-36.18) | 30.41 | (27.91-33.07) |
| | Nov | 27.39 | (24.06-31.05) | 31.63 | (28.11-35.47) | 29.55 | (27.09-32.18) |
| | Dec | 26.58 | (23.30-30.19) | 26.51 | (23.30-30.04) | 26.54 | (24.22-29.03) |
| Age category | 0-4 | 7.12 | (5.20-9.53) | 7.09 | (5.14-9.55) | 7.11 | (5.69-8.77) |
| | 5-9 | 8.76 | (6.61-11.39) | 9.68 | (7.37-12.50) | 9.21 | (7.59-11.08) |
| | 10-14 | 11.11 | (8.78-13.89) | 13.60 | (10.95-16.71) | 12.33 | (10.52-14.36) |
| | 15-19 | 13.51 | (10.93-16.53) | 19.28 | (16.10-22.92) | 16.34 | (14.25-18.64) |
| | 20-24 | 19.37 | (16.26-22.90) | 25.53 | (21.86-29.66) | 22.38 | (19.94-25.04) |
| | 25-29 | 26.39 | (22.74-30.46) | 27.68 | (23.85-31.95) | 27.02 | (24.33-29.92) |
| | 30-34 | 23.66 | (20.14-27.62) | 35.61 | (31.14-40.56) | 29.48 | (26.60-32.58) |
| | 35-39 | 28.65 | (24.84-32.87) | 27.18 | (23.41-31.38) | 27.92 | (25.20-30.86) |
| | 40-44 | 31.49 | (27.69-35.67) | 30.04 | (26.28-34.19) | 30.78 | (28.06-33.68) |
| | 45-49 | 29.17 | (25.52-33.20) | 29.15 | (25.47-33.21) | 29.16 | (26.53-31.98) |
| | 50-54 | 33.27 | (29.40-37.50) | 32.93 | (29.09-37.15) | 33.10 | (30.34-36.05) |
| | 55-59 | 33.52 | (29.72-37.67) | 32.82 | (29.07-36.92) | 33.17 | (30.46-36.05) |
| | 60-64 | 39.76 | (35.06-44.92) | 37.77 | (33.29-42.70) | 38.75 | (35.45-42.26) |
| | 65-69 | 43.30 | (37.66-49.55) | 48.37 | (42.74-54.55) | 45.99 | (41.94-50.33) |
| | 70-74 | 50.85 | (43.97-58.52) | 45.54 | (39.70-52.00) | 47.90 | (43.37-52.77) |
| | 75-79 | 49.14 | (41.55-57.73) | 51.74 | (45.32-58.82) | 50.70 | (45.72-56.09) |
| | 80-84 | 46.08 | (36.69-57.19) | 48.83 | (41.82-56.69) | 47.92 | (42.18-54.22) |
| | 85+ | 35.73 | (25.04-49.55) | 36.21 | (29.68-43.76) | 36.09 | (30.38-42.57) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Group Total | 27.16 | (26.17-28.18) | 29.93 | (28.91-30.98) | 28.57 | (27.86-29.30) |

## 6.3 Appendix 3 – Modelling the effect of a hypothetical confounder on the hazard of foetal death.

**Notation**

| | |
|---|---|
| RR | "True" or fully adjusted exposure relative risk |
| ARR | Apparent (or observed) exposure relative risk |
| $RR_{CD}$ | Association between confounder and disease outcome |
| $P_{C1}$ | Prevalence of confounder in the exposed |
| $P_{C0}$ | Prevalence of confounder in the unexposed |

$$RR_{adj.} = \frac{ARR}{\left[\frac{P_{C1}(RR_{CD}-1)+1}{P_{C0}(RR_{CD}-1)+1}\right]}$$

Table S3.1 The effect of a hypothetical confounder of varying strength and prevalence on the hazard ratio of foetal death in gestational weeks 9-12 (immunity model)

| Fix | X | Y | fix | $Z_2$ | $Z_1$ |
|---|---|---|---|---|---|
| **ARR** | **$RR_{CD}$** | **$P_{C1}$** | **$P_{C0}$** | **$RR_{adjusted}$** | **% Bias** |
| 0.74 | 0.5 | 0.6 | 0.4 | 0.85 | -12.50 |
| 0.74 | 0.6 | 0.6 | 0.4 | 0.82 | -9.52 |
| 0.74 | 0.7 | 0.6 | 0.4 | 0.79 | -6.82 |
| 0.74 | 0.8 | 0.6 | 0.4 | 0.77 | -4.35 |
| 0.74 | 0.9 | 0.6 | 0.4 | 0.76 | -2.08 |
| 0.74 | 0.5 | 0.7 | 0.4 | 0.91 | -18.75 |
| 0.74 | 0.6 | 0.7 | 0.4 | 0.86 | -14.29 |
| 0.74 | 0.7 | 0.7 | 0.4 | 0.82 | -10.23 |
| 0.74 | 0.8 | 0.7 | 0.4 | 0.79 | -6.52 |
| 0.74 | 0.9 | 0.7 | 0.4 | 0.76 | -3.12 |
| 0.74 | 0.5 | 0.8 | 0.4 | 0.99 | -25.00 |
| 0.74 | 0.6 | 0.8 | 0.4 | 0.91 | -19.05 |
| 0.74 | 0.7 | 0.8 | 0.4 | 0.86 | -13.64 |
| 0.74 | 0.8 | 0.8 | 0.4 | 0.81 | -8.70 |
| 0.74 | 0.9 | 0.8 | 0.4 | 0.77 | -4.17 |
| 0.74 | 0.5 | 0.9 | 0.4 | 1.08 | -31.25 |
| 0.74 | 0.6 | 0.9 | 0.4 | 0.97 | -23.81 |
| 0.74 | 0.7 | 0.9 | 0.4 | 0.89 | -17.05 |
| 0.74 | 0.8 | 0.9 | 0.4 | 0.83 | -10.87 |
| 0.74 | 0.9 | 0.9 | 0.4 | 0.78 | -5.21 |
| 0.74 | 0.5 | 0.6 | 0.4 | 0.85 | -12.50 |
| 0.74 | 0.6 | 0.6 | 0.3 | 0.86 | -13.64 |
| 0.74 | 0.7 | 0.6 | 0.3 | 0.82 | -9.89 |
| 0.74 | 0.8 | 0.6 | 0.3 | 0.79 | -6.38 |
| 0.74 | 0.9 | 0.6 | 0.3 | 0.76 | -3.09 |
| 0.74 | 0.5 | 0.7 | 0.3 | 0.97 | -23.53 |
| 0.74 | 0.6 | 0.7 | 0.3 | 0.90 | -18.18 |
| 0.74 | 0.7 | 0.7 | 0.3 | 0.85 | -13.19 |
| 0.74 | 0.8 | 0.7 | 0.3 | 0.81 | -8.51 |
| 0.74 | 0.9 | 0.7 | 0.3 | 0.77 | -4.12 |
| 0.74 | 0.5 | 0.8 | 0.3 | 1.05 | -29.41 |
| 0.74 | 0.6 | 0.8 | 0.3 | 0.96 | -22.73 |
| 0.74 | 0.7 | 0.8 | 0.3 | 0.89 | -16.48 |
| 0.74 | 0.8 | 0.8 | 0.3 | 0.83 | -10.64 |
| 0.74 | 0.9 | 0.8 | 0.3 | 0.78 | -5.15 |
| 0.74 | 0.5 | 0.9 | 0.3 | 1.14 | -35.29 |
| 0.74 | 0.6 | 0.9 | 0.3 | 1.02 | -27.27 |
| 0.74 | 0.7 | 0.9 | 0.3 | 0.92 | -19.78 |
| 0.74 | 0.8 | 0.9 | 0.3 | 0.85 | -12.77 |
| 0.74 | 0.9 | 0.9 | 0.3 | 0.79 | -6.19 |
| 0.74 | 0.5 | 0.6 | 0.3 | 0.90 | -17.65 |
| 0.74 | 0.6 | 0.6 | 0.2 | 0.90 | -17.39 |
| 0.74 | 0.7 | 0.6 | 0.2 | 0.85 | -12.77 |
| 0.74 | 0.8 | 0.6 | 0.2 | 0.81 | -8.33 |
| 0.74 | 0.9 | 0.6 | 0.2 | 0.77 | -4.08 |
| 0.74 | 0.5 | 0.7 | 0.2 | 1.02 | -27.78 |
| 0.74 | 0.6 | 0.7 | 0.2 | 0.95 | -21.74 |
| 0.74 | 0.7 | 0.7 | 0.2 | 0.88 | -15.96 |
| 0.74 | 0.8 | 0.7 | 0.2 | 0.83 | -10.42 |
| 0.74 | 0.9 | 0.7 | 0.2 | 0.78 | -5.10 |
| 0.74 | 0.5 | 0.8 | 0.2 | 1.11 | -33.33 |
| 0.74 | 0.6 | 0.8 | 0.2 | 1.00 | -26.09 |
| 0.74 | 0.7 | 0.8 | 0.2 | 0.92 | -19.15 |
| 0.74 | 0.8 | 0.8 | 0.2 | 0.85 | -12.50 |
| 0.74 | 0.9 | 0.8 | 0.2 | 0.79 | -6.12 |

| | | | | | |
|---|---|---|---|---|---|
| 0.74 | 0.5 | 0.9 | 0.2 | 1.21 | -38.89 |
| 0.74 | 0.6 | 0.9 | 0.2 | 1.06 | -30.43 |
| 0.74 | 0.7 | 0.9 | 0.2 | 0.95 | -22.34 |
| 0.74 | 0.8 | 0.9 | 0.2 | 0.87 | -14.58 |
| 0.74 | 0.9 | 0.9 | 0.2 | 0.80 | -7.14 |

Table S3.2 The effect of a hypothetical confounder of varying strength and prevalence on the hazard ratio of foetal death in gestational weeks 13-24 (immunity model)

| Fix | X | Y | fix | $Z_2$ | $Z_1$ |
|---|---|---|---|---|---|
| **ARR** | **$RR_{CD}$** | **$P_{C1}$** | **$P_{C0}$** | **$RR_{adjusted}$** | **% Bias** |
| 0.59 | 0.5 | 0.6 | 0.4 | 0.67 | -12.50 |
| 0.59 | 0.6 | 0.6 | 0.4 | 0.65 | -9.52 |
| 0.59 | 0.7 | 0.6 | 0.4 | 0.63 | -6.82 |
| 0.59 | 0.8 | 0.6 | 0.4 | 0.62 | -4.35 |
| 0.59 | 0.9 | 0.6 | 0.4 | 0.60 | -2.08 |
| 0.59 | 0.5 | 0.7 | 0.4 | 0.73 | -18.75 |
| 0.59 | 0.6 | 0.7 | 0.4 | 0.69 | -14.29 |
| 0.59 | 0.7 | 0.7 | 0.4 | 0.66 | -10.23 |
| 0.59 | 0.8 | 0.7 | 0.4 | 0.63 | -6.52 |
| 0.59 | 0.9 | 0.7 | 0.4 | 0.61 | -3.12 |
| 0.59 | 0.5 | 0.8 | 0.4 | 0.79 | -25.00 |
| 0.59 | 0.6 | 0.8 | 0.4 | 0.73 | -19.05 |
| 0.59 | 0.7 | 0.8 | 0.4 | 0.68 | -13.64 |
| 0.59 | 0.8 | 0.8 | 0.4 | 0.65 | -8.70 |
| 0.59 | 0.9 | 0.8 | 0.4 | 0.62 | -4.17 |
| 0.59 | 0.5 | 0.9 | 0.4 | 0.86 | -31.25 |
| 0.59 | 0.6 | 0.9 | 0.4 | 0.77 | -23.81 |
| 0.59 | 0.7 | 0.9 | 0.4 | 0.71 | -17.05 |
| 0.59 | 0.8 | 0.9 | 0.4 | 0.66 | -10.87 |
| 0.59 | 0.9 | 0.9 | 0.4 | 0.62 | -5.21 |
| 0.59 | 0.5 | 0.6 | 0.4 | 0.67 | -12.50 |
| 0.59 | 0.6 | 0.6 | 0.3 | 0.68 | -13.64 |
| 0.59 | 0.7 | 0.6 | 0.3 | 0.65 | -9.89 |
| 0.59 | 0.8 | 0.6 | 0.3 | 0.63 | -6.38 |
| 0.59 | 0.9 | 0.6 | 0.3 | 0.61 | -3.09 |
| 0.59 | 0.5 | 0.7 | 0.3 | 0.77 | -23.53 |
| 0.59 | 0.6 | 0.7 | 0.3 | 0.72 | -18.18 |
| 0.59 | 0.7 | 0.7 | 0.3 | 0.68 | -13.19 |
| 0.59 | 0.8 | 0.7 | 0.3 | 0.64 | -8.51 |
| 0.59 | 0.9 | 0.7 | 0.3 | 0.62 | -4.12 |
| 0.59 | 0.5 | 0.8 | 0.3 | 0.84 | -29.41 |
| 0.59 | 0.6 | 0.8 | 0.3 | 0.76 | -22.73 |
| 0.59 | 0.7 | 0.8 | 0.3 | 0.71 | -16.48 |
| 0.59 | 0.8 | 0.8 | 0.3 | 0.66 | -10.64 |
| 0.59 | 0.9 | 0.8 | 0.3 | 0.62 | -5.15 |
| 0.59 | 0.5 | 0.9 | 0.3 | 0.91 | -35.29 |
| 0.59 | 0.6 | 0.9 | 0.3 | 0.81 | -27.27 |
| 0.59 | 0.7 | 0.9 | 0.3 | 0.74 | -19.78 |
| 0.59 | 0.8 | 0.9 | 0.3 | 0.68 | -12.77 |
| 0.59 | 0.9 | 0.9 | 0.3 | 0.63 | -6.19 |
| 0.59 | 0.5 | 0.6 | 0.3 | 0.72 | -17.65 |
| 0.59 | 0.6 | 0.6 | 0.2 | 0.71 | -17.39 |
| 0.59 | 0.7 | 0.6 | 0.2 | 0.68 | -12.77 |
| 0.59 | 0.8 | 0.6 | 0.2 | 0.64 | -8.33 |
| 0.59 | 0.9 | 0.6 | 0.2 | 0.62 | -4.08 |
| 0.59 | 0.5 | 0.7 | 0.2 | 0.82 | -27.78 |
| 0.59 | 0.6 | 0.7 | 0.2 | 0.75 | -21.74 |
| 0.59 | 0.7 | 0.7 | 0.2 | 0.70 | -15.96 |
| 0.59 | 0.8 | 0.7 | 0.2 | 0.66 | -10.42 |
| 0.59 | 0.9 | 0.7 | 0.2 | 0.62 | -5.10 |
| 0.59 | 0.5 | 0.8 | 0.2 | 0.89 | -33.33 |
| 0.59 | 0.6 | 0.8 | 0.2 | 0.80 | -26.09 |
| 0.59 | 0.7 | 0.8 | 0.2 | 0.73 | -19.15 |
| 0.59 | 0.8 | 0.8 | 0.2 | 0.67 | -12.50 |
| 0.59 | 0.9 | 0.8 | 0.2 | 0.63 | -6.12 |
| 0.59 | 0.5 | 0.9 | 0.2 | 0.97 | -38.89 |
| 0.59 | 0.6 | 0.9 | 0.2 | 0.85 | -30.43 |
| 0.59 | 0.7 | 0.9 | 0.2 | 0.76 | -22.34 |
| 0.59 | 0.8 | 0.9 | 0.2 | 0.69 | -14.58 |
| 0.59 | 0.9 | 0.9 | 0.2 | 0.64 | -7.14 |

Table S3.3 The effect of a hypothetical confounder of varying strength and prevalence on the hazard ratio of foetal death in gestational weeks 9-12 (toxicity model)

| Fix | X | Y | fix | $Z_2$ | $Z_1$ |
|---|---|---|---|---|---|
| **ARR** | **$RR_{CD}$** | **$P_{C1}$** | **$P_{C0}$** | **$RR_{adjusted}$** | **% Bias** |
| 0.56 | 0.5 | 0.6 | 0.4 | 0.64 | -12.50 |
| 0.56 | 0.6 | 0.6 | 0.4 | 0.62 | -9.52 |
| 0.56 | 0.7 | 0.6 | 0.4 | 0.60 | -6.82 |
| 0.56 | 0.8 | 0.6 | 0.4 | 0.59 | -4.35 |
| 0.56 | 0.9 | 0.6 | 0.4 | 0.57 | -2.08 |
| 0.56 | 0.5 | 0.7 | 0.4 | 0.69 | -18.75 |
| 0.56 | 0.6 | 0.7 | 0.4 | 0.65 | -14.29 |
| 0.56 | 0.7 | 0.7 | 0.4 | 0.62 | -10.23 |
| 0.56 | 0.8 | 0.7 | 0.4 | 0.60 | -6.52 |
| 0.56 | 0.9 | 0.7 | 0.4 | 0.58 | -3.12 |
| 0.56 | 0.5 | 0.8 | 0.4 | 0.75 | -25.00 |
| 0.56 | 0.6 | 0.8 | 0.4 | 0.69 | -19.05 |
| 0.56 | 0.7 | 0.8 | 0.4 | 0.65 | -13.64 |
| 0.56 | 0.8 | 0.8 | 0.4 | 0.61 | -8.70 |
| 0.56 | 0.9 | 0.8 | 0.4 | 0.58 | -4.17 |
| 0.56 | 0.5 | 0.9 | 0.4 | 0.81 | -31.25 |
| 0.56 | 0.6 | 0.9 | 0.4 | 0.74 | -23.81 |
| 0.56 | 0.7 | 0.9 | 0.4 | 0.68 | -17.05 |
| 0.56 | 0.8 | 0.9 | 0.4 | 0.63 | -10.87 |
| 0.56 | 0.9 | 0.9 | 0.4 | 0.59 | -5.21 |
| 0.56 | 0.5 | 0.6 | 0.4 | 0.64 | -12.50 |
| 0.56 | 0.6 | 0.6 | 0.3 | 0.65 | -13.64 |
| 0.56 | 0.7 | 0.6 | 0.3 | 0.62 | -9.89 |
| 0.56 | 0.8 | 0.6 | 0.3 | 0.60 | -6.38 |
| 0.56 | 0.9 | 0.6 | 0.3 | 0.58 | -3.09 |
| 0.56 | 0.5 | 0.7 | 0.3 | 0.73 | -23.53 |
| 0.56 | 0.6 | 0.7 | 0.3 | 0.68 | -18.18 |
| 0.56 | 0.7 | 0.7 | 0.3 | 0.65 | -13.19 |
| 0.56 | 0.8 | 0.7 | 0.3 | 0.61 | -8.51 |
| 0.56 | 0.9 | 0.7 | 0.3 | 0.58 | -4.12 |
| 0.56 | 0.5 | 0.8 | 0.3 | 0.79 | -29.41 |
| 0.56 | 0.6 | 0.8 | 0.3 | 0.72 | -22.73 |
| 0.56 | 0.7 | 0.8 | 0.3 | 0.67 | -16.48 |
| 0.56 | 0.8 | 0.8 | 0.3 | 0.63 | -10.64 |
| 0.56 | 0.9 | 0.8 | 0.3 | 0.59 | -5.15 |
| 0.56 | 0.5 | 0.9 | 0.3 | 0.87 | -35.29 |
| 0.56 | 0.6 | 0.9 | 0.3 | 0.77 | -27.27 |
| 0.56 | 0.7 | 0.9 | 0.3 | 0.70 | -19.78 |
| 0.56 | 0.8 | 0.9 | 0.3 | 0.64 | -12.77 |
| 0.56 | 0.9 | 0.9 | 0.3 | 0.60 | -6.19 |
| 0.56 | 0.5 | 0.6 | 0.3 | 0.68 | -17.65 |
| 0.56 | 0.6 | 0.6 | 0.2 | 0.68 | -17.39 |
| 0.56 | 0.7 | 0.6 | 0.2 | 0.64 | -12.77 |
| 0.56 | 0.8 | 0.6 | 0.2 | 0.61 | -8.33 |
| 0.56 | 0.9 | 0.6 | 0.2 | 0.58 | -4.08 |
| 0.56 | 0.5 | 0.7 | 0.2 | 0.78 | -27.78 |
| 0.56 | 0.6 | 0.7 | 0.2 | 0.72 | -21.74 |
| 0.56 | 0.7 | 0.7 | 0.2 | 0.67 | -15.96 |
| 0.56 | 0.8 | 0.7 | 0.2 | 0.63 | -10.42 |
| 0.56 | 0.9 | 0.7 | 0.2 | 0.59 | -5.10 |
| 0.56 | 0.5 | 0.8 | 0.2 | 0.84 | -33.33 |
| 0.56 | 0.6 | 0.8 | 0.2 | 0.76 | -26.09 |
| 0.56 | 0.7 | 0.8 | 0.2 | 0.69 | -19.15 |
| 0.56 | 0.8 | 0.8 | 0.2 | 0.64 | -12.50 |
| 0.56 | 0.9 | 0.8 | 0.2 | 0.60 | -6.12 |
| 0.56 | 0.5 | 0.9 | 0.2 | 0.92 | -38.89 |
| 0.56 | 0.6 | 0.9 | 0.2 | 0.81 | -30.43 |
| 0.56 | 0.7 | 0.9 | 0.2 | 0.72 | -22.34 |
| 0.56 | 0.8 | 0.9 | 0.2 | 0.66 | -14.58 |
| 0.56 | 0.9 | 0.9 | 0.2 | 0.60 | -7.14 |

Table S3.4 The effect of a hypothetical confounder of varying strength and prevalence on the hazard ratio of foetal death in gestational weeks 13-24 (toxicity model)

| Fix | X | Y | fix | $Z_2$ | $Z_1$ |
|---|---|---|---|---|---|
| **ARR** | **$RR_{CD}$** | **$P_{C1}$** | **$P_{C0}$** | **$RR_{adjusted}$** | **% Bias** |
| 0.45 | 0.5 | 0.6 | 0.4 | 0.51 | -12.50 |
| 0.45 | 0.6 | 0.6 | 0.4 | 0.50 | -9.52 |
| 0.45 | 0.7 | 0.6 | 0.4 | 0.48 | -6.82 |
| 0.45 | 0.8 | 0.6 | 0.4 | 0.47 | -4.35 |
| 0.45 | 0.9 | 0.6 | 0.4 | 0.46 | -2.08 |
| 0.45 | 0.5 | 0.7 | 0.4 | 0.55 | -18.75 |
| 0.45 | 0.6 | 0.7 | 0.4 | 0.53 | -14.29 |
| 0.45 | 0.7 | 0.7 | 0.4 | 0.50 | -10.23 |
| 0.45 | 0.8 | 0.7 | 0.4 | 0.48 | -6.52 |
| 0.45 | 0.9 | 0.7 | 0.4 | 0.46 | -3.12 |
| 0.45 | 0.5 | 0.8 | 0.4 | 0.60 | -25.00 |
| 0.45 | 0.6 | 0.8 | 0.4 | 0.56 | -19.05 |
| 0.45 | 0.7 | 0.8 | 0.4 | 0.52 | -13.64 |
| 0.45 | 0.8 | 0.8 | 0.4 | 0.49 | -8.70 |
| 0.45 | 0.9 | 0.8 | 0.4 | 0.47 | -4.17 |
| 0.45 | 0.5 | 0.9 | 0.4 | 0.65 | -31.25 |
| 0.45 | 0.6 | 0.9 | 0.4 | 0.59 | -23.81 |
| 0.45 | 0.7 | 0.9 | 0.4 | 0.54 | -17.05 |
| 0.45 | 0.8 | 0.9 | 0.4 | 0.50 | -10.87 |
| 0.45 | 0.9 | 0.9 | 0.4 | 0.47 | -5.21 |
| 0.45 | 0.5 | 0.6 | 0.4 | 0.51 | -12.50 |
| 0.45 | 0.6 | 0.6 | 0.3 | 0.52 | -13.64 |
| 0.45 | 0.7 | 0.6 | 0.3 | 0.50 | -9.89 |
| 0.45 | 0.8 | 0.6 | 0.3 | 0.48 | -6.38 |
| 0.45 | 0.9 | 0.6 | 0.3 | 0.46 | -3.09 |
| 0.45 | 0.5 | 0.7 | 0.3 | 0.59 | -23.53 |
| 0.45 | 0.6 | 0.7 | 0.3 | 0.55 | -18.18 |
| 0.45 | 0.7 | 0.7 | 0.3 | 0.52 | -13.19 |
| 0.45 | 0.8 | 0.7 | 0.3 | 0.49 | -8.51 |
| 0.45 | 0.9 | 0.7 | 0.3 | 0.47 | -4.12 |
| 0.45 | 0.5 | 0.8 | 0.3 | 0.64 | -29.41 |
| 0.45 | 0.6 | 0.8 | 0.3 | 0.58 | -22.73 |
| 0.45 | 0.7 | 0.8 | 0.3 | 0.54 | -16.48 |
| 0.45 | 0.8 | 0.8 | 0.3 | 0.50 | -10.64 |
| 0.45 | 0.9 | 0.8 | 0.3 | 0.47 | -5.15 |
| 0.45 | 0.5 | 0.9 | 0.3 | 0.70 | -35.29 |
| 0.45 | 0.6 | 0.9 | 0.3 | 0.62 | -27.27 |
| 0.45 | 0.7 | 0.9 | 0.3 | 0.56 | -19.78 |
| 0.45 | 0.8 | 0.9 | 0.3 | 0.52 | -12.77 |
| 0.45 | 0.9 | 0.9 | 0.3 | 0.48 | -6.19 |
| 0.45 | 0.5 | 0.6 | 0.3 | 0.55 | -17.65 |
| 0.45 | 0.6 | 0.6 | 0.2 | 0.54 | -17.39 |
| 0.45 | 0.7 | 0.6 | 0.2 | 0.52 | -12.77 |
| 0.45 | 0.8 | 0.6 | 0.2 | 0.49 | -8.33 |
| 0.45 | 0.9 | 0.6 | 0.2 | 0.47 | -4.08 |
| 0.45 | 0.5 | 0.7 | 0.2 | 0.62 | -27.78 |
| 0.45 | 0.6 | 0.7 | 0.2 | 0.58 | -21.74 |
| 0.45 | 0.7 | 0.7 | 0.2 | 0.54 | -15.96 |
| 0.45 | 0.8 | 0.7 | 0.2 | 0.50 | -10.42 |
| 0.45 | 0.9 | 0.7 | 0.2 | 0.47 | -5.10 |
| 0.45 | 0.5 | 0.8 | 0.2 | 0.68 | -33.33 |
| 0.45 | 0.6 | 0.8 | 0.2 | 0.61 | -26.09 |
| 0.45 | 0.7 | 0.8 | 0.2 | 0.56 | -19.15 |
| 0.45 | 0.8 | 0.8 | 0.2 | 0.51 | -12.50 |
| 0.45 | 0.9 | 0.8 | 0.2 | 0.48 | -6.12 |
| 0.45 | 0.5 | 0.9 | 0.2 | 0.74 | -38.89 |
| 0.45 | 0.6 | 0.9 | 0.2 | 0.65 | -30.43 |
| 0.45 | 0.7 | 0.9 | 0.2 | 0.58 | -22.34 |
| 0.45 | 0.8 | 0.9 | 0.2 | 0.53 | -14.58 |
| 0.45 | 0.9 | 0.9 | 0.2 | 0.48 | -7.14 |

## 6.4 Appendix 4 – Characteristics of pregnancies with missing LMP data

Table S4.1. **Patient characteristics among pregnancies with and without data recorded on LMP date**

| | Delivery | | | | Foetal deat | |
|---|---|---|---|---|---|---|
| | LMP available | | LMP defaulted | | LMP available | LM |
| | n | % | n | % | n | % |
| **Total** | 16,536 | 100 | 19,902 | 100 | 1,288 | 100 |
| **Mean pregnancy length, weeks (SD)** | 41 | *(1.9)* | 41 | *(0.3)* | 18 | *(8.3)* |
| **Unvaccinated weeks** | . | | | | | |
| **weeks 1-12** | 2,198 | 3.0 | 2,699 | 2.8 | 235 | 32.8 |
| **weeks 13-24** | 18,497 | 24.8 | 23,057 | 24.1 | 314 | 43.8 |
| **weeks 25-43** | 53,765 | 72.2 | 69,893 | 73.1 | 168 | 23.4 |
| **Vaccinated (weeks)** | | | | | | |
| **weeks 1-12** | 26,799 | 9.1 | 32,626 | 8.9 | 3,420 | 50.5 |
| **weeks 13-24** | 97,607 | 33.1 | 117,522 | 31.9 | 3,062 | 45.2 |
| **weeks 25-43** | 170,180 | 57.8 | 218,012 | 59.2 | 288 | 4.3 |
| **Maternal age (years)** | | | | | | |
| **Mean (SD)** | 30 | *(5.9)* | 30 | *(6.1)* | 32 | *(6.7)* |
| **11-19** | 467 | 2.8 | 727 | 3.7 | 31 | 2.4 |
| ap **20-34** | 11,395 | 68.9 | 13,955 | 70.1 | 725 | 56.3 |
| **35-40** | 3,645 | 22.0 | 3,949 | 19.8 | 313 | 24.3 |
| **40-44** | 978 | 5.9 | 1,173 | 5.9 | 196 | 15.2 |
| **45-49** | 51 | 0.3 | 98 | 0.5 | 23 | 1.8 |
| **Number of previous spontaneous abortions** | | | | | | |
| **0** | 13,689 | 82.8 | 16,400 | 82.4 | 945 | 73.4 |
| **1** | 2,316 | 14.0 | 2,859 | 14.4 | 278 | 21.6 |
| **2** | 414 | 2.5 | 515 | 2.6 | 50 | 3.9 |
| **>2** | 117 | 0.7 | 128 | 0.6 | 15 | 1.2 |
| **In clinical risk group for influenza vaccination** | | | | | | |
| **No** | 15,561 | 94.1 | 18,743 | 94.2 | 1,205 | 93.6 |
| **Yes** | 975 | 5.9 | 1,159 | 5.8 | 83 | 6.4 |
| **Diabetes** | | | | | | |
| **No** | 16,405 | 99.2 | 19,731 | 99.1 | 1,272 | 98.8 |
| **Yes** | 131 | 0.8 | 171 | 0.9 | 16 | 1.2 |
| **Number of consultations in 6 months before LMP** | | | | | | |
| **0-1** | 4,071 | 24.6 | 4,593 | 23.1 | 304 | 23.6 |
| **2-3** | 3,795 | 22.9 | 4,404 | 22.1 | 311 | 24.1 |
| **4-5** | 2,765 | 16.7 | 3,330 | 16.7 | 184 | 14.3 |
| **6-9** | 3,256 | 19.7 | 4,002 | 20.1 | 250 | 19.4 |
| **10+** | 2,649 | 16.0 | 3,573 | 18.0 | 239 | 18.6 |
| **Pre-pregnancy smoking status** | | | | | | |
| **Smoker** | 3,797 | 23.0 | 5,176 | 26.0 | 304 | 23.6 |
| **Non-smoker** | 9,142 | 55.3 | 10,609 | 53.3 | 714 | 55.4 |
| **Ex-smoker** | 3,532 | 21.4 | 3,959 | 19.9 | 266 | 20.7 |
| **Unknown** | 65 | 0.4 | 158 | 0.8 | 4 | 0.3 |
| **Pre-pregnancy BMI** | | | | | | |
| **<20** | 1,685 | 10.2 | 2,042 | 10.3 | 123 | 9.5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **20-24** | 6,473 | 39.1 | 7,187 | 36.1 | 469 | 36.4 | |
| **25-29** | 3,367 | 20.4 | 3,790 | 19.0 | 288 | 22.4 | |
| **30-34** | 1,194 | 7.2 | 1,448 | 7.3 | 113 | 8.8 | |
| **>34** | 946 | 5.7 | 1,138 | 5.7 | 85 | 6.6 | |
| **Unknown** | 2,871 | 17.4 | 4,297 | 21.6 | 210 | 16.3 | |
| **Pre-pregnancy alcohol consumption** | | | | | | | |
| **Drinker** | 10,201 | 61.7 | 11,605 | 58.3 | 815 | 63.3 | 1 |
| **Non-drinker** | 3,709 | 22.4 | 4,141 | 20.8 | 272 | 21.1 | |
| **Heavy drinker** | 134 | 0.8 | 220 | 1.1 | 16 | 1.2 | |
| **Unknown** | 2,492 | 15.1 | 3,936 | 19.8 | 185 | 14.4 | |

## 6.5 Appendix 5 – ISAC protocols for VAESCO studies

**Establishing background incidence rates for adverse events which commonly follow immunisation using the UK General Practice Research Database**

**Lay Summary of Research**

In the wake of the current H1N1 outbreak the need for reliable incidence rates for adverse events that commonly follow immunisation (AEFI) has been highlighted by a number of regulatory agencies. This study will establish background incidence rates for a number of these AEFI using the UK GPRD. The provision of such rates will allow these agencies to quantify better the risk associated with vaccination in the early stages of an immunisation campaign. We intend to calculate age, sex and calendar year specific AEFI incidence rates for each of the last 10 years by identifying all incident events recorded in the database over this time period. This study is being performed as part of a collaborative European project with the intention of providing results that will inform both UK and European vaccination policy.

**Objectives, specific aims and rationale**

The purpose of this study is to establish reliable background incidence rates for a number of adverse events that commonly follow immunisation. The adverse events of specific interest (AESI) are listed below

- anaphylaxis
- convulsive seizures
- optic neuritis
- encephalitis
- vasculitis
- Guillain-Barré syndrome

- demyelinating disease
- Bell's palsy
- thrombocytopenia
- autoimmune hepatitis
- transverse myelitis

This study is part of a pan-European project to establish background incidence rates for AESI. This data will allow authorities better to assess whether a vaccine is associated with any observed increases in adverse events following vaccination and will allow rates to be readily compared across many European countries.

**Background**

In response to the pandemic H1N1 influenza outbreak, national vaccination campaigns have been set in motion in countries throughout the world. These mass vaccinations have resulted in the immunisation of millions of people with pandemic influenza vaccines (PIV). Given the huge numbers of vaccinations administered it is inevitable that adverse events will be temporally associated with the PIV. These temporal associations may be due to true causative associations, in which case the risk associated with the event will have to be weighed against the benefits of vaccination. A number of past vaccination campaigns have been derailed by the premature reporting of solely temporal associations between adverse events and vaccines, most notably in the late nineties when an association between the MMR vaccine and autism was suggested(1). Given the current level of public scepticism surrounding the safety of the pandemic H1N1 vaccine any similar reports would cause severe damage to the vaccination campaign. The rapid analysis of any suggested association is therefore vital to any vaccination campaign. Many adverse event reporting systems, such as VAERS in the US and the yellow card scheme in the UK may provide early warning of the numbers of temporal associations between adverse events and vaccination; however they cannot produce any evidence of causality(2).

Black *et al.* (2009) emphasise the usefulness of calculating background incidence rates for adverse events following immunization (AEFI)(3). The importance of

calculating such rates has also been highlighted by a number of regulatory bodies(4). Knowledge of the background incidence rates of adverse events should allow authorities to rapidly investigate the risk associated with any adverse event for which a temporal association is suggested by comparison of background incidence rates with rates observed following the introduction of the immunisation campaign. This will leave authorities in a better position to relay accurate, meaningful information to the public regarding any risk, or lack thereof.

One problem with many incidence rates currently available in the literature is that they vary widely across countries. It is unclear whether this is due to true geographic variance in the incidence of events or due to differences in study design and analysis. In order to deal with this issue the ECDC has tasked the VAESCO network with harmonizing H1N1 vaccine safety studies across Europe. To this end, and in response to the current pandemic threat, VAESCO have set up the Pandemic Influenza Vaccine Safety Assessment Network Europe (PIV-SANE). PIV-SANE have identified the generation of internationally harmonized background incidence rates for AESI as a key process in assessing the safety of PIV. This study is therefore one of a number of similar studies taking place throughout Europe. It is hoped that by using similar methodologies in the analysis of data the comparability of results across European countries will be improved.

**Study Type**

This is a descriptive study.

**Study Design**

The study will use a retrospective cohort design to determine the baseline incidence rates of a number of diseases. With regard to combining the data from the different databases across Europe a number of possible options were explored, these ranged from combining all of the source data to performing meta-analyses to combine results of independent studies. The model which we have chosen involves the combination of aggregated data. In this model the data will be analysed locally by each centre participating in the study in order to generate results which can then be compared across study centres. This approach has been validated and works well in the EU-

ADR project. It is also similar to the distributed HMO (VSD) and Sentinel network approach in the USA (5;6).

**Study Population**

Any patient in the GPRD database with 'acceptable' status in a practice with 'up to standard' data contributing data to the GPRD between 01/01/1998 and the 01/01/2009 will be included. Temporary patients will be excluded from the analysis. Based on incidence rates reported in the literature and assuming the GPRD contains ~3.6 million person years of data every year, over a ten year period we estimate the following numbers of relevant patients and confidence intervals in the GPRD;

| | **Incidence[1] (per 100,000 py)** | **Expected number of patients** | **Lower 95% CI** | **Upper 95% CI** |
|---|---|---|---|---|
| Autoimmune hepatitis | 1.38 | 298.8 (7)- 691.2 (8) | 451.39 | 538.61 |
| Anaphylaxis | 7.55 | 2412 (9) - 3024 (10) | 2615.82 | 2820.18 |
| Bell's palsy | 22.60 | 7272 (11)- 9000 (12) | 7959.21 | 8312.79 |
| Convulsive seizures | 56.00 | 20160 (13) | 19881.71 | 20438.29 |
| Demyelinating Disease | 7.58 | 1980 (14)- 3474 (15) | 2624.65 | 2829.35 |
| Encephalitis | 6.34 | 2282 (16) | 2188.37 | 2375.63 |
| Guillain Barré Syndrome | 1.45 | 396 - 648 (17) | 477.22 | 566.78 |
| Optic Neuritis | 1.88 | 525.6 (18)- 828 (19) | 625.81 | 727.79 |
| Thrombocytopaenia | 2.90 | 1044 (20) | 980.67 | 1107.33 |
| Transverse Myelitis | 13.85 | 1116 (20) - 8856 (21) | 4847.60 | 5124.40 |
| Vasculitis | N/A[2] | N/A | N/A | N/A |

[1] Incidence calculated based on median where a range is given for the number of events
[2] No relevant incidence rates found in the literature, all published rates estimate the incidence of vasculitis sub-types as opposed to estimating the incidence of all vasculitides together

Upon stratification of some of our rates we expect the number of patients found to get very small, for example, based on the latest age distribution information published on the GPRD website(22) and the median number of expected events listed above we estimate the following counts and confidence intervals following age stratification of GBS (the AEFI with the lowest expected number of patients)

| **Age groups** | **% of pop. in each age group** | **number of events** | **lower 95% CI** | **upper 95% CI** |
|---|---|---|---|---|
| <= 9 | 9.42 | 49.16 | 35.42 | 62.90 |
| Oct-19 | 12.08 | 63.04 | 47.48 | 78.61 |
| 20-29 | 12.31 | 64.24 | 48.53 | 79.95 |

| | | | | |
|---|---|---|---|---|
| 30-39 | 13.75 | 71.79 | 55.18 | 88.39 |
| 40-49 | 15.48 | 80.81 | 63.19 | 98.43 |
| 50-59 | 12.63 | 65.95 | 50.03 | 81.86 |
| 60-69 | 11.28 | 58.87 | 43.83 | 73.90 |
| 70-79 | 7.51 | 39.20 | 26.93 | 51.47 |
| 80 + | 5.54 | 28.94 | 18.40 | 39.49 |

A range of incidence rates have been reported for GBS(17) with the lowest rate found in children being 0.34/100,000py(23), while the lowest rate in adults is 0.84/100,000py(24). Taking these as the lowest rates we are likely to find in the GPRD we estimate that the following rates, event numbers and 95% CI may be obtained for a single year.

| Incidence rate (per 100,000py) | number of events | lower 95% CI | upper 95% CI |
|---|---|---|---|
| 0.36 | 12.96 | 5.904 | 20.016 |
| 0.84 | 30.24 | 19.46178197 | 41.01821803 |

**Outcomes**

The specific AESI we intend to establish incidence rates for are anaphylaxis, convulsive seizures, optic neuritis, encephalitis, vasculitis, Guillain-Barré syndrome, demyelinating disease, Bell's palsy, thrombocytopenia, autoimmune hepatitis and transverse myelitis. These outcomes were chosen based on guidance from the ECDC. The lists of READ codes that will be used to identify these events were produced using a three step process. Firstly, all relevant codes for each outcome were identified independently by two investigators. After consensus was reached, this list of codes was reviewed by a clinician and then the code list was refined based on the clinician's recommendations. This list of codes was sent to the coordinating centre of the collaboration. The other centres participating in the study use nomenclature systems other than READ codes, namely the International Classification of Primary Care (ICPC) and the International Classification of Diseases (ICD9-CM and ICD-10). Our code list was therefore further refined in order to produce a list of codes that would be as comparable as possible across all of these other code systems. This refined set of codes was then sent back to us and represents the final draft of the code list to be used

in this study. Cases have to be registered with the GPRD for at least one year prior to the occurrence of the event in order to be included. In order to limit the inclusion of prevalent cases patient data will be censored upon first occurrence of the event of interest.

**Data Analysis**

Age-, sex- and calendar year-specific incidence rates for each event will be calculated by dividing the number of incident cases of the event by the total contributed patient time. Indirect standardization will be carried out using the WHO World Standard Population as a reference to account for age differences in comparing the overall rates.

Aggregated data (age-, sex- and calendar year-specific incidence rates) will then be transmitted to the central database within the firewalls of the Erasmus University. All data management pertaining to the generation of the files, including programming language for data elaboration, raw source data, final files, and output files, will be kept locally for a period of at least 10 years.

**Limitations**

The main limitation of this study concerns the potential for misclassification of cases. The likelihood of this occurring, and the direction of any misclassification (false positive/false negative), will vary according to the particular disease we are classifying. The GPRD has been shown to provide reliable incidence estimates for a number of the diseases we are looking at; for example incidence rates for GBS and BP derived from GPRD data(11;25) are similar to those obtained using other data sources(12;17) suggesting that misclassification is not a big problem. Misclassification is more likely to occur when identifying cases of a more complex disease such as vasculitis or convulsive seizures. A specific example of where classification problems may occur is with the identification of encephalitis cases as it is known to have a higher incidence in children aged <1 year old (26); as children of this age are more likely to be seen in a hospital many of these cases may not be recorded in the GPRD.

In the event of a safety alert arising surrounding one of the studied AEFI added funding will become available in order to further validate these incidence rates. This validation may take the form of chart review for individual case validation or data linkage with HES data for more widespread validation. In the event of such a situation arising we will apply for separate approval for access to this data.

In order to identify and remove prevalent cases from the analysis we have set a one year run in period and will censor the person time upon first occurrence of the disease. However it has been shown that when calculating incidence rates for chronic diseases using the GPRD a one year run in period may not be adequate to exclude all prevalent cases (27). A number of the AEFI we are investigating are chronic relapsing and remitting diseases therefore in addition to the one year run in period described in the data analysis we will also carry out sensitivity analyses using two and three year run in periods in order to investigate the likelihood and possible impact of including prevalent cases.

When comparing our results with those of the other European study centres, we anticipate that our results may differ for a number of reasons. Firstly any observed differences may be accounted for by geographical variance in disease incidence. For example the incidence of various forms of vasculitis has been shown to vary substantially between European countries(28), therefore we can expect to observe variability in our estimates. In addition the inherent differences between the data sources being used may also account for some differences. The data sources vary across the clinical setting from which they derive their data (primary care/hospital) and the coding systems they use to record diagnoses (Read, ICD9/10, ICPC). Despite efforts to harmonize code lists (described in the "outcome" section) we still expect the incidence rates to vary across study centres due to this heterogeneity.

Owing to these problems we do not anticipate that pooling of incidence rates across countries will be possible, rather each centre will produce their own country specific rates. Comparison of these rates across geographic location and data source will then be carried out and the effect that omitting certain sub-groups (based on age, calendar year, specific Read codes, etc.) has on the comparability of the rates across sources

will be examined. For example in order to investigate the aforementioned possibility of encephalitis misclassification our rates can be compared with those from study centres using hospital data sources with and without the <1 year age group to see if this affects comparability of rates.

**Plans for disseminating and communicating study results**

Results of the study will be made public. Communication of the study results will be made according to the guidelines set out in the EMA's 'European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring'(4). This document sets down the following principles with regard the communication of results;

> "- If the outcome of a signal assessment is a risk minimisation measure, this should be communicated as appropriate to inform the public without inducing fears; the timing of the finalisation of the assessment and of the decision-making process should be included.
> - When a Member State plans to issue a communication, the other Member States, the EMA and ECDC should preferably be informed in advance. Reference is in this respect made to the existing Memorandum of Understanding between the National Competent Authorities of the European Economic Area and the European Medicines Agency on the sharing of EudraVigilance data and other safety and pharmacovigilance related confidential documents and/or information relating to medicinal products for human use.
> - EMA should lead communications on centrally authorised vaccines."

The findings from this study will also be published for peer-review in international journals and at conferences.

Reference List


(1) Wakefield AJ. MMR vaccination and autism. Lancet 1999 Sep 11;354(9182):949-50.

(2) Varricchio F, Iskander J, DeStefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. Pediatr Infect Dis J 2004 Apr;23(4):287-94.

(3) Black S, Eskola J, Siegrist CA, Halsey N, Macdonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet 2009 Dec 19;374(9707):2115-22.

(4) The European Medicines Agency (EMEA), The European Centre for Disease Prevention and Control(ECDC), The Heads of Medicines Agencies (HMA). European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring. 2009/11/20; 2009.

(5) Holmes JH, Brown J, Hennessy S, Lane K, Langer RD, Lazarus R, et al. Developing a distributed research network to conduct population-based studies and safety surveillance. AMIA Annu Symp Proc 2008;973.

(6) Velentgas P, Bohn RL, Brown JS, Chan KA, Gladowski P, Holick CN, et al. A distributed research network model for post-marketing safety studies: the Meningococcal Vaccine Study. Pharmacoepidemiol Drug Saf 2008 Dec;17(12):1226-34.

(7) Primo J, Merino C, Fernandez J, Moles JR, Llorca P, Hinojosa J. [Incidence and prevalence of autoimmune hepatitis in the area of the Hospital de Sagunto (Spain)]. Gastroenterol Hepatol 2004 Apr;27(4):239-43.

(8) Boberg KM. Prevalence and epidemiology of autoimmune hepatitis. Clin Liver Dis 2002 Aug;6(3):635-47.

(9) Sheikh A, Hippisley-Cox J, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. J R Soc Med 2008 Mar 1;101(3):139-43.

(10) Matsui E. A Population-Based Study of the Incidence, Cause, and Severity of Anaphylaxis in the United Kingdom. Pediatrics 2005 Aug 1;116(2):549-a.

(11) Rowlands S, Hooper R, Hughes R, Burney P. The epidemiology and treatment of Bell's palsy in the UK. European Journal of Neurology 2002 Jan;9(1):63-7.

(12) Martyn CN, Hughes RA. Epidemiology of peripheral neuropathy. J Neurol Neurosurg Psychiatry 1997 Apr;62(4):310-8.

(13) Kotsopoulos IA, van MT, Kessels FG, de Krom MC, Knottnerus JA. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia 2002 Nov;43(11):1402-9.

(14) Alonso A, Jick S, Olek M, Hern+ín M. Incidence of multiple sclerosis in the United Kingdom. Journal of Neurology 2007 Dec 1;254(12):1736-41.

(15) Hirst C, Ingram G, Pickersgill T, Swingler R, Compston DA, Robertson NP. Increasing prevalence and incidence of multiple sclerosis in South East Wales. J Neurol Neurosurg Psychiatry 2009 Apr;80(4):386-91.

(16) Jmor F, Emsley H, Fischer M, Solomon T, Lewthwaite P. The incidence of acute encephalitis syndrome in Western industrialised and tropical countries. Virology Journal 2008;5(1):134.

(17) McGrogan A, Madle GC, Seaman HE, de Vries CS. The Epidemiology of Guillain-Barre Syndrome Worldwide A Systematic Literature Review. Neuroepidemiology 2009;32(2):150-63.

(18) Jin YP, de Pedro-Cuesta J, Soderstrom M, Stawiarz L, Link H. Incidence of optic neuritis in Stockholm, Sweden 1990-1995: I. Age, sex, birth and ethnic-group related patterns. J Neurol Sci 1998 Jul 15;159(1):107-14.

(19) Soderstrom M. The clinical and paraclinical profile of optic neuritis: a prospective study. Ital J Neurol Sci 1995 Apr;16(3):167-76.

(20) Klein NP, Ray P, Carpenter D, Hansen J, Lewis E, Fireman B, et al. Rates of autoimmune diseases in Kaiser Permanente for use in vaccine adverse event safety studies. Vaccine 2010 Jan 22;28(4):1062-8.

(21) Young J, Quinn S, Hurrell M, Taylor B. Clinically isolated acute transverse myelitis: prognostic features and incidence. Multiple Sclerosis 2009 Nov;15(11):1295-302.

(22) Facts and Figures: Number of currently registered patients in FF-GPRD in 10-year age bands by gender. GPRD 2010 [cited 2010 May 12];Available from: URL: http://www.gprd.com/gprd/patientsingprd.asp

(23) Beghi E, Bogliun G. The Guillain-Barre syndrome (GBS). Implementation of a register of the disease on a nationwide basis. Italian GBS Study Group. Ital J Neurol Sci 1996 Oct;17(5):355-61.

(24) Kinnunen E, Junttila O, Haukka J, Hovi T. Nationwide oral poliovirus vaccination campaign and the incidence of Guillain-Barre Syndrome. Am J Epidemiol 1998 Jan 1;147(1):69-73.

(25) Hughes RA, Charlton J, Latinovic R, Gulliford MC. No association between immunization and Guillain-Barre syndrome in the United Kingdom, 1992 to 2000. Arch Intern Med 2006 Jun 26;166(12):1301-4.

(26) Koskiniemi M, Korppi M, Mustonen K, Rantala H, Muttilainen M, Herrg+Ñrd E, et al. Epidemiology of encephalitis in children. A prospective multicentre study. European Journal of Pediatrics 1997 Jun 7;156(7):541-5.

(27) Lewis JD, Bilker WB, Weinstein RB, Strom BL. The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiol Drug Saf 2005 Jul;14(7):443-51.

(28) Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? Best Pract Res Clin Rheumatol 2005 Apr;19(2):191-207.

## Evaluating the Possible Association between Pandemic Influenza Vaccination and Guillain-Barré Syndrome using the UK General Practice Research Database

### Lay summary of research

One of the main safety concerns surrounding the current pandemic influenza vaccination campaign is the occurrence of neurological adverse events such as Guillain Barré syndrome (GBS) following vaccination. This study aims to estimate the risk of developing GBS following immunisation with a pandemic influenza vaccine (PIV). In order to do this we will utilise two study designs, one of which uses both cases and controls and one of which uses cases only. Each of these designs offers its own distinct advantages and therefore the proposed approach should provide two comparable and reliable estimates of the risk of developing GBS following PIV. This study is part of a collaborative European approach to monitoring vaccine safety, which aims to ensure study centres throughout Europe use a shared methodology in assessing PIV safety. It is hoped that this approach will increase the comparability of results and thereby possibly allow pooling of the data across centres. Given the rarity of GBS this pooling of data across study centres is invaluable as it should enable us to increase the power of our results substantially.

### Objectives, specific aims and rationale

To use the GPRD as part of a Europe-wide initiative to test the hypothesis that there is no increased risk of GBS following receipt of pandemic H1N1 influenza vaccine. Specifically we intend to use two different study designs, a case control and a self controlled case series, to estimate the risk of developing GBS following PIV. Using the two study designs will ensure we can make both rapid and reliable estimates of the risk.

### Background

In response to the ongoing pandemic H1N1 influenza outbreak national vaccination campaigns have been introduced in countries throughout the world. These mass vaccination plans have resulted in the immunisation of millions of people with PIV.

With these numbers of vaccinations having been administered it is inevitable that adverse events will be temporally associated with the PIV. A list of the side effects most commonly associated with vaccination has been drawn up by the ECDC based on previously reported associations. From this list the ECDC have singled out GBS for additional safety monitoring as it has been associated with both pandemic swine influenza vaccines(1-3) and seasonal vaccines(4) in observational studies in the past. Limited evidence also suggests that an association between GBS and influenza vaccination may be biologically plausible(5).

The major problem with conducting a study to monitor this association is that, given the rarity of GBS and the relatively low PIV coverage observed in many countries no single data source worldwide has the capacity to provide sufficiently powered risk estimates to detect a mid to moderate increase in risk (see "Sample Size/Power calculations" section). The possibility of combining results from a number of data sources was therefore investigated by the ECDC. This resulted in the setup of the VAESCO network, the main aim of which is to set up a sustainable infrastructure for post licensure vaccine safety assessment in the European Region. Early VAESCO work has focused on conducting collaborative studies on the safety of the H1N1 vaccine. We are one of several study centres involved in VAESCO that intend to contribute to a Europe wide GBS/PIV safety study in an effort to obtain the necessary power to provide accurate and reliable risk estimates of the association between PIV and GBS.

**Study type**

This is a hypothesis testing study

**Study design**

This study will use both a case-control and self controlled case series (SCCS) design to estimate the increase in risk of GBS associated with PIV.

A case-control design will first be used as its retrospective nature allows the association with GBS to be rapidly assessed. However a key problem with this design is that confounding may have profound effects on the risk estimate.

A SCCS will therefore also be carried out. The main advantage of this design is that it uses only cases. In the SCCS cases act as their own controls; consequently all potential confounding that is constant within patients during the study period is controlled for. The fact that it requires a substantial amount of follow up time after exposure in order to prove efficient means it is less suitable for rapid risk analysis.

With regard to combining the data from the different databases across Europe, a number of options were explored, these ranged from combining source data to performing meta-analyses to combine results of independent studies. The model that we have chosen involves the combination of aggregated data. In this model the data will be analysed locally by each centre participating in the study in order to generate results, which can then be compared across study centres. This approach has been validated and works well in the EU-ADR project(6). It is also similar to the distributed HMO (VSD) and Sentinel network approach in the USA(7;8).

**Study population**

The source population for the case control study will comprise all patients at risk of developing GBS that are registered in the GPRD from the 21st of October 2009 (start of UK H1N1 vaccination campaign) to the 25th of March 2010.

The source population for the SCCS study will comprise all patients at risk of developing GBS that are registered in the GPRD from the 21st of October 2009 to the 21st of October 2010.

Prevalent GBS cases will be identified and excluded from both populations and only those patients that have contributed at least one full year of data before the study start date will be included in the studies. From these source populations we will identify all incident cases of GBS.

**Selection of controls**

In the case control study incidence density sampling will be used to sample 4 controls per case. Controls will be matched on age, sex, GP practice and the index date of the case.

**Sample size/power calculations**

In previous studies the relative risk of GBS associated with vaccination varied between 1.5 and 7(9) and the background incidence of GBS was estimated at approximately 15 per 1,000,000 person years(10). In a total population of around 100 million European inhabitants, we can anticipate 1500 new cases of GBS in a one year period and 375 during a 3 month period. However to obtain the number of vaccinated GBS cases, assuming no increased risk, the expected number of GBS cases has to be multiplied by the vaccine coverage.

If we assume a 42 (i.e. 6 weeks) and 90 day post vaccination risk period and a total follow up of one year then the following relative risks (or relative incidence) can be detected at 5% significance and 80% power for various numbers of GBS events in persons vaccinated during the study period (Table 1).

**Table 1 Detectable RR (or relative incidence) for self-controlled case series**

| Number of events* | Detectable RR (90 day risk window) | Detectable RR (42 day risk window) |
|---|---|---|
| 10 | 4.4 | 5.8 |
| 20 | 3.1 | 4.0 |
| 40 | 2.3 | 2.9 |
| 80 | 1.9 | 2.2 |

*Note that these calculations do not account for age and period effects, which may slightly reduce power.

For the case-control analysis, employing the same assumptions (alpha 5% and power 80%) and assuming a vaccine coverage of 25%, we can detect an odds ratio of 3 with 120 GBS cases matched to 4 controls and an odds ratio of 2 with 280 cases and 4 controls (Table 2).

**Table 2: Number of cases and power in a matched case-control analysis**

| | Detectable odds ratio* | | | | | | |
|---|---|---|---|---|---|---|---|
| **cases** | **0.5** | **0.8** | **1.2** | **1.5** | **2** | **3** | **4** |
| **0** | na | na | na | na | na | na | na |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **20** | na | na | na | na | na | na | na |
| **40** | 0.153 | 0.060 | 0.061 | 0.101 | 0.192 | 0.377 | 0.522 |
| **60** | 0.219 | 0.067 | 0.066 | 0.126 | 0.268 | 0.538 | 0.720 |
| **80** | 0.285 | 0.075 | 0.071 | 0.153 | 0.342 | 0.670 | 0.847 |
| **100** | 0.351 | 0.082 | 0.076 | 0.179 | 0.413 | 0.771 | 0.921 |
| **120** | 0.415 | 0.089 | 0.081 | 0.205 | 0.480 | **0.845** | 0.961 |
| **140** | 0.476 | 0.096 | 0.087 | 0.232 | 0.542 | 0.898 | 0.982 |
| **160** | 0.533 | 0.104 | 0.092 | 0.258 | 0.599 | 0.934 | 0.992 |
| **180** | 0.586 | 0.111 | 0.097 | 0.284 | 0.651 | 0.958 | 0.996 |
| **200** | 0.634 | 0.118 | 0.102 | 0.310 | 0.697 | 0.973 | 0.998 |
| **240** | 0.719 | 0.133 | 0.112 | 0.360 | 0.775 | 0.990 | 1.000 |
| **280** | 0.787 | 0.148 | 0.123 | 0.409 | **0.836** | 0.996 | 1.000 |
| **320** | 0.841 | 0.164 | 0.133 | 0.456 | 0.882 | 0.999 | 1.000 |
| **360** | 0.883 | 0.179 | 0.144 | 0.500 | 0.916 | 1.000 | 1.000 |
| **400** | 0.915 | 0.194 | 0.154 | 0.543 | 0.940 | 1.000 | 1.000 |

- based on 4 controls per case, vaccination degree of 25% and matched correlation of 0.7

Based on preliminary analyses the incidence of GBS in the GPRD is ~14.9 cases/1,000,000 person years; this is in line with previously published incidence rates for GBS (10;11). Therefore based on a GPRD population of ~4million active patients we could expect to see ~20 cases during the study period. These calculations were conducted with an assumed vaccine coverage of 25%, in reality it appears that vaccine coverage in the UK will be closer to 10% of the population. It is clear that based on GPRD data alone such a study would be underpowered to detect increases in the risk of developing GBS. In order to increase the power, and in view of the fact that safety issues may arise early after vaccination, using data from across Europe through the VAESCO project is an essential feature of this study.

**Exposures**

The primary exposure of interest is PIV. The exposure details we intend to collect are "event date" of vaccine administration and vaccination brand (where available).

In addition we will collect data on the event date of any other vaccinations occuring after the 01/09/2009.

**Outcome**

The main outcome of interest is GBS. Previous studies (11;12) and preliminary in-house analyses suggest the incidence of GBS in the GPRD to be in line with the results of recent reviews on the epidemiology of GBS(10;13). In addition a recent

study compared the incidence rate of Guillain Barré syndrome recording in the GPRD with both the admission rate from Hospital Episode Statisitics and the incidence rate in a subset of validated GPRD cases and found no significant differences(14). This is a good indication that most GBS cases are currently captured in the GPRD and that those cases that are identified represent true cases. The specific codes used to identify GBS cases are provided in appendix 1. All cases identified using these codes will be further validated using the information available in the free text. In order to allow pooling and comparison of data across the VAESCO network a common definition of GBS is being used; the definition to be used is that developed by the Brighton Collaboration. The Brighton Collaboration definition categorises cases into different levels according to the level of certainty regarding the diagnosis. Full details of the Brighton Collaborations definition are given in appendix 2. As this definition was not primarily developed for use with database studies we do not expect to have enough case information to classify cases in the top three levels of diagnostic certainty. Most of our cases will therefore meet the criteria to be classed at either level 4(a) or 4(b) of the definition.

**Covariates**

Information on the following covariates will be collected:

In the 6 weeks before the index date;

- Gastrointestinal infection
- Upper respiratory infection
- influenza like illness (ILI)

Anywhere in medical record;

- Epstein-Barr virus infection
- surgeries
- malignancies
- pregnancy
- immunocompromised (i.e. history of HIV or other immunosuppressive disorder, transplantation or use of immunosuppressants)
- autoimmune disorders

Retrieval of covariate information will be identical for cases and controls to minimize information bias.

**Data Analysis**

In the case-control analysis odds ratios and 95% confidence intervals will be calculated using multivariate conditional logistic regression. Covariates will be included into the multivariate model if they are significantly ($p<0.05$) associated with GBS and/or change the point estimate of the association between H1N1 vaccination and GBS by at least 10%. The primary exposure in the analysis is H1N1 vaccination with 'no vaccination' as the reference category, To study the time-effect association we will define different risk windows for exposure: 1-42 days before index date, 43-90 days before index date, and >90 days before index date, with 'no vaccination' as the reference category. In a third analysis, the exposure will be further divided into first and second administrations (i.e. dose-response relationship). The association with different adjuvants will be studied by stratifying the analysis by the type of vaccine and by categorizing exposure in the multivariate model according to the type of vaccine. Finally, any associations with other vaccines (i.e. co-vaccination) during the risk period will be assessed by stratification for 'co-vaccination' and adding an interaction term to the multivariate model. Stratified analyses may be conducted to estimate the effect in specific subgroups e.g. pregnant women, immunocompromised subjects, children and older people.

In the SCCS, we will use conditional Poisson regression to calculate relative risks (or relative incidences) of GBS for a number of risk periods following PIV. Taking into account the possibility of lag time between vaccination and GBS onset, we will define the following risk periods: pre-vaccination, 0-28 days after PIV, 29-42 days after PIV, 43-60 days after PIV and 61-90 days after PIV with the remaining periods serving as the reference period (15-17). As mentioned previously, the SCCS methodology inherently controls for confounders that are constant over time as each person serves as its own control.

If two doses of vaccine are given then the risk period after the first dose will be censored at the point the second is given (18). To adjust for the effect of ILI a 90 day

post ILI risk period will be used. Seasonal vaccine has not been shown to be associated with GBS and will only be included if this factor is significant. If seasonal vaccine is given at the same time as pandemic vaccine then an analysis will be performed looking at this scenario by treating this as a separate exposure. In a secondary analysis we will stratify for age to evaluate the difference in risk estimates in different age groups

**Limitations**

A potential limitation is the (false negative) misclassification of vaccination status as well as a lack of vaccination detail. This will most commonly arise where special risk groups, such as health care workers and certain other employees, may receive their vaccine through the employer rather than the GP or other dedicated authority. This will prove more of a problem with seasonal vaccines as they are provided by many employers and private clinics whereas the vast majority of H1N1 vaccine was administered in GP practices. There is also a possibility that some GP's may have entered a pandemic vaccination under one of the seasonal vaccine codes.

As mentioned previously the potential for false misclassification of GBS diagnosis does not seem likely as incidence rates calculated in the GPRD using our codes are very similar to those in the published literature. However there is a chance that in some cases there will be a time lag between onset of GBS and recording of the diagnosis in the GPRD(14); in these cases the date on which the GBS diagnosis is recorded in the GPRD will actually represent the date of hospital discharge or the date a letter is received from the neurologist. GBS case validation will be carried out using free-text information and discharge summaries in order to decrease the likelihood of false positive misclassification of GBS status and of false recording of the date of GBS onset. If the information contained in the free text provides insufficient information to do this then we will design questionnaires to send to GPs to obtain additional details regarding the GBS cases. In this event separate ISAC approval will be sought for these questionnaires.

With regard to the case-control design we will look at a number of potentially confounding factors however any unidentified confounders will inevitably affect our results. While the SCCS will control for any unidentified non-time varying covariates

there are a number of limitations which must be considered when using it in the current scenario.

The first such limitation is due to the possibility that GBS will be either a contra-indication to vaccination or that individuals diagnosed with GBS are less likely to ever receive the vaccine. Whilst it is possible to control for delayed vaccination in ill individuals by specifying a pre-vaccination 'low risk' period to be removed from the background, it is not possible to use any pre-vaccination person time if GBS cases are less likely to be vaccinated. In order to account for this we will carry out sensitivity analyses using only post vaccination person time. The main problem with this approach, and one of the key reasons for performing the case control analysis, is that it will affect the timeliness of producing results since it will be necessary to wait until sufficient time has accrued after the vaccine risk period (vaccine risk period may last up to 90 days).

Another complicating factor is the analysis of data where two doses of vaccine are given. Given the long post-vaccination risk period it is unlikely to be possible to separate risks after one dose from another. It is probably necessary to combine the post first and second dose risks together as a single risk window. There is also a technical issue that if GBS occurs after a first dose then a second dose may never be given – but as the risk period is much longer than the interval between doses this is unlikely to bias the analysis. In addition we expect only a small number of the population to have received two doses of the vaccine as two doses were only recommended for immuncompromised individuals.

**Plans for disseminating and communicating study results**

Results of the study will be made public. Communication of the study results will be made according to the guidelines set out in the EMAs 'European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring'(19). This document sets down the following principles with regard the communication of results;

> "- If the outcome of a signal assessment is a risk minimisation measure, this should be communicated as appropriate to inform the

public without inducing fears; the timing of the finalisation of the assessment and of the decision-making process should be included.

- When a Member State plans to issue a communication, the other Member States, the EMEA and ECDC should preferably be informed in advance. Reference is in this respect made to the existing Memorandum of Understanding between the National Competent Authorities of the European Economic Area and the European Medicines Agency on the sharing of EudraVigilance data and other safety and pharmacovigilance related confidential documents and/or information relating to medicinal products for human use.
- EMEA should lead communications on centrally authorised vaccines."

The findings from this study will also be published for peer review in international journals and conferences.

## Reference List


**(1) Breman JG, Hayner NS. Guillain-Barre syndrome and its relationship to swine influenza vaccination in Michigan, 1976-1977. Am J Epidemiol 1984 Jun;119(6):880-9.**

**(2) Safranek TJ, Lawrence DN, Kurland LT, Culver DH, Wiederholt WC, Hayner NS, et al. Reassessment of the association between Guillain-Barre syndrome and receipt of swine influenza vaccine in 1976-1977: results of a two-state study. Expert Neurology Group. Am J Epidemiol 1991 May 1;133(9):940-51.**

**(3) Langmuir AD, Bregman DJ, Kurland LT, Nathanson N, Victor M. An epidemiologic and clinical evaluation of Guillain-Barre syndrome reported in association with the administration of swine influenza vaccines. Am J Epidemiol 1984 Jun;119(6):841-79.**

**(4) Lasky T, Terracciano GJ, Magder L, Koski CL, Ballesteros M, Nash D, et al. The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines. N Engl J Med 1998 Dec 17;339(25):1797-802.**

**(5) Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barre syndrome. Drug Saf 2009;32(4):309-23.**

**(6) Trifiro G, Fourrier-Reglat A, Sturkenboom MC, Diaz AC, Van Der LJ. The EU-ADR project: preliminary results and perspective. Stud Health Technol Inform 2009;148:43-9.:43-9.**

**(7) Holmes JH, Brown J, Hennessy S, Lane K, Langer RD, Lazarus R, et al. Developing a distributed research network to conduct population-based studies and safety surveillance. AMIA Annu Symp Proc 2008;973.**

**(8) Velentgas P, Bohn RL, Brown JS, Chan KA, Gladowski P, Holick CN, et al. A distributed research network model for post-marketing safety studies: the Meningococcal Vaccine Study. Pharmacoepidemiol Drug Saf 2008 Dec;17(12):1226-34.**

**(9) Haber P, Sejvar J, Mikaeloff Y, DeStefano F. Vaccines and Guillain-Barre syndrome. Drug Saf 2009;32(4):309-23.**

**(10) McGrogan A, Madle GC, Seaman HE, de Vries CS. The Epidemiology of Guillain-Barre Syndrome Worldwide A Systematic Literature Review. Neuroepidemiology 2009;32(2):150-63.**

**(11) Black S, Eskola J, Siegrist CA, Halsey N, Macdonald N, Law B, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet 2009 Dec 19;374(9707):2115-22.**

**(12) Hughes RA, Charlton J, Latinovic R, Gulliford MC. No association between immunization and Guillain-Barre syndrome in the United Kingdom, 1992 to 2000. Arch Intern Med 2006 Jun 26;166(12):1301-4.**

**(13) Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. J Infect Dis 1997 Dec;176 Suppl 2:S92-S98.**

**(14) Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database. Am J Epidemiol 2009 Feb 1;169(3):382-8.**

**(15) Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med 2006 May 30;25(10):1768-97.**

**(16) Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res 2009 Feb;18(1):7-26.**

**(17) Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. Biometrics 1995 Mar;51(1):228-35.**

**(18) Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. Biostatistics 2009 Jan;10(1):3-16.**

**(19) The European Medicines Agency (EMEA), The European Centre for Disease Prevention and Control(ECDC), The Heads of Medicines Agencies (HMA). European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring. 2009.**

# Appendix I – Pegasus Medical Codes

## Outcome

| Pegasus Medical Codes | Read Term |
|---|---|
| 1607 | Guillain-Barre syndrome |
| 6376 | Acute infective polyneuritis |
| 33841 | Miller-Fisher syndrome |
| 63544 | Acute infective polyneuritis NOS |
| 24216 | Postinfectious polyneuritis |

## Primary Exposure

| Pegasus Medical Codes | Read Term |
|---|---|
| 98183 | PANDEMRIX – first influenza A (H1N1v) 2009 vaccination given |
| 94301 | First pandemic influenza vaccination |
| 98184 | PANDEMRIX – second influenza A (H1N1v) 2009 vaccination given |
| 95092 | Second pandemic influenza vaccination |
| 98217 | 1st pandemic influenza vac give by other healthcare providr |
| 98203 | PANDEMRIX – 1st flu A (H1N1v) 2009 vac by other provider |
| 98234 | CELVAPAN – first influenza A (H1N1v) 2009 vaccine given |
| 98302 | CELVAPAN – second influenza A (H1N1v) 2009 vaccine given |
| 98449 | CELVAPAN – 1stnd flu A (H1N1v) 2009 vacc by other provider |
| 98303 | CELVAPAN – 2nd flu A (H1N1v) 2009 vacc by other provider |
| 98304 | PANDEMRIX – 2nd flu A (H1N1v) 2009 vacc by other provider |
| 98306 | 2nd pandemic influenza vac give by other healthcare providr |

| Pegasus Product Codes | Product Name |
|---|---|
| 41150 | PANDEMRIX vaccine [GLAXSK UK] |
| 41168 | influenza (h1n1) inactivated split virion vaccine |
| 41240 | influenza (h1n1) inactivated whole virion vaccine |
| 41925 | CELVAPAN vaccine [BAXTER] |

**Appendix II – Brighton Case Defintion**

## Level 1 of diagnostic certainty

• Bilateral AND flaccid weakness of the limbs [4, 4a, 4b]

**AND**

• Decreased or absent deep tendon reflexes in weak limbs [4c]

**AND**

• Monophasic illness pattern[5] AND interval between onset and nadir of weakness between 12 hours and 28 days AND subsequent clinical plateau[5a]

**AND**

• Electrophysiologic findings consistent with GBS[6]

**AND**

• Cytoalbuminologic dissociation (i.e., elevation of CSF protein level above laboratory normal value AND CSF total white cell count <50 cells/μl)[7]

**AND**

• Absence of an identified alternative diagnosis for weakness (see Appendix III)[1]

## Level 2 of diagnostic certainty

• Bilateral AND flaccid weakness of the limbs [4, 4a, 4b]

**AND**

• Decreased or absent deep tendon reflexes in weak limbs[4c]

**AND**

• Monophasic illness pattern[5] AND interval between onset and nadir of weakness between 12 hours and 28 days AND subsequent clinical plateau[5a]

**AND**

• CSF total white cell count <50 cells/µl (with or without CSF protein elevation above laboratory normal value)[7]

**OR**

• IF CSF not collected or results not available, electrophysiologic studies consistent with GBS[6]

**AND**

• Absence of identified alternative diagnosis for weakness (see Appendix III)[1]

## Level 3 of diagnostic certainty

• Bilateral AND flaccid weakness of the limbs [4,4a, 4b]

**AND**

• Decreased or absent deep tendon reflexes in weak limbs[4c]

**AND**

• Monophasic illness pattern[5] AND interval between onset and nadir of weakness between 12 hours and 28 days AND subsequent clinical plateau[5a]

**AND**

• Absence of identified alternative diagnosis for weakness (see Appendix III)[1]

## Level 4(a) of diagnostic certainty[8]

• Discharge letter indicating diagnosis of GBS made by a neurologist

**AND**

• Absence of identified alternative diagnosis for weakness (see Appendix III)[1]

## Level 4(b) of diagnostic certainty[8]

• Diagnosis of GBS entered into GP medical record

**AND**

• Absence of identified alternative diagnosis for weakness (see Appendix III)[1]

**Footnotes for Case Definitions**

1. If an **alternative diagnosis** explaining flaccid weakness/paralysis is present (Appendix III), a diagnosis of Guillain-Barré syndrome is **excluded.** However, in many, if not most cases, a comprehensive documentation of testing for various other etiologies will either be incomplete or unavailable. These case definitions are provided to give guidance in the absence of detailed information on investigations for alternative etiologies of flaccid paralysis.

2. It is recognized that there are several clinical syndromes which are considered as part of the spectrum of Guillain-Barré syndrome that may not be captured under these case definitions. However, these are rare and comprise under 1% of overall GBS cases. Thus, the number of cases missed by these definitions is considered to be extremely low. An exception to this is the FS of ophthalmoplegia, ataxia, and loss of tendon reflexes which is generally considered to be a subtype of GBS (see FS case definition).

3. The clinical and electrophysiologic criteria specified in this document were designed to be applicable to all ages. The Working Group recognizes that neurologic features in infants and young children are continually developing and that assessment of infants can be difficult. However, GBS in children under 6 months of age is a very uncommon occurrence. When possible, infants and children under 2 years of age should preferably be evaluated by a clinician familiar with the neurologic evaluation of young children, and such evaluations should be performed in an age-appropriate fashion, taking into account the changing neurologic features in the developing infant.

4. Weakness is usually, but not always, symmetric in nature, and usually has a pattern of progression from legs to arms (ascending). However, other patterns of progression may occur (e.g., beginning in the arms). The degree of weakness can range from mild to moderate to severe, i.e., complete paralysis.

4a. Respiratory or cranial nerve-innervated muscles may also be involved.

4b. It is important that strength be assessed in a manner that takes into account subject age, sex, and level of functioning.

4c. Decreased or absent tendon reflexes may also be seen in limbs without weakness. However, to meet case definition criteria, decreased or absent tendon reflexes must be observed in weak limbs.

5. Fluctuations in level of weakness, before reaching nadir, or during the plateau or improvement phases, occur in some cases, usually associated with the use of disease modifying therapies. Such fluctuations usually occur within the first 9 weeks after onset and are followed by eventual improvement.

5a. The eventual outcome is either stabilization at nadir OR subsequent improvement OR death.

6. Electrophysiologic patterns consistent with polyneuropathy of the types described for GBS. Electrophysiologic studies performed sooner than 7 days after weakness onset may be normal and should thus be repeated at a later time if possible, and "normal" studies may occur in otherwise typical cases of GBS. However, cases with persistently "normal" studies will not meet Level 1 criteria.

7. CSF (cerebrospinal fluid) protein concentrations should be elevated above what is considered normal reference values for the testing laboratory. CSF may be "normal" in otherwise typical cases of GBS; this is particularly true within the first week of illness. However, cases with persistently "normal" CSF, or CSF with >50 WBC, will not meet Level 1 criteria.

8. Although the definition of a level 4 is alluded to in the Brighton Collaboration's definition the specifics of levels 4(a) and 4(b) of diagnostic certainty shown here are not part of the published Brighton Collaboration. These have been developed specifically for this study with a view to creating a definition which is suited to defining cases from databases.

**Full published definition available at:**

**http://www.brightoncollaboration.org/internet/en/index/definition___guidelines/document_download.html**

## Appendix III - Exclusionary Criteria for a Diagnosis of Guillain-Barré Syndrome

There are multiple other pathologic processes that may occur at various localizations in the central and peripheral nervous system that may present with a clinical picture similar to or identical to that of Guillain-Barré syndrome. If such a diagnosis explaining flaccid weakness/paralysis is present, this effectively excludes a diagnosis of Guillain-Barré syndrome, and the subject is considered "Not a case".

Examples of other diagnoses, grouped according to typically affected region, are provided below; this is not intended to be an exhaustive list, but rather to highlight the localizations within the nervous system that lesions or illness might occur, with examples provided:

• **Intracranial**
carcinomatous meningitis
brain stem encephalitis

• **Spinal cord**
infarct, myelitis, compression

• **Anterior horn cells of spinal cord**
polio and other viruses producing poliomyelitis, including West Nile virus

• **Spinal nerve roots**
chronic inflammatory demyelinating polyneuropathy
cauda equina compression

• **Peripheral nerves**
metabolic derangements such as hypermagnesemia or hypophosphatemia
tic paralysis
heavy metal toxicity such as arsenic, gold and thallium
Drug-induced neuropathy, (e.g., vincristine, platinum compounds, nitrofurantoin, paclitaxel)
porphyria
critical illness neuropathy
vasculitis
diphtheria

• **Neuromuscular junction**
myasthenia gravis
organophosphate poisoning
botulism

• **Muscle**
critical illness myopathy
polymyositis
dermatomyositis
hypo/hyperkalemia