Methodological challenges in post-licensure vaccine safety studies using large routinely collected datasets

by

Julia Margaret Toffa-Stowe

A thesis submitted in partial fulfilment of the requirements of the Manchester Metropolitan University for the degree of Doctor of Philosophy by Published Work (Route 2)

Manchester Metropolitan University

2017

Table of Contents

List of abbreviations

BMJ	British Medical Journal
CHIS	Child Health Information System
CTV	Clinical Terms Version
DTP	Diphtheria, Tetanus, Pertussis Vaccine
EHR	Electronic Health Record
EMA	European Medicines Agency
FDA	Food and Drug Administration
GBS	Guillain-Barre syndrome
GP	General Practitioner
GRPD	General Practice Research Database
HES	Hospital Episode Statistics
HPA	Health Protection Agency
HPV	Human Papillomavirus
HSCIC	Health and Social Care Information Centre
ICD	International Classification of Diseases
ICSD	International Classification of Sleep Disorders
ITP	Idiopathic Thrombocytopenia Purpura
MHRA	Medicines and Healthcare Products Regulatory Agency
MMR	Measles, Mumps and Rubella Vaccine
MSLT	Multi Sleep Latency Test
NHS	National Health Service
OPCS	Classification of Intervention and Procedures
PbR	Payment by Results
PHE	Public Health England
PRISM	Post-Licensure Rapid Immunization Safety Monitoring Program
QOF	Quality Outcomes Framework
SCCS	Self-Controlled Case-Series
VAERS	The Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
WHO	World Health Organisation

Glossary

Active Reporting	Reports which have been proactively sought. Registers and data linkage techniques can be used to identify adverse events.
Adverse event	An event which follows the administration of a drug or a vaccine but is not necessarily caused by that event
Passive reporting	Reports where no active measures have been taken to encourage the reporting of safety concerns
Pharmacovigilance	Activities relating to the detection, assessment, understanding and prevention of adverse effects
Primary care	Part of the healthcare system which is accessed through a patient's general practice surgery which can be the first point of contact for patients. The GP coordinates day to day and ongoing care that a patient may need.
Routinely collected data	Electronic data that is collected for purposes other than for scientific research. An example of this is the hospital administration database which schedules appointments.
Secondary care	Services that are based at hospital and patient access the services either by Accident and Emergency departments or by referral from General Practice or other specialities.
Signal	The suggestion of a relationship between a drug/vaccine and a condition which has not been documented previously. The information should be from multiple sources and judged to be sufficient for further investigation

1. Abstract

Robust and responsive epidemiological post-licensure vaccine safety studies are the backbone to having confidence in a vaccination programme. Consideration must be given to the unique methodological challenges inherent when assessing a potential causal association between a vaccine and the condition of interest; these can be present from setting up the study through to communicating the results. Public Health England (PHE) has addressed a number of vaccine safety concerns since the 1990's using routinely collected healthcare data and methods specific to the disease and vaccine under scrutiny.

This thesis comprises of seven published post-licensure vaccine safety studies which were carried out in response to a number of different pertinent safety concerns relevant to the UK's immunisation schedule. As a background to these studies the history of routinely collected data is examined in the context of how we use the data today along with a description of the pre and post-licensure vaccine safety activities which often precede the epidemiological studies. By bringing together the methodological issues of these seven studies and demonstrating the different ways in which these issues have been handled it has created a blueprint for addressing vaccine safety concerns in the future. The seven studies are i) Intussusception and Rotavirus vaccination ii) Narcolepsy in adults and Pandemic Influenza vaccine iii) Convulsions and Pandemic and Seasonal Influenza vaccine iv) Bacterial and Viral Infections and Measles Mumps and Rubella vaccine v) Guillain-Barré syndrome and Seasonal Influenza vaccine vi) Idiopathic Thrombocytopenic Purpura and the second dose of Measles Mumps and Rubella vaccine vii) Bell's Palsy and Seasonal Influenza vaccine.

In conclusion the methodological approaches employed in these studies can be used in the future to assess potential adverse events and the access to routinely collected health data is an essential element of this.

2. Acknowledgements

First and foremost I would like to thank Professor Liz Miller and Professor Nick Andrews who have been wonderful mentors and roles models for me over the years. Both are immensely knowledgeable, kind and patient and have always given me the opportunity to be involved in the great many challenging and exciting studies on vaccine safety which has allowed me to develop in my work. I would also like to thank Professor Brent Taylor for my first experiences in this field and for his humour, expertise and support throughout the years. I will be forever thankful to Angela Bridge for introducing me to the wonders of hospital data and for teaching me so much.

I would like to especially acknowledge my co-authors from the seven papers that make this thesis, for all their individual expertise and their contributions to these studies. My grateful thanks go to Dr Kath Whitehead and Professor Ray Borrow from MMU who have steered me in the right direction during my time with the university.

Profound gratitude goes to my husband Dr Samuel Toffa who has always encouraged me to pursue my career and has made it possible for me to complete this work over the past ten years. Finally special thanks go to my parents for their unfailing support in whatever I do in my life. I would also like to thank Florence and William who everyday inspire me to strive towards my goal.

3. Introduction

The safety of vaccines attracts great interest from both public and scientific communities through media stories and scientific debate. Established methods are in place to assess the safety of vaccines from the development stage through to the pharmacovigilance activities after licensure. These post-licensure activities range from the passive reporting of adverse events to full epidemiological studies to quantify a risk. Key to the post-licensure epidemiological safety study is the ability to identify and use the appropriate data and methods. This thesis will present seven epidemiological studies that were carried out by Public Health England from 2006 to 2016 and use a number of different data sources and methods which all address pertinent vaccine safety concerns.

Chapter 3 briefly describes the history of vaccine safety and its relevance today, the data sources and statistical methods used in the studies and their development and also discuss the ethical and legal frame work which is so critical in the ability to carry out this work. Chapter 4 summarises the seven published studies which this thesis is based on and presents a systematic review of the published evidence on each adverse event under study at the time the research was carried out. Chapter 5 discusses the methodical challenges from setting up a study to communicating the results. This includes a discussion on the many sources of potential bias that are possible when studying such complex conditions in challenging settings and the statistical methods developed to address specific issues in vaccine safety.

3.1 Vaccine safety concerns past and present

There is no doubt that vaccination is one of the most significant health interventions ever developed, successfully controlling many serious diseases and saving countless lives globally. However, as with any medical treatment or drug, vaccination can never be risk-free in terms of unwanted side-effects. Another important factor unique to vaccination is that

unlike therapeutic drugs, vaccines are given prophylactically to healthy individuals, often young children. From the patient's or parent's perspective this changes the benefit to harm balance as the possibility and consequences of a certain serious adverse event occurring outweighs the benefits of being protected by the vaccine from a disease which they know little about. For example, a patient would accept a high incidence of drug-related morbidity in the treatment of cancer but would not tolerate anywhere near this level of distress from a vaccination for a disease which they think will never affect them. The assessment of the risk from an event occurring shortly after vaccination may be incorrect as there may be events that occur in time shortly after vaccination, which would have happened by chance without vaccination. It can be hard to disentangle these temporal associations when there is a strong parental perception that a temporal association is necessarily evidence of a causal association and the timing of the onset of the condition relies on parental recall (Andrews et al., 2002).

Ever since the 18th century when farmer Benjamin Jesty (c. 1736 – 16 April 1816) was one of the first people to deliberately inoculate his wife and two children with cowpox to protect against smallpox, there has been suspicion and mistrust in vaccination (Plotkin & Plokin, 2013). Although Jesty seriously considered the consequences of his actions, and only carried out the procedure when the smallpox outbreak was imminent, he was ridiculed and scorned by his neighbours for injecting his family with an animal disease and never publicised his experiments. Although Jesty was one of the first to deliberately administer the less virulent cowpox to induce immunity to smallpox, it was the work of Edward Jenner, a doctor, twenty years later that was credited with developing the world's first vaccine.

Unfortunately future public health officials did not seem to have Jesty's cautious and thoughtful approach to vaccination when making harm to benefit assessments in the implementation of the new vaccine programmes. In the early 20th century it was a combination of mandatory vaccination programmes and a mild form of smallpox that led to

some people questioning the benefits of vaccination. This together with high profile reports of vaccine related tetanus deaths the anti-vaccine movement began to gain strength. Still today it is these three factors that have damaged vaccination programmes in the developed world. It is this combination of an illness which is perceived not to be a threat, the health official's communication being perceived as dogmatic, combined with notorious historic vaccine safety scares prevalent in the public consciousness. As it did then, more than a hundred years ago, these factors have reduced vaccine uptake and decimated campaigns resulting in the resurgence of the disease (Offit et al., 2013).

Due to the success of vaccination many vaccine preventable diseases are now seen as illnesses confined to history and not a threat to a person's everyday health. Individuals may know others who are unvaccinated but have not been affected by the vaccine preventable disease so feel the optimum strategy is not to be vaccinated and avoid any potential adverse events following the vaccination. These individuals are depending on the indirect protection afforded to them by herd immunity, which relies on the protection afforded to them by others being vaccinated around them. This protection is of course crucial to those who cannot be vaccinated due to an underlying medical condition, but if the vaccine coverage falls below a threshold in the population, this protection can no longer be relied upon. Similarities with the early 20th century anti-vaccine movement can be found with some people disillusioned with the one size fits all approach to medicine turning to alternative practitioners where knowledge is based on personal experience not scientific rigor (Allen, 2007). Often people live and associate with like-minded individuals, so whole communities can be left vulnerable to disease if vaccination is rejected and the benefits afforded from herd protection are drastically reduced as so few in the community are vaccinated.

A key part of ensuring that public confidence in vaccination remains high is to have timely, robust and transparent procedures in place to monitor and investigate vaccine safety

concerns. Although most side-effects from vaccination are minor and self-limiting, such as a fever or a rash at the injection site, on occasion more serious unexpected adverse events can occur (Miller et al., 2007; Stowe et al., 2016a; Stowe et al., 2016b). These can be unexpected adverse events due to the rarity of the adverse event and the limited population available in the pre-licensing clinical trials, or it could occur in a sub-group of the population not significantly represented. Passive reporting systems of adverse events after medicines should identify these rare adverse events if they occur shortly after vaccination, but often a more active surveillance is required. The use of routinely collected healthcare data can be used to investigate and strengthen signals from various sources and to carry out hypothesis-testing epidemiological studies to quantify a risk.

3.2 Routinely Collected Healthcare Data

Healthcare data within the NHS fulfils many purposes, from direct patient care in administration, treatment and diagnosis to being the foundation of the NHS funding system. The data's epidemiological and public health value are seen as secondary purposes. Given epidemiology is not healthcare data's primary role, care must be taken when using such datasets to assess its suitability to address the question being asked and the usefulness in the answer that is produced.

The first statistical study of disease using routinely collected data was carried out by John Graunt in 1662 using 50 years' worth of the weekly Bills of Mortality. He estimated the proportion of live-born children who died before reaching the age of six by producing mortality tables, but as age of death was unavailable he used childhood illness and disease as a proxy for age (Morabia, 2013). Although this early work produced a fairly accurate estimate, the measure of usefulness of any clinical data for epidemiological study is the ability to accurately identify the relevant individual, condition and treatment under study.

Much of the healthcare data within the NHS in England is currently held in physically or logically distinct silos of data. Although secondary care data which includes inpatient, outpatient and emergency episodes are available for all hospitals in England within the NHS, primary care and community health data are held in separate databases with often limited electronic communication between them. Attempts have been made to address this situation with the NHS National Programme for IT (Department of Health, 2011) which endeavoured to have a single, centrally-mandated electronic healthcare record for all patients which would connect primary care and secondary care. This now abandoned but ambitious programme commenced in April 2005 and came under wide criticism in the attempt to deliver this vision due to the spiralling costs, failure to deliver key elements and insufficient attention given to the privacy and security of patient data.

Another difficulty in utilising these data is the manner in which the clinical and diagnostic information are stored. In all these systems' codes are applied to the activities within the health care data or Electronic Healthcare Record (EHR). This enables clinicians, healthcare professionals and financial teams to assess and administer activity. The coding schemes used within each system are unrelated and involve extensive interpretation and understanding to adapt them for epidemiological purposes.

Primary care data

Primary care data is mainly derived from general practitioners in England which are often the first point of contact for many people when they are ill and has the potential to hold a complete medical picture of the patient from birth. Details about the patient's management, treatment, diagnosis, health interventions such as vaccinations, and referrals to secondary care should all be recorded in the GP record.

GP's are paid to carry out specific duties under a national contract, so like the hospital data, information within these systems are also utilised for financial and administrative purposes. A number of systems are used within the NHS and unlike in secondary care there is no national database available for all primary care episodes. This issue was to be addressed by the care.data programme which would collect a minimum dataset for purposes beyond direct care and for the benefit of patient care (NHS England, 2016) in a similar way to HES. In 2014 just months before its implementation the project was irretrievably delayed due to public and clinical concern around privacy and confidentiality.

Primary care data for research can be purchased from a number of providers which have some geographic overlap and usually up to 9% of the population and identifiers such as NHS number and date of birth are unavailable reducing the usefulness of these data in some situations. The main benefit of using these data is the robustness of the immunisation records, for those vaccines given in General Practice, but this is often outweighed by the small population coverage unless the adverse event under scrutiny is fairly common.

Secondary Care Data

The importance of high quality healthcare data has been recognised for many years. Much of this focus has been in secondary care within the NHS which comprises the hospital trusts in England. To fully understand the Hospital Episodes Statistic (Health and Social Care Information Centre, 2016a) data that is used today an explanation is required as to how this data came into existence. A national review of NHS data chaired by Edith Korner produced the first NHS data model which was implemented in April 1987 (NHS/DHSS, 1982). Before this time only 10% of admitted patient records were collected nationally. The focus of the 1982 Korner report was the use of information in the management of care of patients and not for clinical care or epidemiological purposes. It was recognised in the 1982 Kings Fund paper that the manpower and financial data required by Korner was already available and

could be retrieved from personnel and finance departments. The Korner report ambitiously set out to identify a minimum dataset to be collected and included financial, facilities and clinical information all the way through a patient's episode of care. As the dataset was to be focused on the management of patients, it was held in financial years and this has continued today. In order to categorise illness and treatment, individual identification of patients was required. The minimum dataset required the following data to positively identify an individual; sex, geographic code of current address, date of birth, marital status. It was recognised that there were two main concerns; patient confidentiality with holding names on centralised computers and identifying individuals, as twins living at the same address would not be unique. In an article in the BMJ in 1982 commenting on the Korner Report, Black (1982) stated that it is "a matter of fine judgement whether one makes an information system so open that no one will contribute to it, or so confidential that no one can get anything out of it" and noted that excluding names had lessened the clinical and epidemiological value of the system.

The key to the implementation of any healthcare data system is to identify each individual but also strike a balance between usefulness and openness. The NHS number was introduced in 1969 and is a unique person identifier within the NHS system. Prior to 1995 when it was allocated to every birth in England coverage was low. Now it is allocated at the first point of contact with the NHS making it a valuable tool in linking data across the NHS.

This Korner minimum dataset devised in the 1980's now forms the basis of the Hospital Episode Statistics data used in post licensure vaccine safety studies and the NHS number allows linkage to immunisation datasets and the validation of the diagnostic and clinical codes.

Immunisation history data

The national immunisation programme (Public Health England, 2006) is mainly delivered

through primary care at GP surgery's but some vaccines which target specific age groups are given elsewhere, for example, teenage girls are given the Human Papilloma Virus vaccine in schools and babies can be given Bacillus Calmette-Guérin (BCG) vaccine at birth in hospital so neither may have their vaccine recorded in the GP system although it is recommended that this should occur.

The main repository for vaccine information for children under 5 years of age in England are the regional Child Health Information Systems (CHIS) (NHS England, 2015). CHIS are used for the scheduling, recording and monitoring of public health programmes in the NHS from pregnancy to children aged up to 5 years old. Child health areas use a variety of different databases from a range of providers and have inconsistent and limited electronic links with neighbouring CHIS and GP systems. All childhood vaccinations in school, at GP surgeries and in hospital should be recorded in their regional CHIS. School immunisations will be recorded in the CHIS local to the school, not the address of the child.

The immunisation data that each system holds does vary but generally the following relevant information is available; vaccine type in a coded format which is often unique to that regional computer system; dose number which may need further interpretation as it may be coded a first dose if it's the first given in that area but care must be taken to look at the age given as previous doses may well have been given elsewhere or missed; date of vaccination, which is held in a non-standard date field so 32nd of the month is often entered if the day of vaccination is not known; batch/lot number is available in some areas for some vaccines which is held in a free text field. Care must be taken when interpreting vaccine information from CHIS as finding no information on a specific vaccine for a registered child may not necessarily mean that they are unvaccinated due to inconsistent and limited links to other CHIS systems.

Other systems are being developed to improve on the weaknesses of the CHIS and to provide a national immunisation dataset for Public Health use.

Clinical coding

The need to have consistent, retrievable comparable classifications has been recognised by scientists for many centuries with Carl Linnaeus (1707-1778) formalising the modern system of naming groups of organisms. It was the work of William Farr (1807-1883) which grappled with the census data to develop better classifications for diseases and enabled the data to have international uniformity of use (Dunn, 2002). Farr developed a "statistical nosology" which described 27 fatal disease categories to be used by registrars when recording the cause of death in local death registers (Halliday, 2000). Importantly, Farr, in his role as the first Medical Statistician for the General Register Office of England and Wales, saw the need to extend the system of nomenclature from mortality to non-fatal diseases that caused disability (World Health Organization, 2010). This is the basis of The International Statistical Classification of Disease (ICD) which we use today in secondary care data with the classification of diseases that caused morbidity included from 1938 onwards.

In the EHR it is the accuracy of the clinical and diagnostic coding which gives the data its value. Coding within the hospital setting in carried out by trained administrative staff but as Black stated clinicians should accept the responsibility of making diagnostic coding as accurate as possible (Black, 1982). This accuracy has been incentivised over recent years with the Payment by Results scheme (PbR), where certain activities within the hospital are linked to funding. This activity is recorded through the diagnosis and procedure coded data and errors in this data can have a substantial financial impact on the hospital (Peeraully et al., 2016). PbR made clinical coding even more essential although it is still carried out by trained administrative staff. The completeness of coding is variable, with admitted patient care very well completed but not so in outpatient and emergency care data, but it is intended to be an important expansion of the PbR scheme in the future (Department of Health, 2013a). Similarly in primary care the Quality and Outcomes Framework (QOF) is an annual reward

incentivisation programme which changes annually, targeting key indicators such as blood pressure or ethnicity. This is a voluntary process and as it changes annually interpretation of such data items must be done so cautiously.

Types of coding

Within the HES admitted patient care data diagnoses are coded using the ICD10 system. This classification system translates diagnosis of disease and other health problems into alphanumeric codes. Each episode of care can be given up to 20 diagnosis codes with the first diagnosis code being the primary reason for admission. Within each of these episodes, Classification of Interventions and Procedures (OPCS-4) codes can also be applied for operation or procedure carried out within that episode.

The data within General Practitioner databases currently are Read coded, which is also known as Clinical Terms Version 2/3 (CTV3). Developed by Dr James Read, this coding system has been maintained by the HSCIC. It is a much more complex coding system than ICD and contains thousands of terms covering all aspects of patient care including signs and symptoms, treatment, investigations, diagnosis and prescriptions.

When data were held in small databases, interrogation of the information was simpler but in an EHR there needs to be the ability to grow in function and complexity but also for coding to be maintained and relevant (Cimino, 1998). Due to parts of the Read code vocabulary being full, new codes have had to be allocated to unrelated areas in the dictionary. The decision was made for READ terms to be retired from primary care and a new coding system called SNOWMED CT to be used from financial year 2017/18. SNOWMED CT is a merger of CTV/READ and SNOWMED RT, an American system (Health and Social Care Information Centre, 2016b). SNOWMED CT enables changes to be made more easily and is currently used in 27 countries and in over half of European Union countries. It is envisaged that by April 2020 all the NHS, including secondary and social care, will move to

SNOWMED CT to enable better digital sharing of coded data so a fully integrated personal healthcare record can be realised.

Harmonisation of vaccine safety data

The usefulness and interpretation of the conclusion of any study depends on the comparability and definition of the condition under study. There are many circumstances where the ability to have comparable data in studies is advantageous especially in vaccine safety as often the adverse event is rare and requires a large dataset to power the study. This issue could be addressed by pooling data between countries or in a meta-analysis (Andrews et al., 2012). Even if a study can be carried out successfully in a single country having the ability to compare to other studies can help validate the findings.

The use of standard case definitions can be helpful in this task and the Brighton Collaboration has developed case definitions for many potential adverse events following vaccination through international collaborative working groups (Bonhoeffer et al., 2002). The ability to have comparability between studies is valuable but often, due to the variability of the datasets used, the data items required to fulfil standard case definitions are not available from routinely collected datasets so definitions cannot be implemented. To improve its utilisation conditions such as Guillain-Barré syndrome have levels of diagnostic certainty within their Brighton definition so data from electronic databases can be used to implement the definition.

3.3. Pre –licensure

Vaccines like other pharmaceutical products are assessed through phased clinical trials. The purpose of these in terms of safety is to assess the type and frequency of the common adverse events that may occur, for example fever or swelling. This involves the close monitoring and active follow up of events after vaccination. Due to the intensity of this follow up and

monitoring, the size of the population studied has to be limited. Even the largest clinical trial does not have the ability to detect rare adverse events and events that may occur in a sub group of the population. An example of this was intussusception cases following the administration of the rotavirus vaccine where large pre-licensure trials (Vesikari et al., 2006; Ruiz-Palacios et al., 2006) did not identify an increased risk but these trials lacked the power to detect this rare adverse event.

If suspected adverse events are detected but not confirmed in pre-licensure trials an enhanced post-licensure passive surveillance for the conditions of interest is specified as part of a pharmacovigilance risk management plan. In Europe these conditions are reported using standard case definition to the European Medicines Agency (EMA) passive reporting system, EudraVigilance, along with any fatal or life threatening adverse reactions (European Medicines Agency).

3.4 Post-licensure

There are two main areas in post-licensure safety assessment; firstly the detection of an adverse event and secondly the use of epidemiological studies to investigate a possible association and quantify a risk. Both elements are essential to identify and quantify a potential adverse event and must be timely, robust and transparent in order to give the population confidence in the safety of the vaccination programme.

3.4 .1 Signal detection

Many countries have a specific pharmacovigilance system that passively monitor adverse events following vaccination and can detect rare adverse events. In the UK the Medicines & Healthcare products Regulatory Agency (MHRA) administer a passive reporting system for patients and healthcare professionals to report adverse events after utilisation of all healthcare products including vaccines (Medicine and Healthcare Regulatory Agency, 2016). This system called the Yellow Card System monitors these reports to assess whether the background rate of that condition has been exceeded in form of an observed over expected analysis.

As vaccines are often administered in a number of countries and as post-licensure adverse events are rare it is advantageous to pool data in order to detect a signal. EudraVigilance administered by the (European Medicines Agency, 2016) (EMA), is a database intended to be a single repository for all reports of suspected serious adverse events concerning medicines within the European Union. In the United States, the Food and Drug Administration (FDA) run a vaccine specific passive reporting system, The Vaccine Adverse Event Reporting System (VAERS) (Chen et al., 1994). When the pandemic influenza vaccine was introduced in Europe, the core risk management plan stated that individual countries should report certain "Adverse Events of Special Interest" but it was left to the discretion of the countries to monitor other conditions and report to the EMA when necessary. The plan also specified that each country should carry out an observed over expected analysis to assess whether the reports constituted a signal. Any signals raised by the passive reporting system in individual countries or via EudraVigilance were to be discussed by a pandemic pharmacovigilance expert group which was established on a weekly basis discussing any safety concerns.

With an aim to establish a truly global vaccine safety support structure the WHO has established The Global Vaccine Safety Blueprint (World Health Organization, 2012). In low to middle income countries, often pharmacovigilance systems do not exist and this blueprint sets out the minimal capacity needed for a successful pharmacovigilance system. It includes basic principles such as the need for stable funding, designated staff, specific reporting forms and encouraging health professional to report safety issues. These systems will become increasingly important as new vaccines are introduced in such settings.

Another important passive surveillance system which was established in 1978 is the WHO Programme for International Drug Monitoring at the Uppsala Monitoring centre. Its database VigiBase contains spontaneous individual safety case reports and is used by regulatory bodies, the pharmaceutical industry and academia through data requests. It has a

pharmacovigilance network of more than 120 countries but it is dominated by the United States of America which contributed 63% of the reports between 2000 to 2005 (Lindquist, 2008).

Although passive systems can rapidly identify rare adverse events it does rely on the adverse event being seen to be related to the vaccine. Events which occur many weeks after the vaccine, such as narcolepsy, may not be reported to passive systems. This can lead to under ascertainment and reporting bias. Specific statistical methods have been developed to analyse and interpret these passive reports. The proportional reporting ratio compares the proportion of a specific adverse event reports after a vaccine to the reports to another vaccine given to the same age group. Another method is the observed over expected, where an expected incidence of the condition is calculated based on the background incidence and compared to the observed incidence. This method has the advantage of allowing for different levels of under reporting.

A method which tries to address some of these issues with the passive reporting system uses large routinely collected data to identify new adverse events in real time. At regular intervals, the system uses a large dataset to investigate pre-specified adverse events of interest, meaning that issues with selected or underreporting through passive systems are avoided (Leite et al., 2016).

3.4.2 Signal strengthening- active surveillance

Once a signal has been detected often a more detailed investigation is needed before a full epidemiological study is performed. This phase can be called signal strengthening. Ecological studies using large routinely collected datasets are often carried out if the coverage of the vaccination is high in a certain population. It can look at disease rates over time and if a vaccine is newly implemented, before and after the vaccine was introduced. The vaccination status of the individual is not required as it is only the rate of the condition of

interest that is compared. These studies can be used to help identify the need for further hypothesis-testing studies.

3.4 .3 Individual Causality assessment

Epidemiological studies cannot be used assess causation on an individual level but this individual detailed assessment is needed in some instances, for example when a product specific or vaccine delivery issue is suspected. The World Health Organisation has published a methodology to be used to guide health professionals and public health officials to try and assess a causal relationship with the vaccine in a systematic manner (World Health Organization, 2013). It uses information on clinical history and timing to come to a conclusion but this is reliant on timely high quality information. The criteria used to assess the Adverse Events Following Immunisation (AEFI) includes; a temporal relationship; population evidence for causality; biological plausibility; consideration of alternative explanations and evidence of the vaccine causing the same event in the individual previously.

3.4 .4 Hypothesis Testing-epidemiological studies

In order to establish whether the signal seen is associated with the vaccine and to quantify the risk a formal epidemiological study is needed. This requires a pre-specified protocol detailing the population under study, the period after vaccination which an elevated risk is suspected and the methods for case identification and statistical analysis. Most importantly the ascertainment of the condition of interest must be unbiased with respect to vaccination history (Miller & Stowe, 2012).

Few countries have the capacity to carry such studies in the timely manner needed to address imminent vaccine safety concerns as pre-established systems are needed with timely data in the population of interest. In the US, the Vaccine Safety Datalink (VSD) established in 1990 uses electronic health data from nine health care organisations which includes the date of vaccination, emergency and hospital admissions (Centers for Disease Control and Prevention,

2016). In response to the H1N1 influenza pandemic in the US the Food and Drug Administration (FDA) established a post-licensure rapid immunization safety monitoring program (PRISM) which actively monitors the safety of medical products using electronic health information (Baker et al., 2013). It uses health insurance claims databases and links these with immunisation registries for 50 million individuals making this dataset unique in its size and geographic diversity and its ability to detect rare adverse events following vaccination.

In Demark a national cohort is available with a person identifier linking vaccine history, hospital admissions, and disease registers (Hviid, 2006). Similarly in Finland, where since 2004 up to 90% of primary care centres, where vaccines are given, have computerised medical records making data linkage to hospital records to adverse event monitoring possible (Postila & Kilpi, 2004). Since the early 1990's Public Health England has used national hospital admission data linked on the person identifier to regional vaccine history databases to assess vaccine associated adverse events (Nash et al., 1995). It also uses primary care data for conditions seen in General Practice. For rare conditions, PHE also has the ability to contact an individual's general practitioner to obtain vaccine history data as it has legal permission to use and process such data for the good of public health (The Stationary Office, 2012).

3.4 .5 Epidemiological Statistical methods

Ecological

The ecological design is often used at the signal strengthening stage of post-licensure vaccine safety assessments. An ecological study compares the rate of an adverse event in the relevant population with different vaccine exposures without obtaining information on the individual. This can be most effective when a vaccine has been introduced into a national schedule for a certain age group and high coverage has been achieved. In this situation a pre and post

vaccine assessment can be made in relation to the adverse event under scrutiny. This method has also taken advantage of short catch-up campaigns such as the 2-week mass MMR campaign when all children aged 1-11 in August 1997 were targeted for vaccination because that is when the peak of cases of aseptic meningitis was seen (Dourado et al., 2000).
This design cannot establish causation or quantify a risk but is seen as an exploratory analysis with the view to inform the epidemiological hypothesis-testing stage of the assessment. Ideally this epidemiological hypothesis-testing stage should be carried out in a separate dataset from which the hypothesis was generated or strengthened. If sufficiently large enough the database could be split in half with one half used to conduct an exploratory analysis and the other half to test any hypotheses generated. It must be remembered that any bias in relation to the way the data were collected would be inherent in both studies.

Cohort

Cohort studies need to be very large to detect rare vaccine adverse events and this often makes them impractical for a prospective study. Retrospective cohort designs can use routinely collected data and cases identified by clinical coding but this study design may be disadvantaged by the need to collect a great number of confounding variables. The advantage is that an entire population is studied and relative and absolute incidence estimates can be reported. In a cohort study the risk of developing the condition is compared in the vaccinated and unvaccinated. When studying a vaccine which is given as part of a national schedule and high coverage is achieved, the small unvaccinated group may be very different in terms of underlining illness and demographics from the vaccinated group. Also, care must be taken to insure unvaccinated cases are indeed unvaccinated and the data are not missing. This can occur when regional vaccine datasets are used and transfer and sharing of data are not comprehensive.

Case-Control

A case-control study requires smaller numbers than a cohort study but the same confounding and bias can occur but it also has the added difficulty of selecting the correct controls for comparison. For vaccinations given in the short age range in the first and second year of life the close matching of the controls on date of birth is required. To obtain enough power to assess the required risk, multiple controls per case are often needed. Selecting a relevant control condition can be problematic and a novel approach to address this issue called the test-negative design has been used in measuring influenza vaccine effectiveness (Jackson & Nelson, 2013) and could potentially be used for vaccine safety studies. It uses all patients tested for a certain condition and calculates the ratio of the odds of vaccination in those testing positive for the condition to the odds of vaccination in those testing negative. This design can have two benefits as it can be less prone to misclassification of the condition as it is using a diagnostic test to identify the case but additionally it controls for differences in healthcare-seeking behaviour.

Case Only Methods

The self-controlled case-series method was specially designed for rapid unbiased assessment in vaccine safety studies (Farrington, 2004). The cases act as their own controls as the incidence in pre-defined risk-periods following vaccination are compared to the incidence outside the risk period. As individuals are matched to themselves, individual level confounders are controlled for. Adjustment for time varying confounders such as age is also possible. It has been demonstrated that the power of the SCCS method is nearly as good as a cohort study when uptake is high and risk intervals are short, and it is superior to that of a case control study (Andrews, 2001). A consideration when using the SCCS method is when individuals with the condition of interest postpone vaccination this gives a pre-vaccination low period (Stowe et al., 2009b; Stowe et al., 2009a; Stowe et al., 2011). When this is evident (Figure 1) this pre-vaccination low period should be removed as it is included in the

background rate for the SCCS calculation and if included would bias away from the null hypothesis.

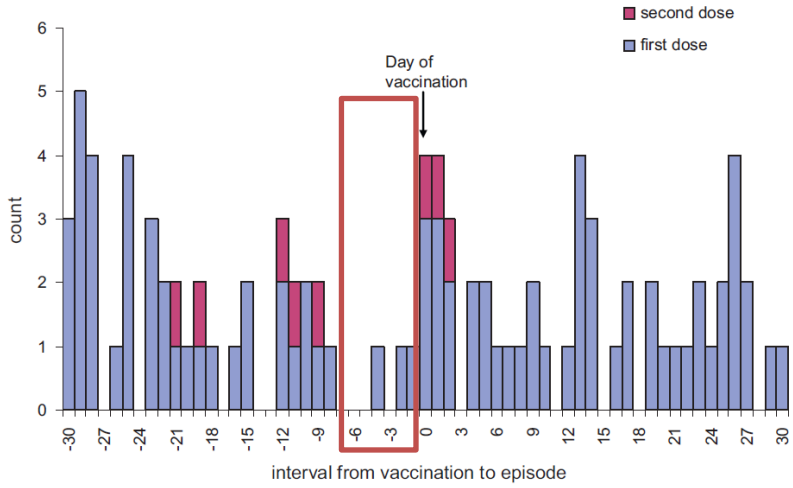


Figure 1: An example of the pre-vaccination low period in episodes of convulsions in the two weeks prior to vaccination with pandemic influenza vaccine

The case crossover design is similar to the self-controlled case-series method and can be used for rare acute conditions when the exposure period is short and has been used in vaccine safety assessments. The proportion exposed is compared in the equally sized risk and control periods and analysed using conditional logistic regression (Andrews, 2001; Maclure, 1991)

The case-coverage design is another approach recently used in vaccine safety studies. It is similar to the screening method but until now has been primarily used for vaccine effectiveness assessment (Farrington, 1993) although it is more limited in terms of adjustment for possible confounders than the SCCS method. Each case is matched to a population coverage estimate and this is then used to see if the number of cases vaccinated is greater than expected. The method uses logistic regression on the odds of vaccination with an offset for the log-odds of the matched population coverage so it is similar to a case control study with 1000's of controls per individual.

3.5 Ethical and Legal Framework

Routinely collected healthcare data is an indispensable tool for epidemiological research but in vaccine safety surveillance these databases can never be used without the consideration of a great number of factors specific to the disease and vaccine under scrutiny. Also underlining every vaccine safety study is the ethical and legal framework within which this work is carried out. The need to carry out vaccine safety studies must be balanced with the rights of the individual to privacy and confidentiality of their medical records against the biases that might arise as a result of selected participation.

Data deemed as identifiable does not necessarily include the identifiers such as name, address or even NHS number, but a combination of different data items such as name of hospital, date of admission and diagnosis that could disclose a person's identity. Due to this deductive disclosure there is often a requirement for small cell numbers to be supressed in Tables when the data are published.

Research studies carried out in the NHS are approved by the Health Research Authority's National Research Ethics Service (Health Research Authority, 2016). The post-licensure vaccine safety surveillance carried out by PHE is not classed as research but public health so ethics committee approval is not required. There are key principles and legalisations which govern how data can be used in vaccine safety studies and these are outlined here.

Data Protection act

The main piece of law in the UK that protects an individual's data is The Data Protection Act and provides a way of individuals to control the information held about themselves (Great Britain, 1998). It covers all types of data on living people both administrative and health. The act defines "personal data" as any data that can be used to identify an individual. It also describes eight protection principles. Under the act individual consent is required to collect and use the data

Health Service (Control of Patient Information) Regulations 2002

Although the Data Protection Act 1998 specifies that individual consent is required for use of data, in England and Wales there is a legal basis for using patient identification information without individual patient consent. Public Health England is able to process identifiable data under Regulation 3 of The Health Service (Control of Patient Information) (Secretary of State for Health, 2002). This is for purposes related to communicable diseases and other risks to public health and includes the delivery, efficacy and safety of immunisation programmes and adverse reactions to vaccines and medicines.

Caldicott review

A review was commissioned by the Chief Medical Officer in England in 1997 to investigate concerns around the use of patient information in the NHS and to ensure confidentiality was maintained. These concerns stemmed from the growing use of electronic data and its ability to quickly distribute sensitive personal data. The review was chaired by Dame Elizabeth Caldicott and six key principles were established. These principles, known as the Caldicott Principles, set out who, what and how patient information should be used (Department of Health, 2013b).

A recommendation to come out of the review was the appointment of a Caldicott Guardian in every NHS organisation. This person should be a senior health professional who has the responsibility to keep patient data secure and ensure the Caldicott Principles are upheld in the management and use of data in their organisation.

Assumed consent

When a person is absent from a dataset it can be difficult to assess the reason for this. It could be for a number of reasons such as they have not had the opportunity to opt in or were not aware of the need for this or actively did not want to participate. The reasons behind this

are also multi-factored but it is crucial if the reason for non-participation is related to vaccination. The advantage of many routinely collected databases is that assumed consent is applied allowing investigators to have a representative population. This assumption has been challenged recently when an NHS initiative was launched to make all GP records centrally available for purposes beyond direct care (NHS England, 2016). In an attempt to address the issue of deemed consent a leaflet was delivered to every household in England stating that anyone wanting to opt out "should speak to" their GP. Unfortunately many did not receive this leaflet and those that did were left not knowing who was to have access to their data and a public debate in the media ensued around the transfer and use of patient and health data.

Paradoxically this NHS initiative which aimed to maximise the potential of patient data has had the opposite effect and has now been abandoned but with serious consequences for epidemiology. The misinformation surrounding data sharing and its importance has led to many patients applying to a new Government scheme to allow patents to opt out and not to have anything that could identify themselves shared beyond their GP practice. A bias towards the null hypothesis could occur if the vaccinated patients who have also had the adverse event under study opt out of sharing their data. This would be more likely to happen if the hypothesis is in the public consciousness for example with in the erroneous association with MMR and Autism.

Opt-out requests are not carried out in certain situations including when the data are used to support the management of communicable disease under Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002 under which the vaccine safety work at PHE is carried out. Statistics on the opt-out rate from July 2016 show that 2.2% of patients have opted out but this ranges from 0.2 to 13.3% in some areas (Health and Social Care Information Centre, 2016c). It is important that the public are confident in the systems in place to protect their data and that it is being used in a responsible manner. This confidence

is gained if systems are transparent and their effectiveness and usefulness demonstrated in a robust manner.

3.6 Summary

Many of these issues are discussed in the seven studies presented here in this thesis. The studies optimise routinely collected coded data from various data sources for vaccine safety assessments carried out over a ten year period in which the legal framework has evolved. Going forward the demonstration of the value of patient data from such studies will be needed in any conversation with the public on data sharing. There is a responsibility to use the data in the appropriate manner and so in this thesis the epidemiological methods used are critically appraised and the challenges highlighted in order to inform future studies.

4. Critical account of published works

Seven studies have been selected which have focused on a number of different safety concerns and demonstrate the epidemiological methods needed to quantify a risk, if any, of an adverse event after vaccination. The studies described here were the first studies in England and in many cases the first in Europe to test the specific hypothesis. The results from these studies have been used to support the national immunisation programme by advising health professionals and policy makers.

This thesis is comprised of seven publications which are presented in Chapter 7. A full list of the publications in the area of vaccine safety is given in Appendix II. The seven studies are summarised in Table 1 detailing the study question, data sources, design and results.

In this chapter each study in the thesis is critically reviewed and a systematic review carried out using PubMed, a search engine accessing the MEDLINE database which holds abstracts and references in the fields of life and biomedical sciences (United States National Library of Medicine, January 1996).

4.1 Study 1: The risk of intussusception following rotavirus vaccination

Aim: Using hospital admission data this study investigated the risk of intussusception following either the first or second dose of the Rotavirus vaccine (RV1) in infants in England.
Systematic review: A systematic review was carried out using the following search terms: rotavirus"[MeSH Terms] OR "rotavirus"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]) AND ("intussusception"[MeSH Terms] OR "intussusception"[All Fields]).
This search retrieved 209 articles (Appendix 1). There were 199 published prior to our study with the first from the US VAERS passive reporting system reporting an increase of intussusception after the now withdrawn rotavirus vaccine- Rotashield™ (Centers for Disease

& Prevention, 1999). Eleven of the studies investigated the risk after this now withdrawn vaccine, Rotashield™. In 2004 a new rotavirus vaccine was introduced into Mexico (Perez-Vargas et al., 2006) with the US following in 2006 (Centers for Disease et al., 2008). The epidemiological studies carried out before the introduction of the new generation of Rotavirus vaccines assessed the characteristics of intussusception cases and looked at the background rates in various populations in preparation for the introduction of the vaccine, so that passive reports could be interpreted accurately (Kramarz et al., 2001; Chang et al., 2001; Saez-Llorens & Guevara, 2004).

There were 10 epidemiological hypothesis-testing studies that investigated the risk after the monovalent Rotavirus vaccine (RV1), the vaccine that is used in the UK childhood schedule. All but 2 studies (Perez-Vilar et al., 2015; Buttery et al., 2011) reported a small increased risk after the first dose of this new rotavirus vaccine. The risk after the second dose remained uncertain (Patel et al., 2011; Carlin et al., 2013; Yih et al., 2014; Yung et al., 2015; Velazquez et al., 2012; Weintraub et al., 2014; Haber et al., 2015; Bauchau et al., 2015).

Summary: Intussusception was first identified as an adverse event following rotavirus vaccination in the 1990's. Intussusception is a telescoping of the intestine and the most common cause of bowel blockage in infants. The first rotavirus vaccine, Rotashield® was withdrawn from the market after it was shown in the United States to have a 20 to 30 times increased risk of intussusception (Murphy et al., 2001). Now two new rotavirus vaccines have been developed the monovalent Rotarix (RV1) and pentavalent Rotateq (RV5). The work which this study concentrated on concerns the monovalent Rotarix which was introduced in the UK in July 2013. It was shown to be effective. The uptake of the rotavirus vaccine was immediately high and a reduction in rotavirus cases was seen in both laboratory confirmed cases and hospital cases of gastroenteritis (Atchison et al., 2016).

To determine whether there was a risk of intussusception after Rotarix vaccination in England, Hospital Episode Statistics (HES) data was used to identify infants aged 42 to 183

days from the start of the national Rotavirus immunisation programme until October 2014, with an ICD10 code for intussusception from any of the 1-20 diagnosis fields in their record (Stowe et al., 2016a). Using a questionnaire, rotavirus vaccine histories were independently ascertained from individual's General Practioners (GPs) as this is where the vaccine had been given. In order to identify the date on which the symptoms of intussusception started, data was initially collected from GPs as primary care is often the first point of contact following adverse vaccination events. In addition, a copy of the hospital discharge summary from the GP was requested so that the hospital coding could be validated and the Brighton diagnostic certainty levels assigned without knowledge of the vaccination status (Bonhoeffer et al., 2002). To assist with the Brighton classification any relevant surgical or procedure codes specific to the intussusception admission and treatment was also extracted from HES.
Using the self- controlled case- series method, three risk periods after vaccination were assessed, 1-7, 8-21 and 1-21 days overall. In addition a meta-analysis was performed combining these results with studies from Australia, Mexico, Brazil and Singapore, where the same vaccine was used.

New knowledge gained from this study: This study was able to estimate that the rotavirus vaccine programme had caused around 21 intussusception admissions annually in England. As a previous study had shown that the vaccination programme had prevented 25,000 gastro-intestinal infection admissions (Atchison et al., 2016) this study was able to conclude that the overall benefit/risk profile remains strongly positive. This study was the first in the European region to demonstrate an association and the first using a schedule in which the second dose is given at 3 months of age (a lower age than most schedules) which is of importance as the risk of intussusception increases with age.

There have been eight studies published since this study. The eight papers include three investigating the impact of the vaccine on the disease but no further epidemiological

hypothesis-testing studies quantifying the risk of intussusception from the Rotavirus vaccine have been published.

4.2 Study 2: Narcolepsy in adults following the administration of the Pandemic Influenza Vaccine

Aim: To assess the association, if any, between narcolepsy and pandemic influenza vaccine in adults using data from sleep centres in England and vaccine histories independently obtained from GP practices.

Systematic review: A systematic review was carried out using the following search terms: ("narcolepsy"[MeSH Terms] OR "narcolepsy"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND ("vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields]) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields])

This search retrieved 38 articles (Appendix 1) with 36 published prior to our study. From these 36 studies nine studies were epidemiological hypothesis-testing studies but only two included adults in their study (Persson et al., 2014; Dauvilliers et al., 2013).

Both of these studies had significant methodological challenges; in the French case-control study (Dauvilliers et al., 2013) 28% of potential cases declined to take part and the onset of the narcolepsy symptoms were based on patient recall which could lead to an overestimation of an association. The Swedish study saw no overall increase in adult cases but the diagnosis date was used as the index date which could potentially lead to an underestimation of the association (Persson et al., 2014). The remaining articles were narcolepsy incidence studies, commentary articles or laboratory studies looking at the possible biological mechanism.

Summary: In this study the risk of narcolepsy in adults following pandemic influenza vaccine was assessed. An increased risk of this serious sleep disorder following the 2009 pandemic influenza vaccine, Pandemrix, had been established in children in a number of countries including England where Miller et al. (2013) confirmed a 14-fold increase risk in 4 to 18 year olds but studies in adults remained inconclusive. Stowe et al. (2016b) looked at the risk in adults using a similar methodology to the Miller et al. (2013) study. Unlike other conditions it was found that Narcolepsy was not reliably coded in HES. It was possible to use HES to assess which centres diagnosed narcolepsy but extensive manual searches of databases were required and were then supplemented with the HES cases. A possible 1446 cases were identified but most were excluded as their symptoms started before 2009 or were not narcolepsy when the notes were reviewed. To independently assign the case definition to the remaining possible cases, an independent panel of narcolepsy experts was convened to assign the diagnostic criteria without knowledge of their vaccine history.

As the vaccine was given by GPs, a questionnaire was designed which requested a first symptom date, their vaccine history and in addition whether the patient had a condition that put them in a risk group to make them eligible for the pandemic vaccine.

Using the 40 confirmed cases, the case-coverage analysis method was applied and gave a significantly increased risk, with an odds ratio of 4.24 (95% confidence interval 1.45-12.38) and an attributable risk of 0.59 cases per 100,000 doses, but this was lower than the risk seen in the childhood study with an attributable risk of 1.74 per 100,000 (Miller et al., 2013).

New knowledge gained from this study: This study showed the causal association between narcolepsy and pandemic influenza vaccine was not confined to children as had been previously thought. This study will have implications for those who are seeking compensation for vaccine injury as previously only epidemiological evidence for children had been available.

Subsequent to this study only one study has been published. This is a statistical methods paper analysing the effect of multiple bias in the epidemiological hypothesis-testing studies.

4.3 Study 3: Convulsions following Pandemic and Seasonal Influenza Vaccines

Aim: To use the General Practice Research Database to investigate whether there was an increased risk of convulsions following monovalent H1N1 influenza vaccine in the 2009/10 season and also following administration of the seasonal influenza vaccine.

Systematic review: A systematic review was carried out using the following search terms: ("safety"[MeSH Terms] OR "safety"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]) AND ("seizures"[MeSH Terms] OR "seizures"[All Fields] OR "convulsions"[All Fields])

This search retrieved 41 articles (Appendix 1) with 10 published prior to our study. There were three papers from passive reporting systems reporting fever and seizure as the two most common serious adverse events after influenza vaccine. A rise in febrile convulsions after a specific brand of influenza vaccine was also reported in New Zealand (Petousis-Harris et al., 2011). In a study looking at passive reports after the pandemic MF59-adjuvanted H1N1 vaccine, no increase in reporting was seen when compared to the seasonal vaccine (Banzhoff et al., 2011).

Summary: In this third study the risk of convulsions was assessed after the pandemic and seasonal influenza vaccine was administered. Febrile convulsions can occur in young children and are due to a sudden rise in body temperature which can be caused by an infection or a vaccine. The pandemic influenza vaccine was known to be reactogenic

especially for fever in children and there had been limited studies assessing the risk of this following vaccination with the seasonal influenza vaccine.

Stowe et al. (2011) used primary care data to look at the question of an increase in convulsions after vaccination with the pandemic and seasonal vaccine. The convulsion coding had previously been validated in a study (Andrews et al., 2010) by reviewing the free text comment entered by the GP around the time of the consultation and it had been found it to be robust. A code list was developed for the exposures, the pandemic and seasonal influenza vaccine and the outcome of interest, the convulsions. It was found that a specific code for "febrile" convulsions was not available within the coded data. HES data admissions for convulsions in children under 10 years of age were also extracted so that the age distribution could be compared to the General Practice Research Database (GPRD) and this was found to be similar.

Using the self-controlled case-series method it was demonstrated that there was no increased risk of convulsions in the week after receiving either of the vaccines but it was determined that there was a signal of an elevated risk in the first few days after the second dose of the pandemic vaccine 3.48 (95% confidence interval 0.86-14.07).

New knowledge gained from this study: Although the pandemic influenza vaccine had been reported to be reactogenic especially for fever in children this study saw no increased risk of convulsions following either the pandemic or seasonal influenza vaccine. As influenza itself can cause fever, convulsions and serious neurological disorders (Moore et al., 2006; Chiu et al., 2001; Kwong et al., 2006), this study provides evidence for extending the current UK influenza programme in healthy children.

Following this study the risk of febrile seizures after inoculation of the influenza vaccine has been closely monitored through passive reporting and active surveillance systems and it has been reported that the risk differs according to the brand of influenza vaccine administered (Petousis-Harris et al., 2012; Brady et al., 2014).

4.4 Study 4: The risk of Bacterial and Viral Infections following Measles Mumps and Rubella Vaccine (MMR) Vaccine

Aim: Using data linkage techniques and data from hospital admissions and regional immunisation databases, the hypothesis was tested that infections should increase after vaccination due to the vaccine inducing an "immune overload" allowing for opportunistic bacterial and viral infections.

Systematic review: A systematic review was carried out using the following search terms: Immune[All Fields] AND overload;[All Fields] AND ("Mil Med Res"[Journal] OR "mmr"[All Fields]) AND ("measles"[MeSH Terms] OR "measles"[All Fields]) AND ("mumps"[MeSH Terms] OR "mumps"[All Fields]) AND ("rubella"[MeSH Terms] OR "rubella"[All Fields])

This search retrieved 5 articles (Appendix 1) with 3 published prior to our study. These included a study published in 2005 reporting that physicians decline or delay their own children's combined vaccinations, such as MMR (Posfay-Barbe et al., 2005). Another study reported British parents' concern with regards to their child's immune system being able to cope with combined vaccines (Hilton et al., 2006).

Summary: The hypothesis that multi-antigen vaccines, such as the MMR, might overload the immune system and make an individual susceptible to other infections was being debated around the time when many parents were still concerned about these vaccines due to the erroneous link between MMR and Autism. Stowe et al. (2009b) used established record linkage methods (Nash et al., 1995) to link child health immunisation data from the Child Health Information System (CHIS) to hospital admission records from the North Thames region. After a code list was designed to identify a number of bacterial and viral infections,

children aged 12-23 months with a relevant ICD9 or 10 codes were linked by NHS number or by sex, date of birth and postcode to the immunisation history data.

Using the self-controlled case-series method, no evidence of an increase in bacterial and viral infections following vaccination using the MMR vaccine was seen, except for an increase in herpes infections in the 31-60 days post vaccination (Relative Incidence 1.69 95% confidence interval 1.06-2.70). Analysis was also carried out on data from individuals those given the Meningococcal serogroup C (MCC) vaccine concomitantly, in which no increased risk was seen. Thus, this work concluded that the study did not support the hypothesis of an induced immune deficiency due to overload of the immune system from multi-antigen vaccines.

New knowledge gained from this study: At the time of publication uptake of the MMR vaccine remained sub-optimal so this study gave reassurance to parents concerned about giving multi-antigen vaccines such as MMR. This work continues to be of relevance and provides reassurance as new vaccines are developed and added to the childhood immunisation schedule in the UK.

Since this work was published there has been one study published in relation to this topic which discusses parents' decision-making ten years following the MMR controversy (Brown et al., 2012). This study also has relevance to the non-specific effects hypothesis which suggests that a live vaccine, such as MMR, not only protects against the pathogens to which the vaccine being administrated is specific but it also has other broader effects (Sorup et al., 2014).

4.5 Study 5: Investigation of the risk of Guillain-Barré syndrome (GBS) following Seasonal Influenza vaccine

Aim: The General Practice Research Database (GPRD) was used to test the hypothesis that

there was an increased risk of Guillain-Barre syndrome post vaccination with parenterally administered inactivated influenza vaccine and also after influenza-like-illness.

Systematic review: A systematic review was carried out using the following search terms: ("guillain-barre syndrome"[MeSH Terms] OR ("guillain-barre"[All Fields] AND "syndrome"[All Fields]) OR "guillain-barre syndrome"[All Fields] OR ("guillain"[All Fields] AND "barre"[All Fields] AND "syndrome"[All Fields]) OR "guillain barre syndrome"[All Fields]) AND ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields]) AND ("vaccination"[MeSH Terms] OR "vaccination"[All Fields])

This search retrieved 215 articles (Appendix 1) with 64 published prior to our study. This included the first reports of GBS following the swine influenza vaccine in military personnel in 1976 and an epidemiological study which reported a risk of one case per 100,000 vaccinations. Further epidemiological studies followed in the subsequent influenza seasons with no increased risk reported (Schonberger et al., 1979; Kaplan et al., 1982; Roscelli et al., 1991; Lasky et al., 1998). More recently some studies have reported a small risk (Juurlink et al., 2006). In passive reporting systems such as VAERS in the United States (US) GBS remains the most reported neurological condition following vaccination with seasonal influenza vaccine (Haber et al., 2004).

Summary: This study was carried out before the influenza pandemic in 2009 as part of the pre-pandemic preparedness work. Stowe et al. (2009c) carried out a study looking at the risk of Guillain-Barré syndrome (GBS) after seasonal influenza vaccination because the 1976 national program for swine influenza vaccination in the United States was suspended after an increased risk of GBS was seen following vaccination and also because further studies had found conflicting results.

GPRD data was used because most symptoms of GBS are initially reported to primary care

providers and then referred to hospital for tests and formal diagnosis. The cases were selected using the relevant READ codes and a two stage validation was carried out for those who had received at least one dose of vaccine. Firstly the patient profile was reviewed, which was a summary of the whole patient record, in order to identify confirmatory symptoms such as limb weakness at the time of diagnosis and to identify the onset date of any earlier symptoms. The anonymised free-text comments recorded by the GP for one week before the coded GBS consultation and 23 weeks after that date were also used. To validate the recording of GBS in the primary care setting, HES admission records for GBS over the same period were compared and found to follow a similar seasonal pattern with a peak incidence of admissions in January. Along with the influenza vaccine records, influenza-like illness records were also identified to assess the risk. The self-controlled case-series method was used and found no evidence of an increased risk in the 90 day period following vaccination but in contrast an increased risk was seen following influenza-like illness which was consistent with anecdotal reports of GBS following respiratory illness.

New knowledge gained from this study: This study identified a risk of GBS following influenza-like illness but not following the influenza vaccine and it was used in the 2009 influenza pandemic as it had important implications for the risk/benefit assessment of using pandemic vaccines in England.

Following publication of this study and the subsequent 2009 influenza pandemic the risk of GBS following influenza vaccine remains unclear. Although our study saw no increased risk more recent studies have found a small increased risk (Prestel et al., 2014; Kwong et al., 2013; Dodd et al., 2013).

4.6 Study 6: Investigation of the risk of Idiopathic Thrombocytopenic Purpura (ITP) following the second dose of MMR

Aim: Following the establishment of an association between ITP after MMR vaccination, Hospital Episode Statistics data and computerised vaccination records were linked to investigate the hypothesis that there was an increased risk of ITP following the second dose of the MMR vaccine.

Systematic review: A systematic review was carried out using the following search terms: ("purpura, thrombocytopenic, idiopathic"[MeSH Terms] OR ("purpura"[All Fields] AND "thrombocytopenic"[All Fields] AND "idiopathic"[All Fields]) OR "idiopathic thrombocytopenic purpura"[All Fields] OR ("idiopathic"[All Fields] AND "thrombocytopenia"[All Fields] AND "purpura"[All Fields]) OR "idiopathic thrombocytopenia purpura"[All Fields]) AND ("measles"[MeSH Terms] OR "measles"[All Fields]) AND ("mumps"[MeSH Terms] OR "mumps"[All Fields]) AND ("rubella"[MeSH Terms] OR "rubella"[All Fields]) AND ("vaccines"[MeSH Terms] OR "vaccines"[All Fields] OR "vaccine"[All Fields]).

This search retrieved 24 articles (Appendix 1) with 13 published prior to our study. This included three case reports on ITP, three incidence studies using passive reports of ITP after vaccination, a statistical methods paper using ITP vaccine safety data and five hypothesis-testing studies assessing the risk after MMR (Black et al., 2003; Andrews et al., 2007; Rajantie et al., 2007; Miller et al., 2001b; Farrington et al., 1995). None of these five studies assessed the risk specifically after the 2nd dose of MMR vaccine. When a search was carried out using PubMed using the search terms “idiopathic thrombocytopenia purpura, measles mumps and rubella vaccine, second dose” no articles were found that were published prior to our study.

Summary: An estimated risk of 1 in 22,000 in the 6 weeks following the first dose of MMR vaccine had previously been reported by Miller et al. (2001a) but the risk after the second dose had not been assessed. Stowe et al. (2008) extracted HES admission records for ITP in

children aged 3 to < 6 years and linked these to CHIS immunisation records for the second dose of MMR vaccine. Validation of the hospital discharge diagnosis coding had previously been performed to confirm the validity of the coding and was therefore not repeated for this study.

Analysis was carried out using the self-controlled case-series method and a relative incidence during the 6 weeks after vaccination was estimated to be 1.04 (95% confidence interval 0.37-2.92) and the study concluded that there was no evidence of an increased risk during the 6 weeks following the second dose of MMR.

New knowledge gained from this study: This study provided reassurance that the established small risk after the first dose of MMR does not extend to the second dose.

The risk of ITP following MMR continues to be observed (Bertuola et al., 2010; Svanstrom et al., 2010; Owatanapanich et al., 2014) but this risk has not been seen following other childhood vaccines (O'Leary et al., 2012).

4.7 Study 7: Investigation of the risk of Bell's Palsy following Seasonal Influenza Vaccine

Aim: The General Practice Research Database (GPRD) was used to investigate the signal indicated by the passive reporting systems and to test the hypothesis that there is an increased risk of Bell's palsy post parenteral inactivated influenza vaccine

Systematic review: A systematic review was carried out using the following search terms: ("bell palsy"[MeSH Terms] OR ("bell"[All Fields] AND "palsy"[All Fields]) OR "bell palsy"[All Fields] OR ("bell's"[All Fields] AND "palsy"[All Fields]) OR "bell's palsy"[All Fields]) AND ("influenza vaccines"[MeSH Terms] OR ("influenza"[All Fields] AND "vaccines"[All Fields]) OR "influenza vaccines"[All Fields] OR ("influenza"[All Fields] AND "vaccine"[All Fields]) OR "influenza vaccine"[All Fields])

This search retrieved 20 articles (Appendix 1) with 8 published prior to our study. This included two studies that used from passive reporting systems, a case-control study reporting an increased risk, three letters commenting on these studies and two studies not related to vaccine safety, one study on the benefits of the vaccine in inducing a local mucosal response and a study on Bell's palsy as a condition.

Our study was the first epidemiological hypothesis-testing study to be carried out following publication of the case control study from Switzerland reporting a risk of Bell's palsy following the intranasal vaccine (Mutsch et al., 2004). Prior to this the VAERS passive reporting systems in the US saw a possible signal between influenza vaccines and Bell's palsy (Zhou et al., 2004). Since the introduction of the new live attenuated influenza vaccine nasal spray for children in the US, the VAERS passive reporting system has shown no unexpected serious risks with this specific influenza vaccine in its first two seasons (Izurieta et al., 2005).

Summary: The question of a possible risk of Bell's palsy following vaccination with the influenza vaccine was raised after a Swiss study by Mutsch et al. (2004) found an increased risk following the nasal inactivated formulation of the vaccine. Cases of Bell's palsy usually present in primary care, therefore Stowe et al. (2006) selected the GPRD to carry out this study. After selection of the cases a validation of the data was carried out using the patient profile of a randomly selected sample of cases and a diagnosis was confirmed if a relevant prescription was found within a month of diagnosis and no other reason for this prescription was identified. The GP's free text comments were also assessed for the episodes where the diagnosis could not be confirmed using the patient profile and for events on the day of vaccination. When the analysis was carried out using the self-controlled case-series method there was no increased risk seen in the three months following vaccination. However, when the cases on the day of vaccination were compared, a significantly increase in risk of Bell's Palsy was seen (RR 4.38 (95% confidence interval 2.47-7.79)). These cases of Bell's palsy on

the day of vaccination were reviewed by reading the free text held within the electronic record and it was found that the Bell's palsy cases were historical and were opportunistically recorded when the patient came for their influenza vaccination.

New knowledge gained from this study: This study provided reassurance to the UK influenza vaccine programme because no increased risk was seen of Bell's palsy in the three months following the paternal influenza vaccine and it indicated that the risk seen with the intranasal vaccine may be specific to that vaccine.

Following our study it has been confirmed that the adjuvant in the nasal vaccine was a causal factor in the increase of Bell's palsy (Lewis et al., 2009). Although we found no association with the parenteral vaccine case reports have been published (Chou et al., 2007) and an increased risk has been reported after administration with the pandemic influenza vaccine (Bardage et al., 2011; Lee et al., 2011).

Table 1: Details of data sources and study questions

Study number	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Details	Intussusception/ rotavirus vaccination	Narcolepsy in adults/Pandemic Influenza Vaccine	Convulsions/ Pandemic and Seasonal Influenza Vaccine	Bacterial and Viral Infections/MMR Vaccine	Guillain-Barré syndrome/Seasonal Influenza vaccine	Idiopathic Thrombocytopenic Purpura/second dose of MMR	Bell's Palsy/Seasonal Influenza Vaccine
Source of the question	Previous vaccine shown to have increased risk/ passive surveillance	Follow up from childhood study	Vaccine was known to be reactogenic especially for fever	In response to the immune overload hypothesis	Pre pandemic preparedness	Follow up study after risk found after 1st dose of MMR	Risk seen in nasal formulation of vaccine
Year of question	2013/14	2014	2011	2008	2008/9	2007	2006
Adverse event	Intussusception	Narcolepsy	Convulsion	Bacterial and viral infections	Guillain-Barré syndrome	Idiopathic Thrombocytopenic Purpura	Bell's Palsy
Data source of cases	HES	Sleep centres/HES	GRPD/HES	HES	GPRD	HES	GPRD
Coding	ICD10/OPCS	ICD10/ OPCS	READ/ICD10	ICD9/10	READ	ICD10	READ
Age of cases	48-183 days old	>18 years	under 10 years	12-23 month	All ages	3 to <6 years	All ages
Validation	Medical notes from GP- Brighton Criteria	Multiple data sources cross referenced. Expert panel for diagnosis	previously validated by case note review	previously validated	Patient profile/ Free text/HES cases	previously validated by case note review	patient profile/prescription data/free text
Vaccine data source	GP	GP	in GPRD dataset	Child health	in GPRD dataset	Child health	in GPRD dataset
Statistical analysis	SCCS	Case-Coverage	SCCS	SCCS	SCCS	SCCS	SCCS
Result	RI 4.53 (CI 2.34-8.58) after 1st dose and 2.60 (1.43-4.81) after 2nd dose in 1-21days post vaccine	OR 9.06 (1.90–43.17) attributable risk of 0.59 cases per 100,000 doses	H1N1 vaccine - IRR 0.99 (CI 0.61–1.60) TIV 1st dose IRR 0.89 (CI 0.53–1.52) in week after vaccine	Bacterial RI = 0.68,(CI 0.54–0.86) Viral RI=0.68 (CI 0.49–0.93) 0-30 days after vaccine	RI 0.76 (CI 0.41-1.40) 90 days after vaccination	RI 1.04 (95% confidence interval 0.37-2.92) in 6 weeks after vaccination	RI 0.92 (95% confidence interval 0.78–1.08)

5. Methodological Challenges in Post-Licensure Vaccine Safety Studies.

The methodological challenge in post-licensure vaccine safety studies is the ability to select appropriate epidemiological methods and data so timely robust studies can answer vaccine safety concerns before confidence in the vaccination programme is lost or to confirm a risk to enable appropriate risk-benefit assessments. This challenge has many facets from the study design and case identification through to analysis and publication. For each study question methods should be adapted and potential biases considered in the context of the population under study, the dataset being utilised and the hypothesis being tested.

5.1 Setting up the study

Once the need for an epidemiological hypothesis-testing study is identified there are many scientific and practical issues to address in setting up the study in a timely manner. A clear hypothesis is needed and an unbiased data source with a sufficient number of cases needs to be identified. This hypothesis may come out of any signal strengthening activities carried out, such as an ecological analysis. Once this is decided a detailed study protocol should be written and should include an introduction, study aim, design and assessment of feasibility, the definition of the population of interest, the case definition and timing of outcome, details on the exposure of interest and interval of exposure, key confounding variables, method of analysis, descriptive analysis, sensitivity analysis, data management with data security considerations. Once the protocol is complete it can be advantageous for the document to be reviewed by an independent expert.

The first practical consideration is capacity, as personnel and funding need to be in place; with the appropriate expertise it is possible to carry out a study with very few staff. At PHE

in England the studies over the past 17 years were carried out with three key personnel and experts brought in for specific disease areas. In the adult narcolepsy study (Stowe et al., 2016b) the sleep experts at the study centres were co-authors which enabled the PHE team to build good relationships. Key to the study was to understand the process of the narcolepsy diagnosis in each hospital so cases could be ascertained in an appropriate manner. Having staff dedicated to the area of vaccine safety allows for rapid response, sustained data flows and retention of expertise. However this requires dedicated resources to be identified.

Often the ethical permissions to access the information needed can be a barrier. Specific datasets will have ethics committees, such as the Independent Scientific Advisory Committee (ISAC) for the GPRD. These committees will consider the medical, epidemiological and methodological aspects of the proposed study. If ethics approvals are needed this will have a considerable impact on the timeliness and responsiveness of the study. PHE has previously been able to obtain generic permissions to gain access to immunisation data in order to respond to future safety concerns. A key aspect especially when dealing which rare outcomes is whether the database has sufficient cases to give a statistically useful answer. In England large datasets are available such as the Hospital Episode Statistics but linkage to vaccination histories is incomplete as no national immunisation register is available. PHE is able to supplement this system by contacting GPs for the immunisation histories using the high level approval under Regulation 3 of The Health Service (Control of Patient Information) without the permission of the patient.

5.2 Study Design and Dealing with Confounding

Due to the problems in carrying out large cohort studies and the difficulties with selecting the correct controls in case-control studies as previously described, case only methods have been extensively used and have now become the gold standard for vaccine safety analysis (Stowe et al., 2011; Stowe et al., 2016a; Stowe et al., 2009b; Stowe et al., 2006; Stowe et al., 2009a).

The Self-Controlled Case-Series method also has its own difficulties when certain assumptions which are central to the method are not followed. The standard method will not work if the event itself alters the exposure under study; for example when the condition under study is a contraindication for the vaccine of interest. This occurred in the rotavirus vaccine and intussusception study (Stowe et al., 2016a) as the vaccine is contraindicated in patients with a history of intussusception due to the previous rotavirus vaccine being associated with intussusception. To enable the method to be used in such situations an adaptation has been developed (Farrington et al., 2009). The SCCS method also requires a risk period to be pre-specified which is then compared to the baseline in the analysis. The definition of the risk period can usually be calculated from other studies or the biological mechanism of the suspected association. In the study of narcolepsy and pandemic influenza vaccine in children in England, a SCCS analysis was performed with a pre-specified risk period of six months following vaccination as defined by the initial cases from Scandinavia. The actual risk period was much longer than initially thought and four of the 11vaccine associated cases had their onset of symptoms after six months from vaccination and as a consequence were allocated in to the background reducing the relative incidence (Miller et al., 2013). It is often useful to present the data visually with a frequency graph with the count of episodes by interval from vaccination to episode (Figure 1) but this should only be carried out after the post vaccination risk periods have been documented in the analysis plan.

Another approach recently used for investigating narcolepsy after pandemic influenza vaccine is the case-coverage design (Farrington, 1993). This method was used in both the childhood and adult narcolepsy and H1N1 influenza vaccine studies carried out in England (Miller et al., 2013; Stowe et al., 2016b). The case-coverage method relies on the representativeness of the vaccine coverage data used in the analysis so if a comparison can be sought this can be advantageous as demonstrated when the RCGP and GPRD coverage data were compared and found to be similar (Stowe et al., 2016b).

5.3 Case Identification

A great advantage of using an administrative dataset setup for purposes other than the question you are investigating is that it has the potential to be a non-biased set of cases. HES for example should be independent of the vaccine history which is more difficult to ascertain if relying on clinicians' reports. As previously described, the use of codes is an efficient way of identifying the required case in most routinely collected data. A combination of diagnosis, prescription or treatment codes can be used to assist in the identification of the case. An example of this is in the study assessing the risk of intussusception after rotavirus vaccine in England (Stowe et al., 2016a) when not only the ICD code for the diagnosis for intussusception was used but addition procedure codes such as "Open reduction of intussusception of ileum" was used in conjunction to validate the diagnosis. Often a number of different codes are used to describe a condition especially in primary care data where a greater variety of codes are available for each condition. Care must be taken if a procedure or diagnosis is incentivised through government targets such as the QOF or Payment by Results which can result in an increase of cases in particular years or populations.

The issue of retrospective recording of conditions often needs to be addressed at this stage and this can occur in primary care data on the day of vaccination. An example of this was in the study of Bell's Palsy and influenza vaccine (Stowe et al., 2006) and it can also be seen in hospital admission data if secondary diagnosis codes are used when studying chronic conditions such as GBS.

In some instances no routine data are available, for example, in identifying cases of narcolepsy, so case lists need to be built from a number of different data sources (Stowe et al., 2016b). When a case list is being developed all potential cases need to be included even if when reviewed they are excluded, so this stage should have a high sensitivity. In the adult narcolepsy study 1,446 possible cases were initially identified through multiple sources which were then reduced to 40 cases after thorough case note review and validation. Cases

should be identified independent of vaccine history and care must be taken when *ad hoc* cases are identified in study centres when the study hypothesis is known. This may lead to a biased set of cases in relation to vaccination history due to preferential reporting of vaccinated cases.

To minimise this bias, PHE linked computerised hospital cases on NHS number to computerised immunisation histories for many of its studies. Due to the lack of a national immunisation register in England this is only feasible when the study outcome is common, for example in the study investigating bacterial and viral infections following MMR vaccine where 2077 admissions were successfully linked to an MMR record (Stowe et al., 2009b). This linkage was also possible when studying ITP and the second dose of MMR where adequate numbers of hospital episodes were identified for the area for which there was vaccine information (Stowe et al., 2008). When the condition is rare and linkage to a vaccination register is not feasible writing to the GP to request details of the immunisation history has been successfully carried out at PHE. Care must be taken when designing the questionnaire which ideally should not exceed one page so as not to discourage the completion and ensure the highest possible return rate. In many studies the diagnosis coding and date of the onset of the symptoms have been successfully verified when requesting the vaccine history. Care must also be taken in the wording of questions to ensure the correct hospital admission is being discussed in terms of first symptom date, as this can be important when studying chronic conditions with multiple admissions (Stowe et al., 2016b; Andrews et al., 2011).

5.4 Defining index dates

Accurately identifying when a symptom of the condition under study commenced and when the vaccine was given is a key requirement in vaccine safety studies in order to correctly

assess whether a case falls within the pre-defined risk period after vaccination. In some studies, for example, rotavirus vaccine and intussusception (Stowe et al., 2016a), the risk period was within a few weeks following vaccination but for other conditions, such as narcolepsy and pandemic influenza vaccine, the risk period was more prolonged (Stowe et al., 2016b). If the first symptoms date is not available, the diagnosis date is often used as the index date, but this can lead to inaccuracies in assessing the risk if there was a long period of time between the first symptom and diagnosis. This was demonstrated in the PHE childhood narcolepsy study when data analysed using the first symptom date and the diagnosis date showed a bias towards the null when analysed by diagnosis date (Miller et al., 2013).

The assignment of the vaccine status in each of the cases under study needs careful consideration. Recall of vaccination date from patient interviews should not be relied upon and independent recording of vaccination status should always be sought. Vaccination status may be inaccurate if based on the status at the time of an event which is after the date of symptom onset in the cases. Evidence of vaccination must be recorded prior to the symptoms onset and not retrospectively documented after the event, however if the vaccination is given at outreach clinics it may take time to be recorded on the computer system. An example of this was during the pandemic influenza vaccination campaign when clinics were held in local communities and also for the HPV vaccine where it delivered in schools. It is essential however that the vaccination event is recorded before the specific adverse event hypothesis is established. This can often be determined from a field in the electronic database which documents the data entry date.

5.5 Cleaning data

Once the data has been extracted the process of cleaning the dataset and identifying the pertinent information begins. As previously described these databases are primarily a tool for patient administration so the data needs to be explored and understood in order to correctly

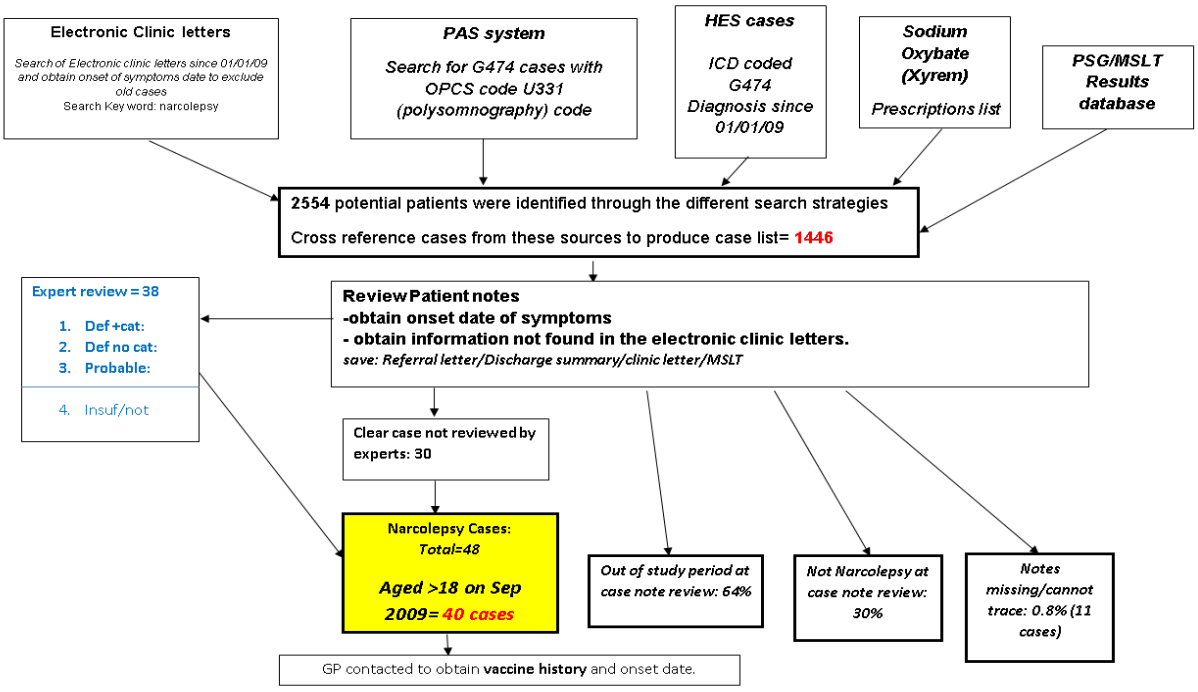
interpret the data and correctly answer the study question. It is often difficult to define incident cases of a condition in large electronic databases as no one database comprehensively holds a patient's medical history from birth to death. There are often multiple recordings of a patient's diagnosis throughout their stay in hospital so it becomes necessary to de-duplicate the records. Depending on the condition under study it must be decided now many days between repeat episodes constitutes the same episode. For example, in the study looking at convulsion and influenza vaccine an episode with ten days of a previous constituted a new episode (Stowe et al., 2011) but when looking at GBS a six month period was allocated (Stowe et al., 2009a).

Basic internal validation to assess the accuracy of the data needs to be carried out for example no events recorded before the date of birth or no age more than 115 years. Often databases have "acceptable status" or "up to standard dates" which are a flag in the data to aid such data cleaning. Other recording errors in the database need to be uncovered; for example in the study on Bell's palsy after influenza vaccination some patients were found with more than one dose of influenza vaccine in a season so these cases were excluded due to likely recording errors as only one dose is recommended, except in children who have not had an influenza vaccine previously where two doses are recommended (Stowe et al., 2006).

An issue especially in primary care data is the retrospective recording of a person's medical history when a patient joins a new practice, resulting in previous long standing or significant clinical conditions being recorded on the day of registration. This issue was addressed in the study assessing the risk of convulsions after influenza vaccine when the data in the three month period after the patients first registration date was excluded (Stowe et al., 2011). This can also occur in hospital inpatient data when there is up to 20 diagnosis fields so often long standing conditions or illnesses, not the primary reason for the current admission, can be recorded in diagnosis fields 2-20. It is recommended that a review of the cases is carried out

to establish the timings of the symptoms and diagnosis or only cases with the relevant ICD code in the primary diagnosis field are used (Stowe et al., 2016a) (Figure 2).

Figure 2: Algorithm for identifying adult narcolepsy cases



5.6 Media attention

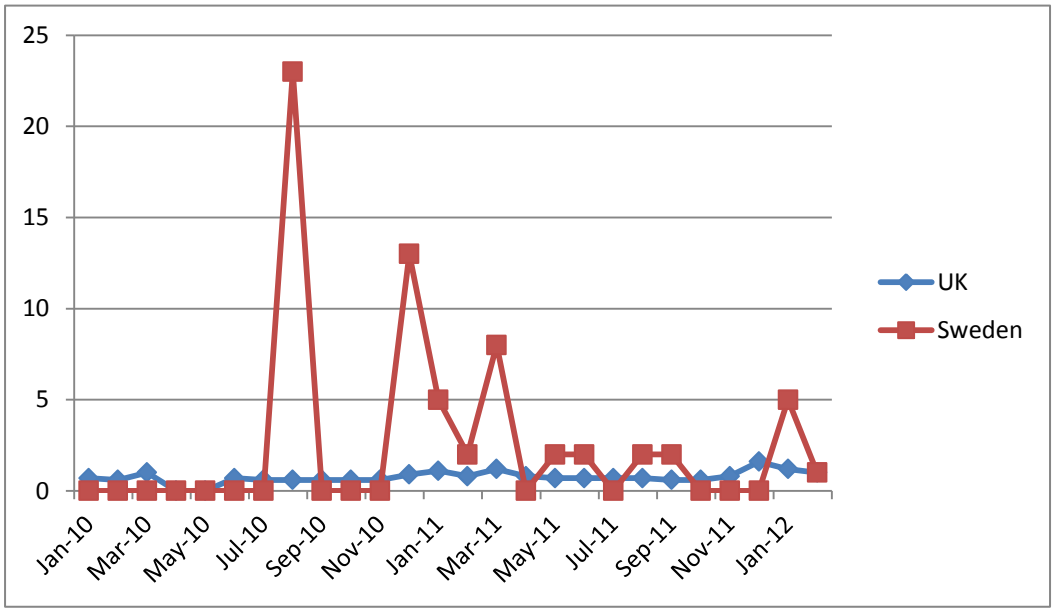
The awareness of the hypothesised association which may lead to increased reporting of cases has two aspects; public awareness and professional awareness. Firstly, this heightened awareness may lead to vaccinated individuals presenting to health care and diagnosed earlier than unvaccinated cases leading to ascertainment bias. If a condition has an insidious onset making the recall of the first symptom difficult to determine media attention may lead to a differential recall of the symptom onset date in the vaccinated cases.

Using source documents which were created prior to any media attention in the country of study has been used as a method to address this potential recall bias. Professional awareness is likely to occur even if media attention is low as health professionals in the field of interest will be aware of current topics of interest through professional bodies and literature.

Differential misclassification bias will occur if cases known to have been vaccinated are more likely to be assigned a diagnosis of narcolepsy than unvaccinated cases. In the narcolepsy studies we were able to assess public awareness of the association by analysing Google searches for "narcolepsy" in the period of interest and found there was little activity in the UK compared to Sweden (Miller et al., 2013) (Figure 3).

. **Figure 3: Googles searches for "narcolepsy" or narkolepsi" from UK and Sweden**

relative scaling is based on the ratio of searches in each month to the long term average



5.7 Validation

It is important to use cases with a diagnosis validated by objective criteria, such as the Multi Sleep Latency Test (MSLT) in the narcolepsy studies (Stowe et al., 2016b) or procedures specific to the diagnosis such as an air enema in the treatment of intussusception (Stowe et al., 2016a). It has demonstrated that prescription data can also be used to validate cases (Stowe et al., 2006). For informed interpretation of medical records an expert panel may be required to assess each case according to internationally recognised criteria as demonstrated

by the use of the International Classification of Sleep Disorders criteria (ICSD-2) in narcolepsy studies in England (Stowe et al., 2016b; Miller et al., 2013). It is important the relevant information is available to the panel in order to make the assessment against the appropriate criteria. The use of an international criterion can greatly strengthen the comparability and generalisability of the study results but this needs to be weighed up against excluding cases due to information not being available. If clinic letters which are to be given to a panel for review include details of the vaccination status of the patient this needs to be removed or the relevant information abstracted (Stowe et al., 2016b).

In some primary care datasets free-text information is available but it can be costly as any personal identifiable information need to be manually removed. Often it cannot be viable to validate all the cases but a random subset can be validated as was carried out in the studies assessing the risk of Bell's palsy and GBS after influenza vaccine using the GPRD (Stowe et al., 2006; Stowe et al., 2009a).

If potential index dates are available from multiple sources for the same individual, for example from hospital admission data, primary care data or from the medical records, the earliest recorded date can be used in the final analysis or a sensitivity analysis can carried out using the earliest and latest dates available for that individual (Stowe et al., 2016b; Stowe et al., 2016a). The use of un-validated cases from electronic databases reduces specificity and can lead to random misclassification which biases the result towards the null.

5.8 Publication

The most common type of publication bias is when a positive result has a better chance of publication and is often published earlier (Dubben & Beck-Bornholdt, 2005). In the case of vaccine safety studies there may also be less expert scrutiny by journals of the scientific quality of the work and potential conflicts of interest by the authors if the study reports a novel association of high public interest. Such factors may have influenced the decision to

publish the high profile study which linked MMR and autism which was subsequently retracted by the journal (Wakefield et al., 1998).

There may be other reasons which influence the likelihood of a manuscript being published for novel associations with no clear biological mechanism and this is evident in recent vaccine safety studies. The first narcolepsy and Pandemrix studies were initially published without peer review on the internet and many of the studies were not published in a peer reviewed journal for many years after this initial publication. It is likely the reason for this was the need to get the information into the published domain swiftly along with the reluctance of a journal to publish the results.

Publication by peer review is the backbone of the dissemination of scientific knowledge and in the field of vaccine safety especially this needs to be carried out in a timely manner. It is important that robust methods, data and results are disseminated so others can assess the risk and carry out complementary studies where necessary.

5.9 Communication of a risk

If a risk is found following a vaccine, the way this risk is communicated is important so the audience are able to put the risk into the context of the benefit it is providing in preventing a disease. As the events of interest are rare it is often useful to give an attributable risk per 100,000 doses instead of a relative risk which can be misinterpreted. In the studies looking at the risk of narcolepsy following pandemic influenza the childhood study in England found an odds ratio of 14.4, but the attributable risk was 1.74 cases per 100,000 doses (Miller et al., 2013). Similarly in the adult study the odds ratio was 9.06 with an attributable risk of 0.59 cases per 100,000 (Stowe et al., 2016b), this was because of the rarity of the event. This allowed the audience to put the risk into perspective in terms of risk per dose. In the study assessing the risk of intussusception after the rotavirus vaccine (Stowe et al., 2016a) a 2-3 fold elevated risk was found with an attributable risk of 1.91 per 100,000 after the first dose

and 1.49 per 100,000 after the second dose. However the number of intussusception cases the rotavirus vaccine programme had caused, which was 21, was calculated and this was set against the 25,000 gastro-intestinal infection admission the programme prevented concluding that the benefit/risk profile of the vaccine remained strong.

6. Conclusions

The studies described here have been carried out over a ten year period at Public Health England and have contributed to maintaining confidence in the national vaccination programme in England. The methods employed have been tailored for each hypothesis and dataset, in order to minimise bias and give a robust measurement of the risk. Knowing the strengths and weaknesses in the dataset being analysed is critical so checks and validation of the data can be performed. With increasing numbers of vaccines in the routine schedule it is essential that adverse events are reported to pharmacovigilance systems so assessments can be made in a timely manner before confidence in the vaccine is reduced. The ability to have available individual level national healthcare databases is central but it has been demonstrated here that even when datasets are not suitable for the study question, a dataset can be constructed using information from various sources.

Future vaccines safety concerns cannot be forecast but as new vaccines are introduced into the national schedule safety concerns from similar products should be monitored. Examples of which include the intranasal influenza vaccine in children in relation to Bell's Palsy and the newly introduced Meningitis B vaccine, which is known to be pyrogenic, and febrile convulsions.

Vaccines are now being manufactured and introduced in a global market with many countries using similar schedules and timings. At the same time countries are seeing the benefits of developing large linked healthcare datasets so in the future there may be an increase of available data for post licensure vaccine safety epidemiological research. This will then give the opportunity for studies to be carried out and then validated on a global level. Currently international epidemiological vaccine safety studies have been carried out using a common protocol (Dodd et al., 2013) or pooled data (Dieleman et al., 2011).

Such approaches maximise the potential of a country's data which can be beneficial when the availability of data is limited as it can result in a much larger number of cases than any one country alone increasing the power of the study. These approaches highlight the need for a transparent information governance and ethics framework on a global level. When designing an international study, consideration of the appropriate data and methods should be the main priority. If this is not done the results and conclusions from the study could be confusing. This was demonstrated in a multi European country study assessing the risk of narcolepsy after Pandemrix (VAESCO) when the study reported no risk outside the "signalling" countries including the UK when a risk was robustly demonstrated when appropriate methods were employed (Miller et al., 2013).

With the devolution of NHS healthcare many regions in England carry out public health surveillance. Cities and regions are putting resources into linking healthcare datasets on a local level and seeing the benefits such data can provide (Greater Manchester Academic Health Science Network, 2016). Vaccine safety surveillance requires very large numbers in order to identify these rare adverse events so regional datasets are of little benefit. The future of individual level national healthcare databases is unclear. The implementation of a new harmonised coding system should assist in the flow of data between primary and secondary care and the public's concern around confidentially and the use of their personal data needs to be carefully addressed. To assist in this the methods used in vaccine safety studies need to be communicated in such a manner that public are informed and reassured so that they are content with their data being used for this purpose. The basis of this discussion should be the acceptance that vaccination does carry a small risk but this risk needs to be put into perspective. It is essential that the rapid assessments of safety signals through robust epidemiological studies are carried out to ensure that public confidence is maintained in the national immunisation schedule.

7. Published Works

Intussusception / Rotavirus vaccination

Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine. 2016 Jul 12;34(32):3684-9. doi: 10.1016/j.vaccine.2016.04.050. PubMed PMID: 27286641.

Narcolepsy in adults / Pandemic Influenza vaccine

Stowe J, Andrews N, Kosky C, Dennis G, Eriksson S, Hall A, Leschziner G, Reading P, Shneerson JM, Donegan K, Miller E. Risk of Narcolepsy after AS03 Adjuvanted Pandemic A/H1N1 2009 Influenza Vaccine in Adults: A Case-Coverage Study in England. Sleep. 2016 May 1;39(5):1051-7. doi: 10.5665/sleep.5752. PubMed PMID: 26856903;

Convulsions / Pandemic and Seasonal Influenza vaccine

Stowe J, Andrews N, Bryan P, Seabroke S, Miller E. Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: a database study. Vaccine. 2011 Nov 28;29(51):9467-72. doi: 10.1016/j.vaccine.2011.10.029. PubMed PMID: 22019757.

Bacterial and Viral Infections / Measles Mumps and Rubella vaccine

Stowe J, Andrews N, Taylor B, Miller E. No evidence of an increase of bacterial and viral infections following Measles, Mumps and Rubella vaccine. Vaccine. 2009 Feb 25;27(9):1422-5. doi: 10.1016/j.vaccine.2008.12.038. PubMed PMID: 19146903.

Guillain-Barré syndrome / Seasonal Influenza vaccine

Stowe J, Andrews N, Wise L, Miller E. Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenza like illness using the United Kingdom General Practice Research Database. Am J Epidemiol. 2009 Feb 1;169(3):382-8. doi: 10.1093/aje/kwn310. PubMed PMID:19033158.

Idiopathic Thrombocytopenic Purpura / second dose of Measles Mumps and Rubella vaccine

Stowe J, Kafatos G, Andrews N, Miller E. Idiopathic thrombocytopenic purpura and the second dose of MMR. Arch Dis Child. 2008 Feb;93(2):182-3. PubMed PMID: 17962371.

Bell's Palsy / Seasonal Influenza vaccine

Stowe J, Andrews N, Wise L, Miller E. Bell's palsy and parenteral inactivated influenza vaccine. Hum Vaccin. 2006 May-Jun;2(3):110-2. PubMed PMID: 17012908.

Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation

Julia Stowe[a,*], Nick Andrews[b], Shamez Ladhani[a], Elizabeth Miller[a]

[a] Immunisation and Blood safety Department, Public Health England, 61 Colindale Avenue, London NW9 5EQ, United Kingdom
[b] Statistics and Modelling Economics Unit, Public Health England, London NW9 5EQ, United Kingdom

ARTICLE INFO

Article history:
Received 27 January 2016
Received in revised form 13 April 2016
Accepted 18 April 2016
Available online xxx

Keywords:
Intussusception
Rotavirus
Vaccine safety
Self-controlled case-series

ABSTRACT

Objective: To investigate the risk of intussusception after monovalent rotavirus vaccine (RV1) given to infants aged 2 and 3 months in England.
Methods: Hospital Episode Statistics (HES) were used to identify infants aged 48–183 days admitted between 11/03/2013 and 31/10/2014 with intussusception. Diagnosis was confirmed from medical records and HES procedure codes. Vaccination status was obtained from general practitioners. The risk of admission within 1–7 and 8–21 days of vaccination was analysed using the self-controlled case-series (SCCS) method with age effect adjustment by including historical data before RVI introduction in July 2013.
Results: A total of 119 cases were identified during the study period and intussusception confirmed in 95 of whom 39 were vaccinated 1–21 days before onset. An increased relative incidence (RI) in this period was found, 4.53 (95% confidence interval 2.34–8.58) and 2.60 (1.43–4.81) respectively after the 1st and 2nd doses with an attributable risk of 1.91 and 1.49 per 100,000 doses respectively. The peak risk was 1–7 days after the first dose, RI 13.81 (6.44–28.32), with an estimated 93% of the 15 cases being vaccine-attributable. Mean interval between onset and admission, and clinical features were similar between vaccine-associated and background cases. Despite intussusception being a contraindication to rotavirus vaccination, 10 infants received a further dose; none had a recurrence. The RIs in a meta-analysis combing our results with Australia, Mexico, Brazil and Singapore using RV1, a 2, 4 month schedule and SCCS gave pooled RI estimates of 2.35 (1.45–3.8) and 1.77 (1.29–2.43) in the 21 day period after the 1st and 2nd doses, respectively. The earlier age at the 2nd dose in England did not affect the risk.
Conclusion: We estimate that the RVI programme causes around 21 intussusception admissions annually in England but, since it prevents around 25,000 gastro-intestinal infection admissions, its benefit/risk profile remains strongly positive.

1. Introduction

Rotavirus infects nearly every child by five years of age and is the leading cause of gastroenteritis worldwide [1]. In healthy infants in developed countries the infection results in a mild self-limiting illness with low mortality though it has a high healthcare burden and causes parental anxiety [2]. It is estimated that in England and Wales in the absence of vaccination rotavirus infection is responsible for around 45% of hospitalisations, 20% of accident and emergency attendances and 25% of primary care consultations for acute gastroenteritis in children under five years of age, corresponding to annual incidences per 1000 of 4.5, 9.3 and 28–44 consultations respectively [3].

The first rotavirus vaccine, Rotashield®, was shown to have an attributable risk of intussusception of between 10.5 and 21.4 per 100,000 infants vaccinated [4] and was withdrawn from the market. Subsequently two new rotavirus vaccines were licensed, one containing a monovalent attenuated human rotavirus strain (RV1) and the other a pentavalent human-bovine reassortant vaccine. Although a risk of this magnitude was not seen with these new rotavirus vaccines in randomised controlled trials, they lacked the power to rule out a small risk [5,6]. In post-licensure studies, an increased risk of intussusception after the first dose of these vaccines has been reported in the 1–7 day post-vaccination period with an attributable risk after the first dose of between 1.1 to 4.3 per 100,000 [7–12]. The risk following the second dose appears to

* Corresponding author. Tel.: +44 2083277485.
E-mail address: Julia.Stowe@phe.gov.uk (J. Stowe).

http://dx.doi.org/10.1016/j.vaccine.2016.04.050

be smaller, with most studies not finding a significantly increased risk.

In the United Kingdom (UK) the rotavirus vaccine was first added to the routine vaccination programme in July 2013 using the RV1 vaccine, Rotarix® (GlaxoSmithKline). It is given as a 2 dose schedule at 2 and 3 months with the second dose to be given by 24 weeks of age to avoid coinciding with the peak in the background incidence of intussusception around this time [13]. Rotarix® is contraindicated for infants who have had a prior intussusception episode or an uncorrected congenital malformation of the gastrointestinal tract that would predispose to intussusception. Since its introduction in the UK, the uptake of rotavirus vaccine has been high, with a 77% decline in laboratory-confirmed rotavirus infections and a 26% decline in all-cause acute gastroenteritis-associated hospitalisations compared with the pre-vaccination era [14].

In this study, we investigate whether there is an increased risk of intussusception following either the first or second dose of RV1 vaccine in infants in England. We also examine the timeliness of presentation to hospital which is essential in preventing complications from this rare event.

2. Methods

The Hospital Episode Statistics (HES) [15] database was used to identify cases of intussusception in infants eligible to receive at least one dose of rotavirus vaccine from the start of the national programme until 31/10/2014. The HES database contains details of all admissions to National Health Service hospitals in England. Infants aged 42–183 days old at the start of their admission with an ICD-10 code for intussusception in the primary diagnosis field and born from 11/03/2013 were selected as the vaccine was made available to any babies born up to 15 weeks prior to vaccine introduction on 1st July 2013. Office of Population Censuses and Surveys (OPCS) Classification of Interventions and Procedures version 4 codes attached to each admission were also extracted to investigate any procedures or operations during that admission. An admission for intussusception within 3 days of a previous one was treated as the same admission.

As rotavirus vaccine is delivered in primary care, infants' general practitioners were contacted to ascertain whether the vaccine was given and, if so, the date(s). Each case was categorised according to the Brighton Criteria for intussusception which contain 3 levels of diagnostic certainty [16]; level 1 is the highest level of certainty requiring confirmation by surgical or radiological reduction of the intussusception; level 2 is assigned by the evidence on a number of diagnostic features including intestinal obstruction, intestinal invagination and blood per rectum. Level 3 cases, which comprise those where the diagnostic evidence was less robust, were excluded from the analysis, together with cases for whom clinical information was lacking.

Diagnosis level was assigned without knowledge of vaccination status based on three sources of information; OPCS codes that indicated whether a surgical or radiological procedure was undertaken to reduce the intussusception, any additional information from the GP on treatment and symptoms, validated by a copy of the hospital discharge summary where available, and if no information was available from the HES database or GP, the paediatrician involved in the patient's care was contacted. Information from the GP and the discharge summaries was used to ascertain the date of first symptoms. For the analysis a single event date was determined which was the date of onset identified by the GP or in the hospital letters, or where this information was lacking, the date of hospital admission. Where the onset of symptoms was more than 3 days prior to admission this was only taken as the episode onset if on blinded review the events on this date were clearly part of the intussusception event.

The self-controlled case-series (SCCS) method was used to test the hypothesis of an increased risk of intussusception in three risk periods of 1–7, 8–21 and overall 1–21 days after rotavirus vaccination, where day 0 is the day of vaccination. The SCCS method [17] automatically controls for time-invariant confounding and has been used in previous studies investigating vaccine and intussusception [7,8,10,18]. We used the adaptation of the method developed by Farrington et al. [19] because the standard SCCS approach could not be used as intussusception is a contraindication to vaccination, thus violating the assumption that vaccination is not dependent on the occurrence of the event.

Age adjustment was by 2 weekly intervals, but age had a degree of collinearity with vaccine risk periods due to the lack of control person time around the time of vaccination because the doses were only given a month apart and the risk interval was 3 weeks. To address this, a pre-specified additional analysis was planned where five years of historical HES intussusception data from the period prior to vaccine introduction was included to enable better estimates of age effects. For these cases, hospital admission date was used as the index date.

Sample size calculations based on HES incidence data by age indicated that the expected number of cases from a year of follow-up post-vaccine introduction in the 7 day period after doses one and two was 1.6 and 4.0 respectively. This would enable detection of risks (80% power, 5% significance) of about 5–6 fold after dose 1 and 3–4 fold after dose 2.

The attributable risk was calculated from the relative incidence (RI) estimates. First the attributable fraction (AF) was calculated as (RI-1)/RI for each period after each dose. This was then applied to the cases observed to get an attributable number of cases, and finally this was divided by the estimated number of vaccine doses given to the population from which the cases arose.

To compare cases that were likely to be vaccine-associated with those that were not the features of the cases, including treatment, duration of admission and length of time from symptoms to admission in the 1–7 day risk interval after the first dose were compared to those outside the 1–21 day risk period after either dose. Logistic regression was used to adjust for age when comparing these groups.

A random effects meta-analysis was performed, combining our results with those from four other countries using RV1 and reporting RI estimates by the SCCS method [7,8,10,11]. Estimates for the 8–21 and 1–21 day post-vaccination risk periods were not reported for every country; however, these could be derived from the reported estimates in other risk periods. Pooled estimates were then obtained for the 1–7, 8–21 and 1–21 day post-vaccination periods using the point estimates and 95% confidence intervals (CIs) from each country. Analysis was carried out using Stata version 13 (StataCorp, College Station, TX).

3. Results

A total of 590 admissions in the period 1/07/08 to 31/10/2014 were identified from HES, with age at admission from 42 to 183 days and a K561 ICD-10 code for intussusception in the primary diagnosis field. There were 471 episodes in the 5 years prior to vaccine introduction with a date of birth before 11/03/2013 (age distribution shown in Fig. 1), and 119 with a date of birth after 10/03/2013 and, therefore, eligible for vaccination. Of the 119 episodes in the vaccine-eligible period, 90 were confirmed as Brighton level 1 after review and five as Brighton level 2. Of the remaining 29, one episode was assigned level 3, eight did not fit the criteria for intussusception and, for the remaining 15, the relevant information could not

Please cite this article in press as: Stowe J, et al. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.04.050

Table 1
Description of the 95 Brighton level 1 and 2 intussusception cases included in the risk analysis, that are in the risk period 1–21 days after dose 1 or 2 of rotavirus vaccine.

Variable	Level	Count of cases in risk period	Count of cases outside the risk period	Total count (%)
Sex	Male	29	37	66 (69%)
	Female	10	19	29 (31%)
Radiological reduction	No	17	26	43 (45%)
	Yes	22	30	52 (55%)
Surgery	No	23	34	57 (60%)
	Yes	16	22	38 (40%)
Brighton	1	38	52	90 (95%)
	2	1	4	5 (5%)
Vaccine doses	0	0	13	13 (14%)
	1	12	7	19[a] (20%)
	2	27	36	63[b] (66%)
Age	6w–9w/6d	10	4	14 (15%)
	10w–13w/6d	11	8	19 (20%)
	14w–17w/6d	15	12	27 (28%)
	18w–21w/6d	2	16	18 (19%)
	22w–26w/1d	1	16	17 (18%)

[a] 1 individual had onset before vaccination.
[b] 12 individuals had onset before vaccination (2 before first dose, 10 between doses).

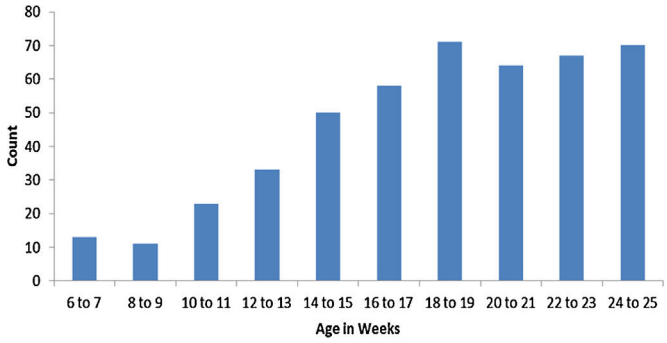


Fig. 1. Age distribution of the historic cases.

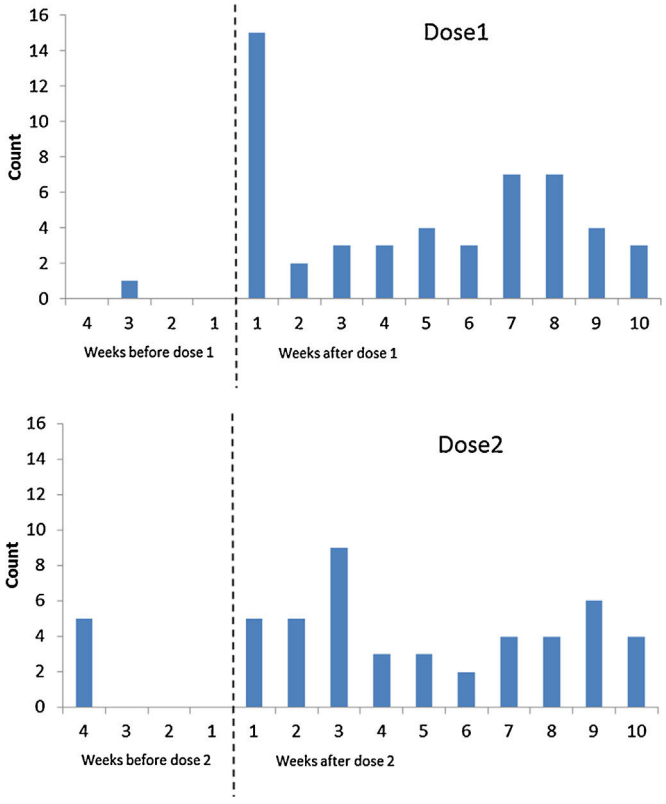


Fig. 2. Distribution of intussusception events 4 weeks before to 10 weeks after monovalent rotavirus vaccine doses 1 and 2.

be traced. Copies of medical discharge summaries and letters were available for 72 of the 95 level 1 and 2 cases (76%). Of the 95 cases, 66 (69%) were in males with an age range of 6–26 weeks (Table 1).

Overall there were 20 intussusception events 1–21 days after dose one and 19 events in the same period after dose two (Table 2 and Fig. 2). After the first dose, 15 of the 20 cases occurred in the 1–7 day period, with the interval between vaccination and onset of symptoms ranging from 4 to 6 days. After the second dose, there were 5 cases in the 1–7 day post-vaccination risk period and 14 in the 8–21 day risk period. A significantly increased risk was seen in the overall 1–21 day period post-vaccination for both the first and second dose of rotavirus vaccine (RI, 4.53; 95% CI, 2.34–8.58, and RI, 2.60; 95% CI, 1.43–4.81, respectively) (Table 2). When this post-vaccination risk period was spilt into 1–7 days and 8–21 days, the RI in the period 1–7 days after the first dose and 8–21 days after the second dose remained significantly elevated (Table 2). When the cases born before 11/03/2013 were included, the age effects were better specified which improved precision of the vaccine risks. The model incorporating the historic data also happened to give a lower background incidence in the younger age groups than the model without these data which led to higher relative incidence estimates for the vaccine risk periods (Table 2).

Using the model with the historical age data, the attributable fractions for days 1–7 and 8–21 after doses one and two were 93%, 37%, 55% and 64%, respectively, and the estimated number of vaccine-attributable cases 13.91, 1.86, 2.73 and 8.94 respectively. Based on dose one and two national vaccine coverage of 93.3% and 88.3% [20] and an England population estimate for infants under 1 year of age of 664,517 [21] and 1 year 4 months follow-up, the number of first and second doses given were around 826,659 and 782,358, respectively. The attributable risk in the 1–21 day period after dose one was, therefore, 15.77/826,659 (1.91 per 100,000 doses) and 11.67/782,358 (1.49 per 100,000 doses) after dose two. For the 1–7 day period after dose one only, the attributable risk is 1.68 per 100,000 doses.

Fifty-two (55%) of the 95 cases had their intussusception reduced radiologically, 38 (40%) underwent surgery and 5 had no intervention. In the 15 infants with intussusception in the 1–7 days after the first dose, 8 (53%) had radiological reduction and 7 (47%)

Please cite this article in press as: Stowe J, et al. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.04.050

Table 2
Relative incidence of intussusception in risk periods after first and second monovalent rotavirus vaccine doses.

Historical cases for age effect	Dose	Risk period (days)	Cases in risk period	RI (95% CI[a])
Yes	1	1–7	15	13.81 (6.44–28.32)
		8–21	5	1.59 (0.34–3.75)
		1–21	20	4.53 (2.34–8.58)
	2	1–7	5	2.20 (0.50–5.02)
		8–21	14	2.77 (1.36–5.32)
		1–21	19	2.60 (1.43–4.81)
No	1	1–7	15	8.50 (3.27–28.75)
		8–21	5	1.18 (0.28–3.99)
		1–21	20	3.13 (1.34–7.57)
	2	1–7	5	1.74 (0.37–5.16)
		8–21	14	2.74 (1.22–5.89)
		1–21	19	2.41 (1.15–5.59)

[a] Percentile bootstrap ($n = 1000$) 95% confidence intervals.

Table 3
Features of the intussusception admissions in infants in the 1–7 day post first dose risk period compared to those outside vaccine risk periods.

Feature	1–7 days post first dose n/N (%)	Out of risk period-baseline[b] n/N (%)	Odds ratio (95%CI)[a]
Treatment			
Radiological	8/15 (53.3%)	30/56 (53.6%)	0.96 (0.24–3.91)
Surgical	7/15 (46.7%)	22/56 (39.3%)	1.58 (0.38–6.59)
Days from onset to admission			
Same day	5/15 (33.3%)	29/56 (51.8%)	1.04 (0.24–4.60)
Mean (range) in days	0.71 (0–4)	0.77 (0–4)	
Duration of admission			
0–1 days	9/15 (60.0%)	32/56 (57.1%)	0.44 (0.11–1.85)
Mean (range) in days	0.33 (0–8)	0.50 (0–12)	
Gender			
Male	10/15 (66.7%)	37/56 (66.1%)	0.54 (0.11–2.58)

[a] Odds ratio adjusted for in age in days.
[b] Not within 1–21 days of dose 1 or 2.

Table 4
Meta-analysis of results from four countries using monovalent rotavirus vaccine: relative incidence and 95% confidence intervals.

Country	Period post dose 1			Period post dose 2		
	1–7 days	8–21 days	1–21 days	1–7 days	8–21 days	1–21 days
Australia	6.76 (2.40–19.01)	3.45 (1.33–8.94)	4.55 (2.21–9.38)[a]	2.84 (1.10–7.34)	2.11 (0.97–4.62)	2.35 (1.28–4.33)[a]
Mexico	5.30 (3.00–9.30)	0.99 (0.52–1.91)[b]	2.43 (1.51–3.90)[a]	1.80 (0.90–3.80)	2.20 (1.40–3.45)[b]	2.07 (1.41–3.04)[a]
Singapore	8.36 (2.42–28.96)	0.10 (0.01–10.0)[c]	2.85 (1.13–7.19)[a]	3.09 (0.41–12.37)	1.54 (0.20–11.69)	2.06 (0.47–8.94)[a]
Brazil	1.10 (0.30–3.30)	0.51 (0.20–1.33)[b]	0.71 (0.33–1.50)[a]	2.60 (1.30–5.20)	1.12 (0.65–1.93)[b]	1.61 (1.05–2.48)[a]
Mexico (2)	6.49 (4.17–10.09)[d]	1.08 (0.90–1.30)[d]	1.75 (1.24–2.48)[d]	1.29 (0.80–2.11)[d]	1.00 (0.84–1.20)[d]	1.06 (0.75–1.48)[d]
England	13.81 (6.44–28.32)	1.59 (0.34–3.75)	4.53 (2.34–8.58)	2.20 (0.50–5.02)	2.77 (1.36–5.32)	2.60 (1.43–4.81)
Pooled[e]	6.03 (3.61–10.07)	1.13 (0.71–1.79)	2.35 (1.45–3.80)	1.83 (1.35–2.50)	1.61 (1.04–2.47)	1.77 (1.29–2.43)

[a] Estimated from combining published 1–7 and 8–21 day period risks.
[b] Estimated from combining published 8–14 and 15–21 day period risks.
[c] Actually zero events in this period, RI of 0.1 with wide 95% CI used.
[d] Estimates are for 0–6, 7–30 and 0–30 days with 7–30 estimated by subtraction of 0–6 from 0 to 30 estimates.
[e] Pooled using random effects method of DerSimonian and Laird (Metan command in stata) due to heterogeneity between countries for some periods.

needed surgical intervention, which was similar to the management of cases outside the vaccine risk periods (Table 3). In the period the vaccine was given and in the 5 years prior to the vaccine's introduction there were no intussusception admissions in which an infant died.

The interval from onset of symptoms to admission ranged from 0 to 4 days. Five of the 15 (33.3%) infants with onset in the 1–7 day risk window after the first dose were admitted on the same day as their symptoms started compared to 29 of the 56 (51.8%) of those outside the vaccine risk periods, although this difference was not statistically significant (Table 3), and not different when adjusting for age. The duration of the admission ranged from 0 to 12 days and was similar in infants with onset shortly after the first dose and those outside the vaccine risk periods (Table 3), and non-significantly lower when adjusting for age.

Although rotavirus vaccine is contraindicated for children with a previous intussusception, 3 infants had an admission for intussusception in the 2 months before receiving their first dose of rotavirus vaccine and 10 children went on to have their second dose after confirmed intussusception following the first dose. No repeat episodes of intussusception were recorded in the HES data.

The pooled results for the meta-analysis showed a significantly increased RI after dose one and dose two 21 days after vaccination (Table 4). A significantly increased RI was also seen following dose one and two in the 1–7 day post-vaccination period and also post dose two in the 8–21 day period.

Please cite this article in press as: Stowe J, et al. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.04.050

4. Discussion

This is the first study of the risk of intussusception after rotavirus vaccine to be reported from the European region and the first using a schedule in which the second dose is given at 3 months of age. Our relative risk estimate of 13.81 (6.44–28.32) for the 1–7 day period after the first dose of RV1 is somewhat higher than those obtained for RVI using the SCCS method in Mexico, Australia and Singapore (Table 4). This may reflect the use of symptom onset in our analysis rather than the later admission date as used by others; had admission date been used instead of onset date for the 15 cases in the 1–7 day period after the first dose, 5 would have been assigned to the 8–21 day risk period, thus decreasing the RI in this earlier interval. Our RI estimate for the 1–7 day period after dose two was within the range reported by the other three countries, indicating that the earlier age at administration of the second dose in England, which is closer to that in countries using the Expanded Programme on Immunisation schedule recommended by the World Health Organisation, is unlikely to influence the vaccine-associated risk of intussusception. When pooling results across the six studies there was an approximate three-fold increased risk 1–21 days after the first dose and two-fold increased risk after the second dose. The characteristics of the cases in the 1–7 day period after the first dose in our study (where we estimated that 93% were vaccine-attributable) were similar to those outside the vaccine risk period, confirming the findings from Singapore [10].

We also found a significantly elevated risk in the 8–21 day period after the second dose but not after the first. The results of the other three SCCS studies for this post-vaccination period were mixed, although the pooled estimate was consistent with our findings. The RI for this period will be affected by whether symptom onset or hospital admission date is used in the analysis, as with the 1–7 day period, though in the opposite direction. Using the overall RI for the 1–21 period should capture all vaccine-attributable cases and, in the meta-analysis, significantly elevated RI estimates for the 1–21 day period were found after both the first and second doses; in our study in England this gave AR estimates of 1.91 and 1.49 per 100,000 doses respectively.

In the UK, the risk of intussusception after rotavirus vaccine is explicit in written guidance provided to healthcare professionals administering the vaccine and parents are told to be aware of abdominal pain, vomiting and redcurrant jelly stools and to contact a doctor immediately to ensure rapid treatment [22]. In April 2015, two deaths from intussusception temporally related to rotavirus vaccination were reported in France in infants who did not receive timely medical care [23]. This led the World Health Organisation Global Advisory Committee on Vaccine Safety to publish a statement underlining the importance of close monitoring of infants after vaccination and the need for prompt medical care for infants with suspected intussusception at any time [24]. In our study, the interval between symptom onset and admission was short (mean <1 day) and similar in cases with a close temporal association with vaccination and those outside the post-vaccination risk period. However, the causal association with vaccination may not be recognised as there was absence of any mention of the vaccination in the medical records in all but one case. This case was one of 10 infants who received a second dose despite confirmed intussusception episode after their first dose. Although none of these infants had a repeat episode following their second dose, greater awareness of the contraindications to vaccination and of the vaccine-associated risk is needed.

This study uses routinely collected hospital data which has the potential for inaccuracy in the diagnostic coding. While we minimised misdiagnoses by excluding cases with insufficient information to confirm the diagnosis according to the Brighton Collaboration criteria, this may have resulted in exclusion of true cases. Furthermore, a recent study found that only 86% of intussusception cases reported to the British Paediatric Surveillance Unit had a HES admission with an intussusception code [25]. Both of these factors would lead to an underestimate of the attributable risk though not the RI estimates, assuming that missed cases were randomly distributed in relation to the timing of vaccination.

The 2–3 fold elevated risk of intussusception after a first and second dose of RV1 demonstrated by our study, would result in an estimated 21 additional intussusception cases each year in England. This number needs to be compared with the 25,000 annual admissions for an acute gastrointestinal infection that the rotavirus vaccine programme has prevented [14]. The benefit/risk profile of the programme is therefore still strongly positive [26]. It is however unclear whether the increased risk of intussusception in the post-vaccination period translates into a sustained increase in the absolute risk of an intussusception episode in the first year of life or whether, as suggested by ecological studies, this overall risk remains unchanged [27]. If so this would suggest that the vaccine acts as a trigger for an event that would anyway occur albeit later. Surveillance of intussusception in infants eligible to receive rotavirus vaccine in England will be continued in order to evaluate the overall ecological impact of the vaccination programme on this rare event.

Conflict of interest: None declared.

References

[1] Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003;9(May (5)):565–72.
[2] Diez Domingo J, Patrzalek M, Cantarutti L, Arnould B, Meunier J, Soriano-Gabarro M, et al. The impact of childhood acute rotavirus gastroenteritis on the parents' quality of life: prospective observational study in European primary care medical practices. BMC Pediatr 2012;12(May):58, http://dx.doi.org/10.1186/1471-2431-12-58.
[3] Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease. Vaccine 2007;25(May (20)):3962–70.
[4] Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001;344(February (8)):564–72.
[5] Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354(January (1)):23–33.
[6] Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354(1):11–22.
[7] Patel MM, López-Collada VR, Bulhões MM, De Oliveira LH, Bautista Márquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med 2011;364(June (24)):2283–92, http://dx.doi.org/10.1056/NEJMoa1012952.
[8] Carlin JB, Macartney K, Lee KJ, Quinn HE, Buttery J, Lopert R, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's national immunisation program. Clin Infect Dis 2013;57(November (10)):1427–34, http://dx.doi.org/10.1093/cid/cit520.
[9] Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN, Platt R, et al. Intussusception risk after rotavirus vaccination in U.S. infants. N Engl J Med 2014;370:503–12, http://dx.doi.org/10.1056/NEJMoa1303164. PMID: 24422676.
[10] Yung CF, Chan SP, Soh S, Tan A, Thoon KC. Intussusception and monovalent rotavirus vaccination in Singapore: self-controlled case series and risk-benefit study. J Pediatr 2015;167(July (1)):163–8.e1, http://dx.doi.org/10.1016/j.jpeds.2015.03.038.
[11] Velázquez FR, Colindres RE, Grajales C, Hernández MT, Mercadillo MG, Torres FJ, et al. Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. Pediatr Infect Dis J 2012;31:736–44.
[12] Weintraub ES, Baggs J, Duffy J, Vellozzi C, Belongia EA, Irving S, et al. Risk of intussusception after monovalent rotavirus vaccination. N Engl J Med 2014;370(February):513–9, http://dx.doi.org/10.1056/NEJMoa1311738.
[13] Samad L, Marven S, El Bashir H, Sutcliffe AG, Cameron JC, Lynn R, et al. Prospective surveillance study of the management of intussusception in UK and Irish infants. Br J Surg 2012;99(March (3)):411–5, http://dx.doi.org/10.1002/bjs.7821.

Please cite this article in press as: Stowe J, et al. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.04.050

[14] Atchison CJ, Stowe J, Andrews N, Collins S, Allen DJ, Nawaz S, et al. Rapid declines in age group-specific rotavirus infection and acute gastroenteritis among vaccinated and unvaccinated individuals within 1 year of rotavirus vaccine introduction in England and Wales. J Infect Dis 2016;213(January (2)):243–9, http://dx.doi.org/10.1093/infdis/jiv398.

[15] Hospital Episode Statistics, Health and Social Care Information Centre. http://www.hscic.gov.uk/hes [accessed 11.01.16].

[16] Tapiainen T, Bär G, Bonhoeffer J, Heininger U. Evaluation of the Brighton Collaboration case definition of acute intussusception during active surveillance. Vaccine 2006;24(February (9)):1483–7.

[17] Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res 2009;18(February (1)):7–26, http://dx.doi.org/10.1177/0962280208092342. PMID: 18562396.

[18] Andrews N, Miller E, Waight P, Farrington P, Crowcroft N, Stowe J, et al. Does oral polio vaccine cause intussusception in infants? Evidence from a sequence of three self-controlled cases series studies in the United Kingdom. Eur J Epidemiol 2002;17(8):701–6.

[19] Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. Biostatistics 2009;10:3–16, http://dx.doi.org/10.1093/biostatistics/kxn013. PMID: 18499654.

[20] Rotavirus immunisation programme: vaccine coverage estimates. Public Health England; 2015 https://www.gov.uk/government/publications/rotavirus-immunisation-programme-vaccine-coverage-estimates [accessed 11.01.16].

[21] Office for National Statistics, Estimated resident population mid-2008 by single year of age and sex on boundaries as at 1 April 2008, www.statistics.gsi.gov.uk/popest [accessed 11.01.16].

[22] Green book Immunisation against infectious disease: Rotavirus Green Book Chapter 27b v3_0, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457263/Green_Book_Chapter_27b_v3_0.pdf [accessed 11.01.16].

[23] Haut Conseil de la Sant Publique. Rotavirus infections: suspension of infant immunization recommendations, http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=501 [accessed 11.01.16].

[24] WHO. GAVCS. Statement on risks and benefits of rotavirus vaccines Rotarix and RotaTeq, http://www.who.int/vaccine_safety/committee/topics/rotavirus/rotarix_and_rotateq/statement_May_2015/en [accessed 11.01.2016].

[25] Samad L, Cortina-Borja M, Sutcliffe AG, Marven S, Cameron JC, Bashir HE, et al. National hospital data for intussusception: data linkage and retrospective analysis to assess quality and use in vaccine safety surveillance. Vaccine 2016;34(January (3)):373–9, http://dx.doi.org/10.1016/j.vaccine.2015.11.041.

[26] Clark A, Jit M, Andrews N, Atchison C, Edmunds WJ, Sanderson C. Evaluating the potential risks and benefits of infant rotavirus vaccination in England. Vaccine 2014;32(June (29)):3604–10, http://dx.doi.org/10.1016/j.vaccine.2014.04.082.

[27] Clarke M, Marshall H. Rotavirus vaccination for prevention of serious acute gastroenteritis and the importance of postlicensure safety monitoring. J Infect Dis 2012;206(1):3–5, http://dx.doi.org/10.1016/j.vaccine.2014.04.082.

Please cite this article in press as: Stowe J, et al. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation. Vaccine (2016), http://dx.doi.org/10.1016/j.vaccine.2016.04.050

pii: sp-00484-15 http://dx.doi.org/10.5665/sleep.5752

NEUROLOGICAL DISORDERS

Risk of Narcolepsy after AS03 Adjuvanted Pandemic A/H1N1 2009 Influenza Vaccine in Adults: A Case-Coverage Study in England

Julia Stowe, BA (Hons)[1]; Nicholas Andrews, PhD[2]; Christopher Kosky, MBBS[3]; Gary Dennis, MD[4]; Sofia Eriksson, PhD[5]; Andrew Hall, MBBChir[6]; Guy Leschziner, PhD[7]; Paul Reading, PhD[8]; John M. Shneerson, DM[9]; Katherine Donegan, PhD[10]; Elizabeth Miller, FRCPath[11]

[1]Research Fellow, Public Health England, London, UK; [2]Senior Statistician, Public Health England, London, UK; [3]Consultant Physician, Guy's and St Thomas' NHS Trust, London, UK; [4]Consultant Neurologist, Royal Hallamshire Hospital, Sheffield, UK; [5]Consultant Neurologist, National Hospital for Neurology and Neurosurgery, London, UK; [6]Consultant in Anaesthesia, Intensive Care and Sleep Disorders Medicine, University Hospitals of Leicester NHS Trust, Leicester, UK; [7]Consultant Neurologist/Clinical Lead – Sleep, Guy's and St Thomas' NHS Trust, London, UK; [8]Consultant Neurologist, South Tees NHS Trust, Middlesborough, UK; [9]Consultant Physician, Papworth Hospital NHS Foundation, Cambridge, UK; [10]Pharmacoepidemiology Research and Intelligence Unit, Medicines and Healthcare Products Regulatory Agency, UK; [11]Consultant Epidemiologist, Public Health England, London, UK

Study Objectives: An increased risk of narcolepsy has been observed in children following ASO3-adjuvanted pandemic A/H1N1 2009 (Pandemrix) vaccine. We investigated whether this risk extends to adults in England.

Methods: Six adult sleep centers in England were visited between November 2012 and February 2014 and vaccination/clinical histories obtained from general practitioners. Suspected narcolepsy cases aged older than 17 y were selected. The risk of narcolepsy following Pandemrix was calculated using cases diagnosed by the time of the center visits and those with a diagnosis by November 30, 2011 after which there was increased awareness of the risk in children. The odds of vaccination in cases and in matched population data were compared using a case-coverage design.

Results: Of 1,446 possible cases identified, most had onset before 2009 or were clearly not narcolepsy. Of the 60 remaining cases, 20 were excluded after expert review, leaving 40 cases with narcolepsy; 5 had received Pandemrix between 3 and 18 mo before onset. All the vaccinated cases had cataplexy, two received a diagnosis by November 2011 and two were aged 40 y or older. The odds ratio for vaccination in cases compared to the population was 4.24 (95% confidence interval 1.45–12.38) using all cases and 9.06 (1.90–43.17) using cases with a diagnosis by November 2011, giving an attributable risk of 0.59 cases per 100,000 doses.

Conclusions: We found a significantly increased risk of narcolepsy in adults following Pandemrix vaccination in England. The risk was lower than that seen in children using a similar study design.

Keywords: adult, case-coverage, narcolepsy, Pandemrix, vaccination

Citation: Stowe J, Andrews N, Kosky C, Dennis G, Eriksson S, Hall A, Leschziner G, Reading P, Shneerson JM, Donegan K, Miller E. Risk of narcolepsy after AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in adults: a case-coverage study in England. *SLEEP* 2016;39(5):1051–1057.

Significance

Our study shows that the causal association between narcolepsy and the oil-in-water adjuvanted pandemic H1N1 influenza vaccine is not, as previously thought, confined to children and adolescents and will add further impetus to the research into the etiology of this condition. While possession of the DQB1*06:02 gene is clearly implicated, environmental or other triggers appear to be necessary to instigate the onset in susceptible individuals. Further surveillance of populations who have received pandemic strain vaccines is needed in order to document whether the association is seen with other products and to provide insights into the likely auto-immune pathway by which the oil-in-water adjuvant and/or the viral antigens in the HIN1 pandemic strain trigger the pathological process that results in loss of orexin-producing neurons.

INTRODUCTION

Narcolepsy is a disabling and chronic sleep disorder characterized by excessive daytime sleepiness, hypnagogic hallucinations, sleep paralysis, and cataplexy. Narcolepsy is divided into narcolepsy with cataplexy (type 1) and narcolepsy without cataplexy (type 2).[1] Cataplexy is a unique symptom in which there is transient loss of skeletal muscle tone, with preservation of consciousness that is triggered by emotions such as laughter or anger.

The prevalence of narcolepsy with cataplexy is between 25 and 50 per 100,000 people with an incidence of around 0.74 per 100,000 person-years.[2] Onset usually occurs between 15 and 40 y of age and symptoms develop gradually, so time from onset to diagnosis can be many years. Both environmental and genetic factors play a role in its etiology. There is a strong association with the HLA DQB1*06:02 genotype, but this alone is not sufficient for the disease to develop. Narcolepsy is associated with specific loss of cells producing the neuropeptide hypocretin, resulting in low levels of hypocretin in the cerebrospinal fluid.

An H1N1 ASO3-adjuvanted pandemic vaccine (Pandemrix, GlaxoSmithKline Biologicals, Wavre, Belgium) was used in the United Kingdom (UK) from October 2009, initially for people comprising a seasonal influenza vaccine risk group[3] or health or social care workers, followed by children younger than 5 y from November 2009 onward.[4] Approximately 5.5 million people in the UK were vaccinated with Pandemrix.[5] It was the predominant H1N1 vaccine used within the European Union.[6] In August 2010 concerns were raised in Finland and Sweden about a possible association between narcolepsy and Pandemrix. A cohort study in Finland reported a 13-fold increased risk of narcolepsy following Pandemrix in children aged 4 to 19 y.[7] This was confirmed by a study in sleep centers in England, which identified a 14-fold increased risk in those aged 4–18 y.[8] Other studies subsequently published from Ireland and Norway also indicated an increased risk of narcolepsy in children who received Pandemrix.[9,10]

The initial signal in the Scandinavian countries was in children but more recently adult cases have been reported. A small case-control study in 25 adults in France suggested an elevated risk[11] as did a follow-up study in Finland published as an online report.[12] A record linkage cohort study in Sweden found no overall increased risk in adults, although there was a marginally elevated risk in those aged 21–30 y.[13] Using the same

published methodology as the childhood study in England,[8] we investigated whether there was an increased risk of narcolepsy in adults who received Pandemrix.

METHODS

Case Ascertainment and Validation

The sleep centers in England where the largest numbers of cases of narcolepsy are diagnosed were identified through the Hospital Episode Statistic (HES) database.[14] HES episodes in those age 16 y and older with an ICD 10 code of G474 in any diagnosis field were extracted for the period January 2009 to December 2012. Six sleep centers were identified as being the major centers that together covered 33% of the narcolepsy coded episodes in HES during this period. We estimated that within these centers approximately 30 cases may be seen with onsets from 2010 which should give sufficient power to detect at least a fivefold increased risk (80% power, 5% significance level, 5% vaccine uptake).

The six centers were visited between November 2009 and February 2010 (Table S1, supplemental material) and all those aged 16 y and older at the time of diagnosis were ascertained with the aim to include those aged 18 y and olderon September 1, 2009. These cases were found by searching local databases and electronic clinic letters for the keyword *narco* or searching for multiple sleep latency test (MSLT) reports for a diagnosis of narcolepsy. The cases from HES and those identified from the local searches were then merged and deduplicated using National Health Service (NHS) number or surname and date of birth. These potential cases were reviewed using medical records to establish symptom onset details, clinical history, and sleep study results. If any information was missing from the electronic records, the case notes were reviewed to identify the relevant information.

Details of the anonymized cases collated at center visits were evaluated by a review panel (authors GL, JShn, AH, SE) who were blinded to vaccination status. To expedite the review, cases with a clear history of excessive daytime sleepiness (EDS) and cataplexy or EDS with a positive MSLT or cerebrospinal fluid positive for narcolepsy were not all sent to the panel for review; rather, a few examples of these cases were first shown to the panel for their agreement. The four sleep center consultants on the review panel categorized each case as definite narcolepsy with cataplexy; definite narcolepsy without cataplexy; probable narcolepsy and insufficient evidence to confirm a diagnosis of narcolepsy. The panel based their diagnosis on the International Classification of Sleep Disorders, Second Edition (ICSD-2) criteria.[15] A diagnosis based on the consensus view of three of the four panel members was taken, with remaining cases discussed by teleconference.

Pandemrix vaccination histories for cases with definite or probable narcolepsy were obtained from the patient's general practitioner (GP) who was asked for date and batch number of any pandemic vaccine given, the date of first symptoms and/or first consultation for narcolepsy symptoms, presenting symptoms, history of pandemic influenza illness, and whether the patient was in a clinical risk group for which pandemic strain H1N1 vaccine was recommended.

Index Dates: Definitions

The date of symptom onset was defined as the earliest date of EDS or cataplexy as given by the GP or recorded in the sleep center notes or referral letters. When the exact date was not available we used the midpoint of the month of the approximate date and also approximated an earliest and latest date of onset for sensitivity analysis. The date of first known health care contact was the earliest recorded consultation for a sleep related problem as reported by the GP or in the center notes. The date of diagnosis was the date when there was either a clinical history and sleep study confirming narcolepsy or sufficient clinical information to diagnose probable narcolepsy.

Statistical Analysis

We assessed the association between vaccination and narcolepsy using the case coverage method[16] in which the odds of vaccination in cases is compared to the odds of vaccination in matched population data. The analysis is by logistic regression with the outcome as vaccinated (yes/no) in the cases and with an offset for the log odds of the matched coverage. Population vaccine coverage was calculated from the Clinical Practice Research Datalink (CPRD).[17] We used patient-level data to derive cumulative coverage stratified by exact date (from September 2009 to March 2011), age on January 1, 2010 (categorized as 18, 19, 20–24, 25–29, …, ≥ 80 years) and, when matching by risk group, being in a vaccine target clinical risk group. This was then used to look up the appropriate matched coverage for each narcolepsy case based on their age, risk group status (if matching on risk group) and narcolepsy index date (e.g. date of onset). To determine vaccine coverage within 6 mo of an index date, the coverage 6 mo earlier was subtracted from the matched coverage on the index date. Patients were categorized as being in a risk group if there was any clinical code denoting chronic heart disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, chronic liver disease, immunological disorders, multiple sclerosis, or stroke/transient ischemic attack in the 5 y prior to September 2009 for the 2009–2010 vaccination season and September 2010 for the 2010–2011 season. We used similar criteria for allocating narcolepsy cases to a risk group based on the information provided by the GP on clinical conditions considered high risk for influenza.

The primary analysis was restricted to cases diagnosed by November 30, 2011 after which there was increased awareness of the risk seen in children with the potential for accelerated diagnosis in vaccinated cases. It also used first symptoms as the index date and the odds of vaccination at any time before onset. Additional analyses were performed using first health care contact and diagnosis as the index date, all cases diagnosed by the center visit date, not matching coverage by risk group status and calculating the odds of vaccination within 6 mo of the index date. Stratification by age younger than 30 y and age 30 y and older on September 1, 2009 was also done. Sensitivity analyses in which population coverage was increased or decreased by a relative 20% (for example, 10% coverage decreasing to 8% or increasing to 12%) and using the earliest and latest estimated onset dates were also conducted. These analyses were documented in a statistical analysis plan prior to receipt of the data

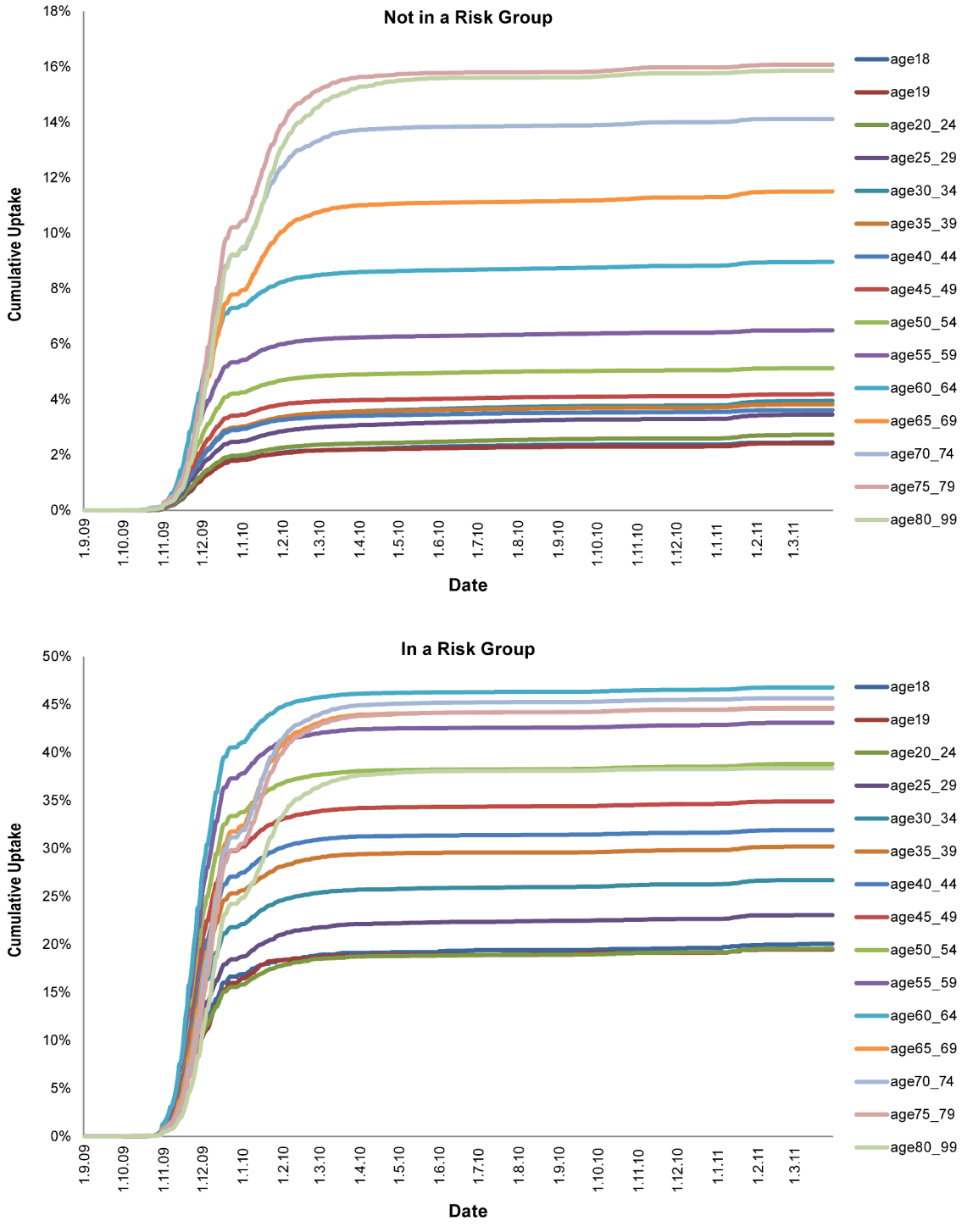


Figure 1—Vaccine uptake by age, risk group, and period from the Clinical Practice Research Datalink (CPRD) by clinical risk group status.

by the statistician (NA) for analysis. Analysis was done using Stata version 13 (StataCorp, College Station, TX).

RESULTS

Vaccine Coverage

Coverage data were obtained from approximately 3.5 million patients aged 18–99 y registered in the CPRD practices on September 1, 2009. Vaccination coverage was low in healthy young adults and increased with age. As expected for those in a risk group, uptake was higher and also increased with age (Figure 1). Most vaccination was during 2009–2010 with only small increases in 2010–2011, which is in agreement with other data.[8]

Study Cases

A total of 2,554 potential patients were identified through the different search strategies and data sources. When cross

Table 1—Demographic features and clinical features of 40 patients with narcolepsy according to ASO3 adjuvanted pandemic A/H1N1 2009 vaccination.

Factor	Level	Unvaccinated	Vaccinated before Onset	Total
Age at September 2009 (years)	18–19	5	1	6
	20–24	7	2	9
	25–29	5	0	5
	30–34	4	0	4
	35–39	3	0	3
	40–44	7	1	8
	45–49	2	0	2
	50–54	1	1	2
	≥ 55	1	0	1
Sex	Male	14	1	15
	Female	21	4	25
Diagnostic category	Narcolepsy with cataplexy	23	5	28
	Narcolepsy without cataplexy	8	0	8
	Probable narcolepsy	4	0	4
HLA DQB1*06:02	Positive	11	2	13
	Negative	3	0	3
	Not known	21	3	24
Comorbidity	No	32	2	34
	Yes	1	3	4
	Not known	2	0	2
Seasonal vaccine before onset (and from 2008/2009)	No	33	2	35
	Yes (before symptoms)	1	2	3
	Not known	1	1	2

HLA, human leukocyte antigen.

referenced and de-duplicated 1,446 patients remained and were taken forward for case note review (Table S1). The majority, 926, had symptom onset before 2009 and 441 clearly did not have narcolepsy when the notes were reviewed; these 1,367 cases were excluded. The case notes of 10 could not be traced and one person was seen in two centres. Of the remaining 68 patients 30 were considered definite cases after reviewing the available information and 38 were sent to the panel for review. The panel members were in initial agreement on 28, with agreement reached after teleconference for the remaining 10. Twenty cases were categorized as not narcolepsy/insufficient evidence and excluded with the remaining 18 cases added to the 30 definite cases. Of the 48 cases, 8 were not included in the final analysis because although age 18 y or older at diagnosis they were younger than 18 y on September 1, 2009. This left a total of 40 adults with narcolepsy of whom 28 were categorized as definite narcolepsy with cataplexy, 8 as definite narcolepsy without cataplexy, and 4 probable narcolepsy.

Four individuals were reported to have an influenza-like illness prior to first symptoms, although only one within 3 mo of symptoms; none of these four cases was vaccinated.

Vaccination History

We obtained vaccination history on all 40 cases and risk group status for 38 (Table 1). Five patients had received Pandemrix prior to first symptoms of whom three were in a clinical risk group recommended for vaccination; all five had cataplexy. One had onset within 3 mo, two within 3 to 6 mo, and two between 7 and 18 mo after vaccination; two had a confirmed human leukocyte antigen (HLA) DQB1*06:02 genotyping, with the other three not tested.

Figure 2 shows the timing of onset for the 40 adult narcolepsy cases by vaccination status and monthly vaccine uptake in the age-matched population. The first vaccinated case had onset in early 2010 and the latest in 2012 after receiving Pandemrix in 2011 when residual stocks were used instead of seasonal vaccine.[18] Mean time from onset to diagnosis using cases with onset in 2009–2011 and diagnosis within 30 mo was 493 days in four vaccinated cases and 434 in 28 nonvaccinated cases (P = 0.69, Kruskal-Wallis test).

Case Coverage Analysis

The primary analysis, which used symptom onset, cases with a diagnosis by November 30, 2011 and matching on risk group, only included two of the five vaccinated cases but showed an elevated odds ratio of 9.06 (1.90–43.17) (Table 2). When including all cases ascertained by the date of the centre visit (five vaccinated cases) the odds ratio was lower but still significant at 4.24 (1.45–12.38). Higher odds ratios (but fewer vaccinated cases) were seen when including only cases with onset within 6 mo of vaccination. When other outcome dates were used such as date of first healthcare contact or date of diagnosis, the odds ratios reduced and some became nonsignificant (Table 2). The sensitivity analyses and age stratification were based on

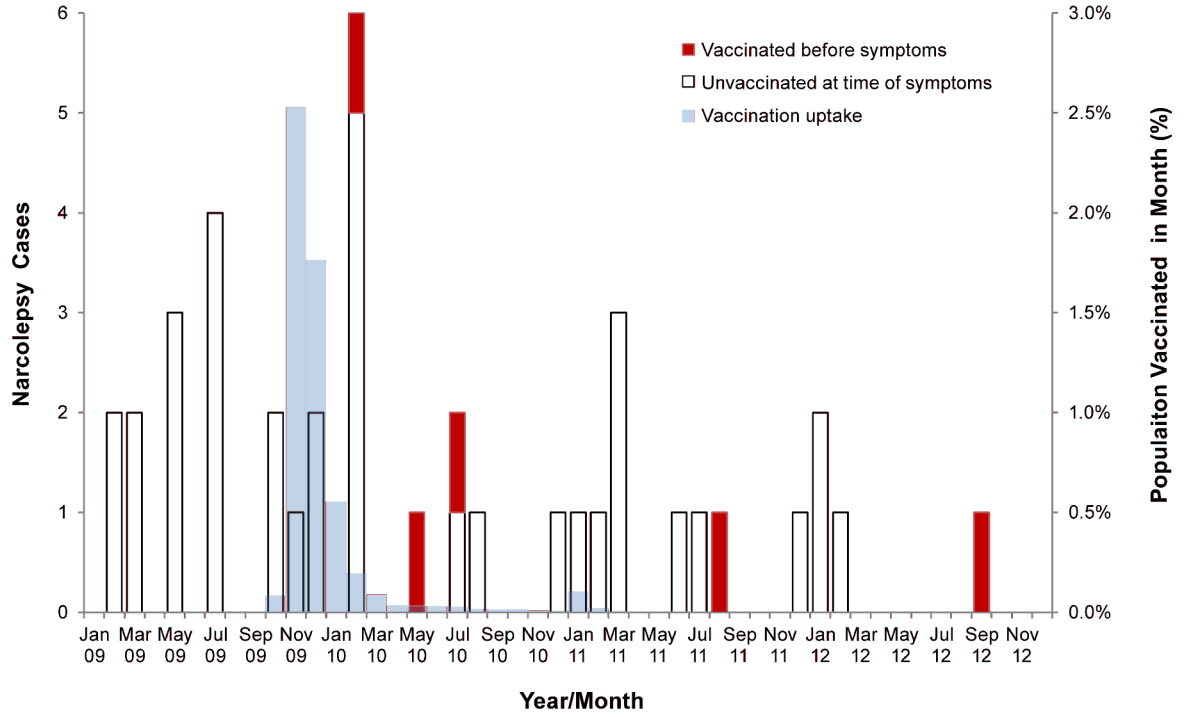


Figure 2—Timing of onset for the 40 adult narcolepsy cases by vaccination status and monthly vaccine uptake in the age matched population.

Table 2—Case coverage analysis in patients with narcolepsy showing odds ratios for receipt of ASO3 adjuvanted pandemic A/H1N1 2009 vaccine before narcolepsy onset using different index dates, follow-up periods, and risk intervals.

Censoring Date for Inclusion by Diagnosis	Interval before Index Date	Number of Patients Vaccinated	Total Patients Eligible for Vaccination in Interval Before Index	Not Matching on Risk Group		Matching on Risk Group	
				Average Coverage	Odds Ratio (95% CI)	Average Coverage	Odds Ratio (95% CI)
USING FIRST SYMPTOMS							
Nov 30, 2011	6 months	2	10	0.026	11.29 (2.05–62.05)	0.016	17.94 (3.34–96.23)
	Any time	2	10	0.043	5.77 (1.02–28.14)	0.027	9.06 (1.90–43.17)
Center visit	6 months	3	22	0.019	9.64 (2.54–36.57)	0.014	12.74 (3.43–47.26)
	Any time	5	27	0.047	4.74 (1.77–12.67)	0.063	4.24 (1.45–12.38)
USING FIRST HEALTH CARE CONTACT							
Nov 30, 2011	6 months	1	12	0.017	6.10 (0.65–57.10)	0.011	9.72 (1.06–88.79)
	Any time	2	13	0.044	4.09 (0.89–18.89)	0.028	6.40 (1.40–29.37)
Center visit	6 months	1	17	0.014	5.16 (0.58–45.73)	0.009	8.05 (0.93–69.76)
	Any time	5	33	0.049	3.54 (1.35–9.27)	0.058	3.37 (1.20–9.48)
USING DATE OF DIAGNOSIS							
Nov 30, 2011	6 months	0	14	0.028	0	0.016	0
	Any time	2	19	0.056	2.03 (0.45–9.14)	0.035	3.32 (0.75–14.66)
Center visit	6 months	0	14	0.028	0	0.016	0
	Any time	5	40	0.054	2.54 (0.98–6.59)	0.057	2.64 (0.97–7.20)

CI, confidence interval.

all cases diagnosed by the center visit date to increase power (Table 3). Results were similar when allowing for uncertainty in the onset date and remained significant when increasing coverage by a relative 20%. Odds ratios were similar for those younger than 30 y and older individuals, but the number of cases in each age group was small.

Table 3—Sensitivity analysis and age stratification using vaccination at any time prior to first symptoms and all cases diagnosed by the center visit date.

Analysis	Number of Patients Vaccinated prior to First Symptoms	Total Patients Eligible for Vaccination prior to First Symptoms	Average Coverage Matching on Risk Group	Odds Ratio (95% CI)
Best estimate of onset date	5	27	0.063	4.24 (1.45–12.38)
Earliest onset date	5	23	0.066	5.25 (1.72–16.02)
Latest onset date	5	28	0.061	4.13 (1.42–12.00)
Coverage reduced by relative 20%	5	27	0.050	5.42 (1.87–15.73)
Coverage increased by relative 20%	5	27	0.075	3.45 (1.18–10.14)
Age 18–29 y on September 1, 2009	3	16	0.059	4.36 (1.11–17.17)
Age 30 y or older on September 1, 2009	2	11	0.067	4.07 (0.73–22.63)

CI, confidence interval.

Attributable Risk

The calculation for the vaccine-attributable risk used the odds ratio of 4.24 based on symptom onset at any time (Table 2). Using the odds ratio to approximate relative risk (RR), the attributable fraction ((RR−1)/RR)) is (3.24/4.24), which applied to the five vaccinated patients in the analysis gives an estimate of 3.82 attributable cases. HES data indicate that the sleep centers visited provided a diagnosis for approximately 33% of the narcolepsy cases in England in the study period, giving an estimated total of 3.82/0.33 = 11.6 attributable cases in England. Counting pandemic vaccine doses administered to those aged 18–59 y gives a total of 1,975,000 based on the final cumulative uptake and the Office for National Statistics population data for England in 2009.[19] The attributable risk is therefore 11.6/1,975,000 = 0.59 per 100,000 doses

DISCUSSION

We found a significantly increased risk of narcolepsy in adults following AS03 adjuvanted pandemic strain vaccine in England. The odds ratio in adults was 9.06 (1.90–43.17) in the primary analysis and 4.24 (1.45–12.38) using all cases with a diagnosis by the date of the sleep centre visit, with an estimated attributable risk 0.59 per 100,000 doses. This risk is lower than we found in children where the comparable odds ratios were 14.4 (4.3 to 48.5) and 8.3 (3.1 to 22.3) respectively, and attributable risk of 1.74 cases per 100,000 doses.[8] As in the Finnish adult study,[12] the risk was highest within 6 mo of vaccination with an odds ratio of 12.74 (3.43–47.26).

The mechanism by which narcolepsy with cataplexy is associated with Pandemrix is not known. HLA DQB1*06:02 is present in 95% of patients with narcolepsy with cataplexy (type 1).[20,21] In this study, all five vaccinated narcolepsy patients developed narcolepsy with cataplexy. The two tested patients were positive for HLA DQB1*06:02. It is possible that Pandemrix provides a second hit in those patients with a genetic vulnerability to the development of narcolepsy with cataplexy. Pandemrix may result in the development or augmentation of autoantibodies to hypocretin-producing cells and the destruction of these cells results in the development of narcolepsy with cataplexy. Others have speculated on autoimmunity as a mechanism to explain the link between narcolepsy and Pandemrix.[21] As with the pediatric study in England,[8] there was no evidence that prior swine influenza infection was a risk factor, with only one study case reporting influenza-like-illness in the 3 mo prior to their narcolepsy symptoms. Recent research, however, suggests that vaccine-induced narcolepsy may be associated with the induction of antibodies to the H1N1 nucleoprotein of the Pandemrix strain that cross-react with hypocretin receptors.[22,23]

Our odds ratio for the primary analysis is lower than found in the French case control study which reported an odds ratio of 16.8 (1.9–149.1) for cases aged 18 years and over using symptom onset as the index date.[11] In that study 28% of eligible cases declined to participate and onset date was based on patient recall, allowing the potential for participation and recall bias which would likely lead to an overestimate of the association. In the Swedish record linkage study, which failed to find an elevated risk in those aged 20 y and older,[13] the narcolepsy diagnosis was not verified and the index date was date of diagnosis, which would likely underestimate the association. In our study, cases were verified by an expert panel according to ICSD-2 diagnostic criteria, and onset date was independently obtained from referral letters, hospital notes, and GP records. Based on this information, we defined the earliest and latest possible date of first symptoms; odds ratios generated with these extreme dates were similar to the odds ratio using the most likely onset date.

To ensure as complete case ascertainment as possible, cases were identified by actively searching local electronic patient records and databases and cross-checking with cases in the national hospital database. This approach should avoid selection bias arising from differential ascertainment of diagnosed cases in vaccinated and unvaccinated individuals, as might occur if reliant on clinician recall. In the primary analysis, data were censored to only include cases diagnosed by November 30, 2011 to limit potential bias from accelerated diagnosis in patients in whom an association with vaccination was suspected once the association had generated media interest in December 2011.[8] We found that the odds ratio using cases diagnosed by the center visit date was lower than that using cases diagnosed by November 30, 2011 rather than higher, which might have occurred if there was a tendency for more rapid diagnosis of vaccinated cases after the association was publicized.

Our case-coverage approach relies on the representativeness of the coverage data used. In this study we used information

from the CPRD, a different GP dataset than we used in the pediatric narcolepsy study.[8] It was reassuring that age- and risk group–specific coverage estimates were similar in both GP datasets (data not shown) and were comparable to national coverage data.[17] The sensitivity analysis showed that even if we have underestimated coverage by as much as a relative 20% (for example, due to vaccination given outside of general practice not getting on the record) the association would still be significant, odds ratio 3.45 (1.18–10.14) for vaccinated at any time before onset.

In conclusion, we found evidence of an increased risk of narcolepsy in adults following AS03 adjuvanted pandemic strain vaccine in England. We were unable to define how the risk varied with age due to the relatively small numbers of cases. However, the data do not suggest a threshold age above which the risk is zero as vaccine-associated cases were identified across the age range studied. Further studies in collaboration with other European countries that used Pandemrix may help to more accurately define the age-specific risk in adults.

REFERENCES

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.
2. Longstreth WT Jr, Koepsell TD, Ton TG, Audrey F. Hendrickson AF, van Belle G. The epidemiology of narcolepsy. Sleep 2007;30:13–26.
3. Public Health England. Immunisation against infectious disease. Influenza: the green book, chapter 19. Accessed January 22, 2016. Available from: https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book.
4. Joint Committee on Vaccination and Immunisation. Advice on the H1N1v vaccination programme. Friday 8th January 2010. Accessed January 22, 2016. Available from: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_112665.pdf.
5. Sethi M, Pebody R. Pandemic H1N1 (Swine) Influenza Vaccine Uptake amongst Patient Groups in Primary Care in England 2009/10. Accessed January 22, 2016. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215977/dh_121014.pdf.
6. European Medicine Agency. Assessment report: Pandemrix. Accessed January 22, 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000832/WC500118056.pdf.
7. Nohynek H, Jokinen J, Partinen M, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PloS One 2012;7:e33536.
8. Miller E, Andrews N, Stellitano L, et al. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. BMJ 2013;346:f794.
9. O'Flanagan D, Barret AS, Foley M, et al. Investigation of an association between onset of narcolepsy and vaccination with pandemic influenza vaccine, Ireland April 2009-December 2010. Euro Surveill 2014 May 1;19:15–25.
10. Heier MS, Gautvik KM, Wannag E, et al. Incidence of narcolepsy in Norwegian children and adolescents after vaccination against H1N1 influenza A. Sleep Med 2013;14:867–71.
11. Dauvilliers Y, Arnulf I, Lecendreux M, et al. Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France. Brain 2013;136(Pt 8):2486–96.
12. Jokinen J, Nohynekm H, Honkanenm J, et al. Working paper: Association between the pandemic vaccine and narcolepsy in adults. Accessed January 22, 2016. Available from: http://urn.fi/URN:ISBN:978-952-245-921-3.
13. Persson I, Granath F, Askling J, Ludvigsson JF, Olsson T, Feltelius N. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. J Intern Med 2014;275:172–90.
14. Health & Social Care Information Centre. Hospital Episode Statistics. Accessed January 22, 2016. Available from: http://www.hscic.gov.uk/hes.
15. American Academy of Sleep Medicine. International Classification of Sleep Disorders, 2nd ed. Diagnostic and coding manual. Westchester, IL: American Academy of Sleep Medicine, 2005.
16. Farrington CP. Control without separate controls: evaluation of vaccine safety using case-only methods. Vaccine 2004;22:2064–70.
17. The Clinical Practice Research Datalink (CPRD). Accessed January 22, 2016. http://www.cprd.com.
18. Begum F, Pebody R. Seasonal influenza vaccine uptake amongst GP patient groups in England, Winter season 2010-11. Accessed January 22, 2016. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216393/dh_129856.pdf.
19. Office for National Statistics. Population Estimates Unit. Estimated resident population mid-2009 by single year. Accessed January 22, 2016. http://www.ons.gov.uk.
20. Mignot E, Lammers GJ, Ripley B, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553–62.
21. Thebault S, Vincent A, Gringras P. Narcolepsy and H1N1 vaccination: a link? Curr Opin Pulm Med 2013;19:587–93.
22. Ahmed SS, Volkmuth W, Duca J, et al. Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2. Sci Transl Med 2015;7:294ra105.
23. Vaarala O, Vuorela A, Partinen M, et al. Antigenic Differences between AS03 Adjuvanted Influenza A (H1N1) Pandemic Vaccines: Implications for Pandemrix-Associated Narcolepsy Risk. PLoS One 2014;9:e114361.

ACKNOWLEDGMENTS

The authors thank Professor Stephen Evans, London School of Hygiene and Tropical Medicine for review of the statistical analysis plan. The authors gratefully acknowledge Joanne Williamson, Anne Brooks, Rebecca Chadwick, and Anne Yendley for their assistance at each of the study centres. We also acknowledge Paul Gringras for his help in setting up the study. We thank the general practitioners who assisted with the follow up. The HES data are re-used with permission of the Health and Social Care Information Centre. All rights reserved. Authors' contributions; EM, NA, JS, and CK developed the study protocol. Authors CK, JShn, AH, SE, PR, and GD designed data collection tools and monitored data collection at their individual centres. JS extracted clinical information from the centre notes. JS extracted the HES cases and conducted the GP follow up. KD extracted the CPRD data. Authors GL, JShn, AH, SE formed the review panel. NA conducted the statistical analysis and JS wrote the first draft of the paper. All authors contributed to subsequent revisions and approved the final version.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August, 2015
Submitted in final revised form December, 2015
Accepted for publication January, 2016

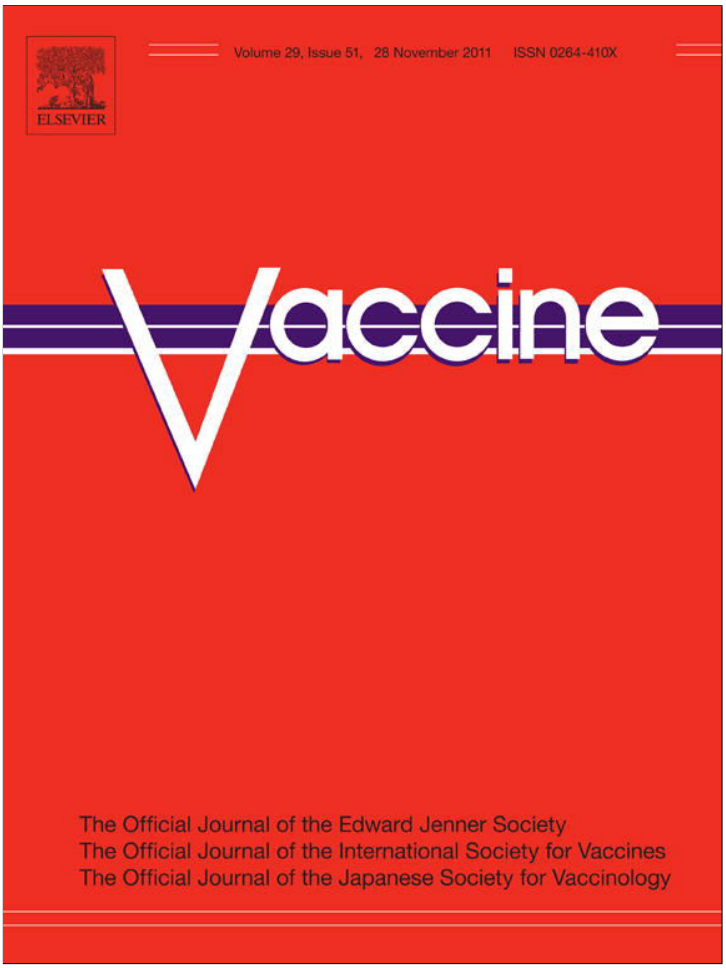
Address correspondence to: Julia Stowe, BA (Hons), Public Health England, 61 Colindale Avenue, London NW9 5EQ; Email: Julia.Stowe@phe.gov.uk

DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Eriksson and Dr. Dennis have participated in speaking engagements for UCB Pharma and Eisai Pharma. The other authors have indicated no financial conflicts of interest. Ethics approval: PHE has approval for England from the National Information Governance Board for Health and Social Care (NIGB) (PIAG ref: PIAG 03-(c)/2001), which allows us access to patient identifiable information for vaccine safety monitoring purposes.

Table S1—Numbers of potential cases ascertained at each centre, numbers excluded and numbers included in the final analysis.

Centre	Centre visit date	Number of potential cases identified at centre visits	Reasons for initial exclusions at centre visits			Expert review			Final number (aged ≥18 years at September 2009)
			First symptoms before 2009	Diagnosis of narcolepsy not confirmed by centre	Notes missing/ duplicate	Clear case not reviewed by experts	Reviewed by expert panel	Not narcolepsy/ insufficient evidence after panel review	
St Thomas' London	09/11/2012	220	171	26	0	7	16	7	16 (2)
UCL, London	15/04/2013	76	58	14	0	3	1	0	4
Cambridge	21/06/2013	368	197	152	0	8	11	9	10 (2)
Sheffield	20/11/2013	167	101	61	1	4	0	0	4
Leicester	12/06/2013	249	108	135	0	3	3	3	3 (1)
Middlesbrough	04/02/2014	366	291	53	10	5	7	1	11 (3)
All		1446	926	441	11	30	38	20	40 (8)



Vaccine 29 (2011) 9467–9472

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: A database study

Julia Stowe[a,*], Nick Andrews[b], Phil Bryan[c], Suzie Seabroke[c], Elizabeth Miller[a]

[a] Immunisation, Hepatitis and Blood Safety Department, Health Protection Agency, London, United Kingdom
[b] Statistics Unit, Health Protection Agency, London, United Kingdom
[c] Vigilance & Risk Management of Medicines, Medicines and Healthcare products Regulatory Agency, London, United Kingdom

ARTICLE INFO

Article history:
Received 2 June 2011
Received in revised form
30 September 2011
Accepted 11 October 2011
Available online 20 October 2011

Keywords:
Convulsions
Influenza vaccine
Monovalent H1N1 vaccine
Vaccine associated adverse events
Self-controlled case-series method

ABSTRACT

The monovalent H1N1 (2009) pandemic influenza vaccine used predominantly in the UK in 2009/10 was a split virion vaccine with a novel oil-in-water adjuvant (AS03). While this was highly immunogenic it was also reactogenic especially for fever in children. There is a paucity of comparative data on reactogenicity of trivalent influenza vaccine (TIV). Using the General Practice Research Database (GPRD) we investigated whether there was an increased risk of convulsions in children vaccinated with monovalent H1N1 influenza vaccine in the 2009/10 season and also the risk after vaccination with the seasonal TIVs using the self-controlled case-series method. A total of 2366 children aged under 10 years with at least one convulsion recorded in the GPRD and who had received at least one influenza vaccine at anytime (2858 doses of TIV and 1895 doses of the monovalent H1N1 influenza vaccine) were identified between May 2000 and April 2010. Over this period these 2366 children had a total of 3846 convulsion episodes. There was no increase in the incidence rate ratio (IRR) in the week after vaccination for either the monovalent H1N1 influenza vaccine (IRR 0.99, 95% CI 0.61–1.60) or the first dose of TIV (IRR 0.89, 95% CI 0.53–1.52). A signal of an elevated risk in the first few days after the second dose of monovalent H1N1 influenza vaccine was seen with an IRR for days 1–3 post vaccination of 3.48 (95% CI 0.86–14.07). This is consistent with findings of increased fever in a clinical trial. These results neither provide evidence of an increased risk of convulsions following TIV over a 10-year surveillance period nor following a single dose of the AS03 adjuvanted monovalent H1N1 vaccine in 2009/10.

1. Introduction

Febrile convulsions occur in young children peaking at the age of 1 year and are triggered by a sudden rise in body temperature. The fever can be associated with an infection or can occur with some paediatric vaccines. For live vaccines such as the combined measles, mumps and rubella (MMR) vaccine there is an elevated risk of a convulsion 6–11 days later when the viraemia and associated fever occur, the absolute risk being in the range of 1 in 600 to 1 in 3000 doses [1–3]. For inactivated vaccine such as whole cell pertussis-containing vaccines, the risk period is within a day or so of vaccination [3,4] and has been reduced by the switch to acellular pertussis containing vaccines [5–7]. For the inactivated trivalent influenza vaccine (TIV), its use in children has been limited until recently and thus there is a paucity of data on any associated risks of febrile convulsion.

In the UK children aged 6 months and over in a clinical risk group (e.g. chronic respiratory, heart, renal, or neurological disease.) are targeted on an annual basis to receive one dose of TIV each year or two doses if receiving the vaccine for the first time. The H1N1 (2009) vaccine used predominantly in the national programme in England and Wales was a split virion vaccine with an oil-in-water adjuvant ($AS03_B$-Pandemrix™). Compared with the unadjuvanted whole virion vaccine that was also purchased for the national programme (Celvapan™), the $AS03_B$ adjuvanted vaccine was more immunogenic, but also more reactogenic especially for fever at the second dose which was reported in 22.4% of children under 5 years of age vs 8.9% after the first dose [8]. Initially during the H1N1 (2009) influenza vaccination campaign in the UK only those in risk groups were offered the vaccine with a two-dose schedule recommended for children under 10 years of age from November to December 2009. From December 2009 due to concerns about the high fever rate with the second dose, a single dose of the $AS03_B$ adjuvanted vaccine was recommended in the national programme with a second dose only being offered to immunocompromised individuals

Abbreviations: GPRD, General Practice Research Database; TIV, trivalent influenza vaccine.

* Corresponding author. Tel.: +44 020 8327 7485.
E-mail address: julia.stowe@hpa.org.uk (J. Stowe).

0264-410X/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2011.10.029

[9,10]. The whole virion vaccine was recommended for children who were egg allergic and was given as a two-dose schedule.

We investigated whether there was an increased risk of convulsions in children following the monovalent $AS03_B$ adjuvanted pandemic strain vaccine and the risk following vaccination with the seasonal TIV in the period 1st May 2000 to 30th April 2010 using the self controlled case series method with cases identified in the General Practice Research Database (GPRD) [4].

2. Methods

Children were selected from the GPRD if they had received either monovalent H1N1 (2009) influenza vaccine or seasonal TIV or both and had a Read coded convulsion while aged less than 10 years in the period 1st May 2000 and 30th April 2010. The General Practice Research Database, which is one of the world's largest primary care databases, holds data on consultations, referrals, prescriptions and vaccinations for over 3 million active patients in practices throughout the UK (5.7% of the population). Diagnostic and medical events have very specific Read codes assigned to them, which can be used to identify such events. It not only holds information on activity in the primary care setting but secondary care events are feedback into the system through hospital discharge letters and the electronic reporting of results. If the patient was first registered with the GP surgery within the study period the start date for follow-up was defined as 3 months after first registration to reduce the risk of retrospective reporting of recent events on registration. The end of follow-up was defined as either on the patient's 10th birthday, the date transferred out of the practice or the date of last data download from the practice or 30/4/2010 if any of these was earlier than the patient's 10th birthday patients with an "acceptable" status were selected whose practice record had listed an "up-to-standard" date earlier than the patient's first or new consultation for the condition of interest. The up to-standard date reflects when the practice complied with specific quality measures based on completeness, continuity, and plausibility in key areas. Acceptable status is given to a patient when certain data quality conditions have been met, such as no events recoded before the birth date, age less than 115 years, and a completed gender field.

The exposure of interest was vaccination with either monovalent H1N1 influenza vaccine during the 2009/10 influenza season or seasonal TIV during the 10 years prior to 2009/10. Code lists for influenza vaccines were developed using both the product and medical browsers searching for *flu*, *vaccine*, *celvapan*, *pandemrix*, *H1N1*. Additional searches were also made using BNF Code 14040900. The primary outcome of interest was a diagnosis of a convulsion; a specific diagnosis of febrile convulsions was not distinguished to allow for coding differences within the data. The code list for convulsions was developed using the medical browser searching for 'convulsi', 'seizure', 'fit' to determine an initial list and then further searches based on similar Read Codes.

The age distribution of vaccinated cases with a convulsion identified in the GPRD was compared with that of all children under 10 years of age admitted to hospital in England with a convulsion using Hospital Episode Statistics (HES) [11]. HES data were obtained for the year April 2008 to March 2009 for children under 10 years with a ICD10 code of R56.0 "Febrile convulsion" or R56.8 "Other and unspecified convulsions" in any diagnosis field.

2.1. Statistical methods

To calculate the relative incidence the self-controlled case-series method was used. This is a case only method so only cases of convulsion needed selection from the GPRD. Person time and events for each individual were stratified by age (1 year age bands), calendar period (May 2000–April 2005, May 2005–April 2010), season (March–May, June–August, September–November, December–February) and vaccine risk period (background, 0, 1–3, 4–7 days post vaccination). A pre-vaccination low risk period of 2 weeks was taken out of the background risk to allow for delayed vaccination due to a febrile convulsion. Relative incidence estimates adjusted for age, period and season were obtained by conditional Poisson regression for seasonal vaccine (combined across seasons) and pandemic vaccine for 2009/10. The pandemic vaccine risk was assessed overall and also split by first and second dose. Repeat convulsion episodes within individuals were regarded as new episodes if they occurred at least 10 days apart.

3. Results

A total of 2366 children received a vaccine in the follow-up period and had at least one convulsion episode. The children were followed up for an average of 5.1 years each (range 0.3–10.0 years) and had a total 3846 episodes that were at least 10 days apart. Of the 2366 children, 1721 (72.7%) had one episode, 324 had two, 162 had three and 159 had four or more episodes. The children received a total of 2858 doses of seasonal TIV and 1895 doses of monovalent H1N1 (2009) vaccine.

The number of children receiving TIV increased each year over the study period with the influenza season 09/10 having the highest number of children vaccinated. Consistent with how the vaccination campaign was implemented, of the children who received monovalent H1N1 (2009) vaccine only 227 (13.6%) went on to have a second dose (Fig. 1). Of these 227 who went on to have a second dose 1 had an event on the day of vaccination, 1 on day 1 and 1 on day 2. In the study population the peak of convulsions occurred at the age of 1 year. This is similar to the age distribution seen in hospital admitted children with convulsions for the year 08/09 (Fig. 2). The distribution of cases by season suggested a rise in cases in the winter months with 917 in September to November, 1121 in December to February, 1011 in March to May and 797 cases occurring in June to August.

In the 30 days either side of vaccination with the H1N1 (2009) vaccine there is a suggestion of an excess of cases on the day of vaccination and just afterwards (Fig. 3). However, the self controlled case series analysis showed no evidence of an increased relative incidence in any of the pre-determined risk periods for either the seasonal TIV or pandemic strain vaccine (Table 1). When H1N1 (2009) was stratified by first and second dose the relative incidence estimates were higher post second dose, particularly for day 0 and days 1–3, however, numbers were small and 95% confidence intervals wide (Table 2). A post hoc analysis of the H1N1 (2009) vaccine cases grouping days 0–2 together, based on the apparent excess on days 0–2, was carried out. This relative incidence was 1.69, 95% confidence interval (CI) 0.93–3.07 overall and, when stratified by first and second dose, was 1.35 (95% CI 0.67–2.72) for the first dose and 5.21 (95% CI 1.66–16.33) for the second dose.

In the 2 weeks prior to vaccination there were significantly fewer convulsion episodes for children who went on to receive a first dose of the monovalent H1N1 (2009) vaccine, relative incidence 0.37 (95% CI 0.20–0.68) but this is not evident in the 2 weeks prior to the receipt of seasonal TIV, or for those receiving a second dose a the monovalent H1N1(2009) vaccine (Tables 1 and 2).

4. Discussion

Seasonal TIV differs from other routinely administered vaccines as its composition changes annually in response to the circulating virus strains and there may be adjustment to the manufacturing

Table 1
Incidence rate ratio (IRR) estimates for the onset of a convulsion episode in relation to the timing of influenza vaccination and type of vaccine administered.

Vaccine	Period	IRR (95% CI)	Events
Trivalent influenza vaccine	Background	1.00	3795
	2 Weeks pre-vaccine	1.00 (0.70–1.42)	32
	Day of vaccination	1.23 (0.39–3.83)	3
	1–3 Day post vaccine	0.98 (0.47–2.07)	7
	4–7 Days post vaccine	0.96 (0.50–1.86)	9
	0–7 Days post vaccine	1.00 (0.64–1.59)	19
Monovalent H1N1 vaccine	Background	1.00	3816
	2 Weeks pre-vaccine	0.44 (0.25–0.76)	13
	Day of vaccination	1.83 (0.68–4.90)	4
	1–3 Day post vaccine	1.08 (0.51–2.28)	7
	4–7 Days post vaccine	0.70 (0.31–1.57)	6
	0–7 Days post vaccine	0.99 (0.61–1.60)	17

processes without the necessity for large annual clinical trials. Such modifications have on occasion changed the safety profile of the vaccine, as for example with the appearance of a novel adverse event, ocular respiratory syndrome, in the 2000/2001 influenza season in Canada associated with one manufacturer's vaccine [12].

To ensure the success and public acceptance of the seasonal TIV programme any vaccine safety concerns need to be robustly assessed especially if the scope of the seasonal programme were to be expanded in the future to include the routine immunisation of otherwise healthy children.

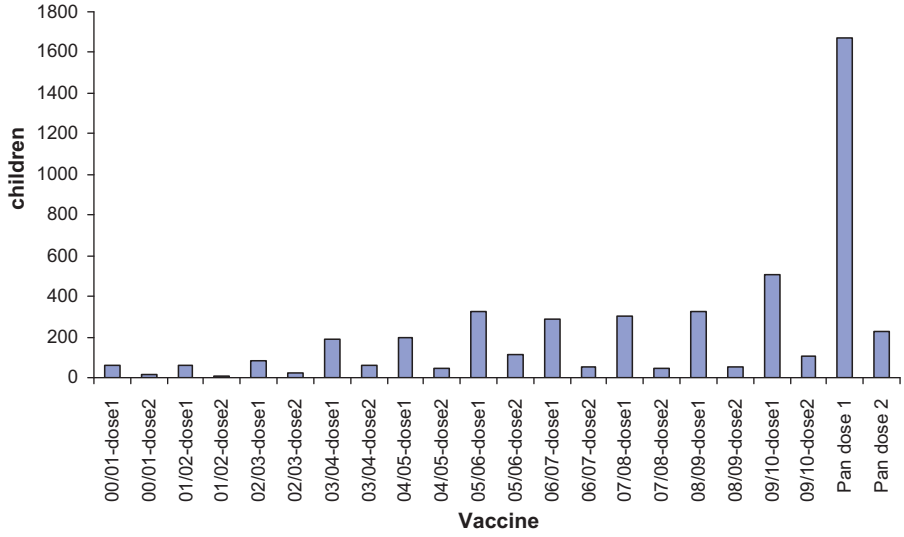


Fig. 1. Number of children aged under 10 years receiving seasonal trivalent influenza vaccine and monovalent H1N1 vaccine doses by flu season 2000/01 to 2009/10.

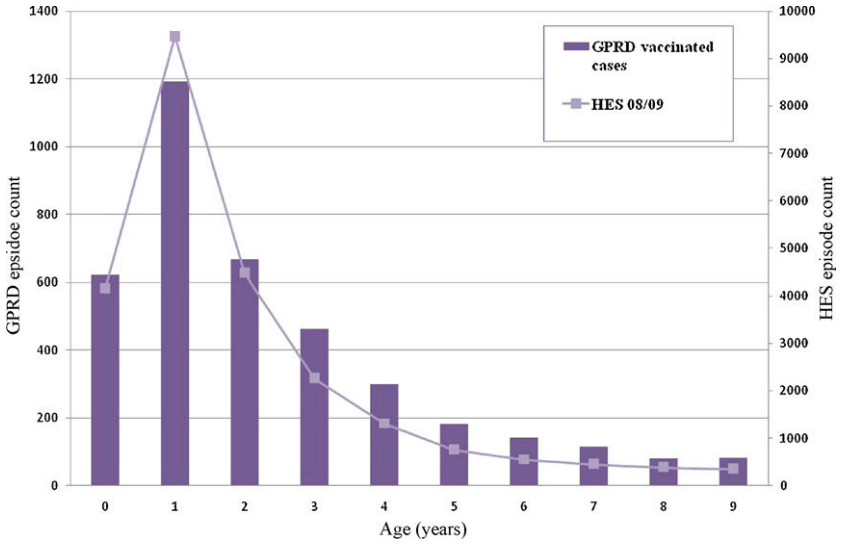


Fig. 2. Proportion of episodes of convulsion by age in vaccinated children under 10 years of age recorded in the GPRD between January 2000 and December 2010, and proportion of all admissions for convulsion recorded in the Hospital Episode Statistics (HES) database between April 2008 and March 2009.

Table 2
Incidence rate ratio (IRR) estimates for the onset of a convulsion episode in relation to the timing of monovalent H1N1 vaccine.

	Dose 1		Dose 2	
	IRR (95% CI)	Events	IRR (95% CI)	Events
2 Weeks pre-vaccine	0.37 (0.20–0.68)	10	1.24 (0.40–3.88)	3
Day of vaccination	1.52 (0.49–4.73)	3	5.24 (0.73–37.41)	1
1–3 Day post vaccine	0.85 (0.35–2.04)	5	3.48 (0.86–14.07)	2
4–7 Days post vaccine	0.77 (0.34–1.72)	6	0(–)	0
0–7 Days post vaccine	0.89 (0.53–1.52)	14	1.96 (0.62–6.14)	3

In response to the H1N1 pandemic in the UK the monovalent H1N1 (2009) vaccine, Pandemrix™, containing a novel oil-in-water adjuvant was used for the first time. The effectiveness of this vaccine given as a single dose to children was high [13] though at the cost of increased reactogenicity, especially fever [8]. In our data most children received just one dose of the $AS03_B$ adjuvanted monovalent H1N1 (2009) vaccine, which reflects the one dose schedule recommended from December 2009 in the UK with only those who are immunocompromsied recommended to receive two doses [9,10]. In the UK there was no safety signals concerning convulsions raised from the passive surveillance in response to the one dose H1N1 (2009) pandemic vaccine campaign [14] and its safety profile was considered similar of that of TIV, although slightly more reactogenic [15]. However, given the increased reactogenicity seen in clinical trials with the $AS03_B$ adjuvanted vaccine [8] it was considered important to formally assess the risk and to compare it with that after the unadjuvanted TIV vaccine used in previous years. Our study shows no evidence of an increased risk of a convulsion in the 7 days following a first dose of the monovalent H1N1 (2009) pandemic vaccine when given to young children. These results are

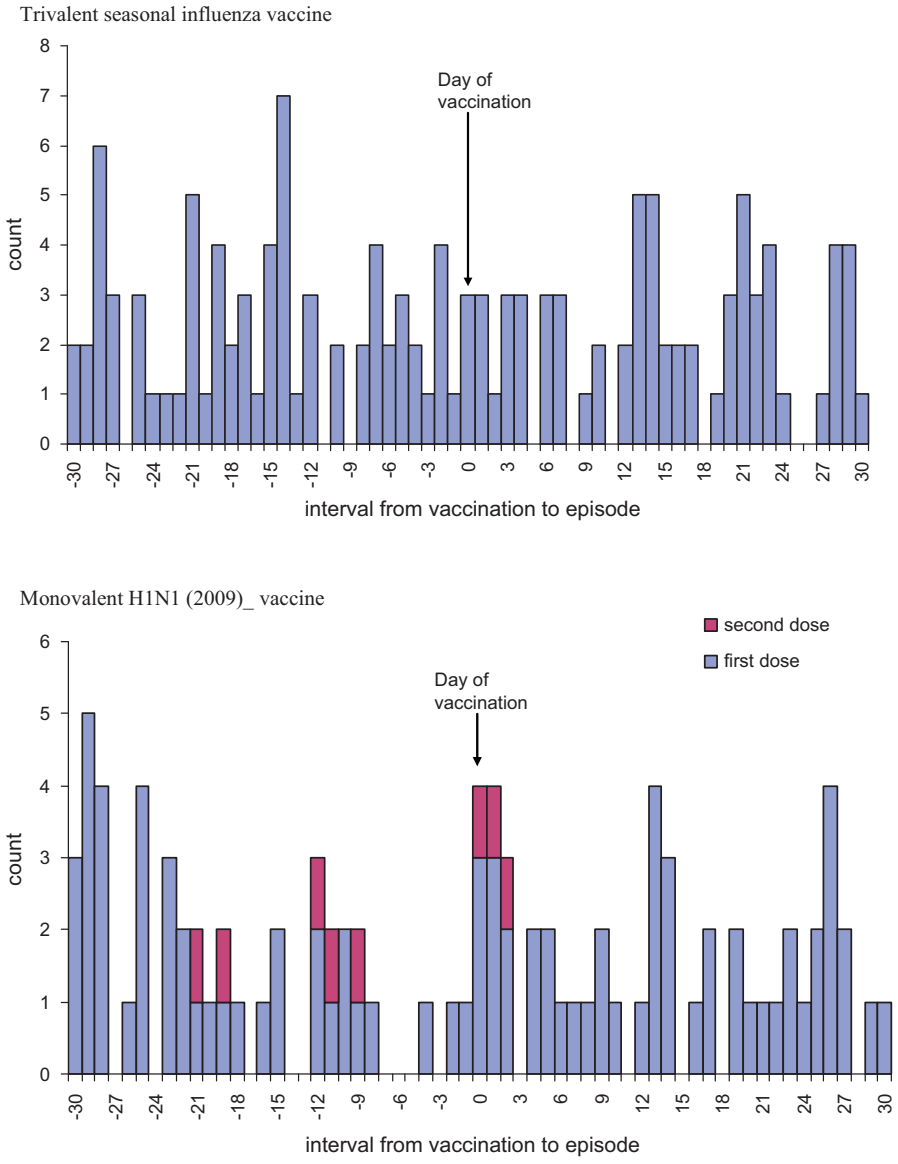


Fig. 3. Onset of convulsion episode as recorded in the GPRD in relation to the timing of influenza vaccination.

reassuring, given that the 2009/10 pandemic was the first time that an influenza vaccine containing this new adjuvant had been used for mass immunisation of young children. A post hoc assessment of the timing of the events within the 7 days after each dose of monovalent H1N1 (2009) pandemic vaccine did suggest a possible increased risk in the 0–2 day period following the second dose for which there were 3 events. Although this finding was not statistically significant it is consistent with the increased fever seen after the second dose of adjuvanted vaccine in a clinical trial [8] and supports the Department of Health's decision to recommend a single dose for all but the immunocompromised on account of the increase fever after the second dose seen in the clinical trial.

The absence of any evidence of an increased risk of a convulsion after seasonal TIV is also reassuring as some of those recommended to receive the vaccine will have underlying chronic conditions that increase the risk of a febrile convulsion. In the 2010 seasonal influenza vaccination campaign in Western Australia a large number of children under 5 years of age experienced fever and convulsions following TIV. This subsequently led to the suspension of the TIV vaccination programme for the under 5-year olds in Australia [16]. Investigation suggested that the risk was associated with one manufacturer's vaccine widely used in Australia and so in July 2010 the vaccine programme resumed using the two other available brands [17,18]. Febrile convulsions are predominantly seen in children under 5 years peaking at 1 year. However, in Australia increased reactogencity was seen up to 9 years of age and so in response we assessed the risk of convulsions after TIV in children up to 10 years of age. The age distribution of vaccinated children with a convulsion was similar to that seen in the general population of children admitted to hospital with a convulsion. There was an increase in the numbers of children receiving the TIV over the study period, corresponding to government initiatives to improve uptake in all risk groups.

In the period 2 weeks before vaccination there are significantly fewer convulsions in children who subsequently receive a single dose of the monovalent H1N1 vaccine. This pre-vaccination low risk period is often seen before vaccination as it reflects the patient waiting to be well after an event such as a convulsion before receiving the vaccine [19–21]. Unlike other studies, and in this study with the first dose of pandemic strain vaccine, a pre-vaccination low risk period was not seen prior to the administration of seasonal TIV or prior to a second pandemic dose. A possible explanation could be that seasonal TIV and the two-dose schedule of monovalent H1N1 vaccine was given to children in risk groups who would be routinely offered TIV vaccine each year, so they may have had the vaccine previously and their parents may feel more confident for their child to be vaccinated shortly after a convulsion. The single dose of the monovalent H1N1 (2009) vaccine was targeted to all children 6 months to 5 years. Parents of such children may be more hesitant about their child receiving the vaccine shortly after a convulsion as it may have been the first time their child received an influenza vaccine.

This study has some limitations, particularly in relation to the lack of validation of the clinical diagnoses of a convulsion recorded in the GPRD. However, we have previously used the GPRD data for investigating the relationship between convulsions and administration of pertussis vaccines [5] in which the diagnoses were validated by reviewing the "free text" recorded by the GP around the time of the consultation and by verifying other symptoms relating to the diagnosis. This showed that the Read codes used for recording convulsions in the GPRD are reliable and that analyses based on these codes can detect differences between vaccines. We have also shown that the age distribution of the children with convulsions recorded in the GPRD was similar to that in the HES database. The ICD codes used in HES have been previously validated and shown to be specific [4].

Although Pandemrix and Celvapan Read codes were sought many records were coded with a generic "H1N1" code but since the national vaccine programme in England and Wales predominantly used Pandemrix™ it is valid to assume the data primarily reflects the uptake of Pandemrix ™ [25]. A challenge remains in assessing a risk when more that one vaccine brand is used as databases such as the GPRD have limited power to identify a product-specific risk and there is year on year variation between brands. Systematic recording of manufacturer and batch number is needed in routinely collected data to enable analysis and evaluation.

In conclusion we found no evidence of an increased risk of convulsion in children following a single dose of the monovalent $AS03_B$ adjuvanted pandemic strain vaccine or following vaccination with the seasonal TIV over a 10-year period using the self controlled case series method. Although some influenza vaccines may present a risk of convulsions in certain circumstances, as recently documented in Australia, this should be balanced against the risk of influenza virus itself, which can cause fever, convulsions and also more serious neurological disorders [22,23,24]. Our study provides evidence that extension of TIV programmes to healthy children, potentially supplemented by the addition of novel oil in water adjuvants to influenza vaccine to improve protection [13], is likely to have an overall beneficial effect on convulsions in this target age group.

Acknowledgements

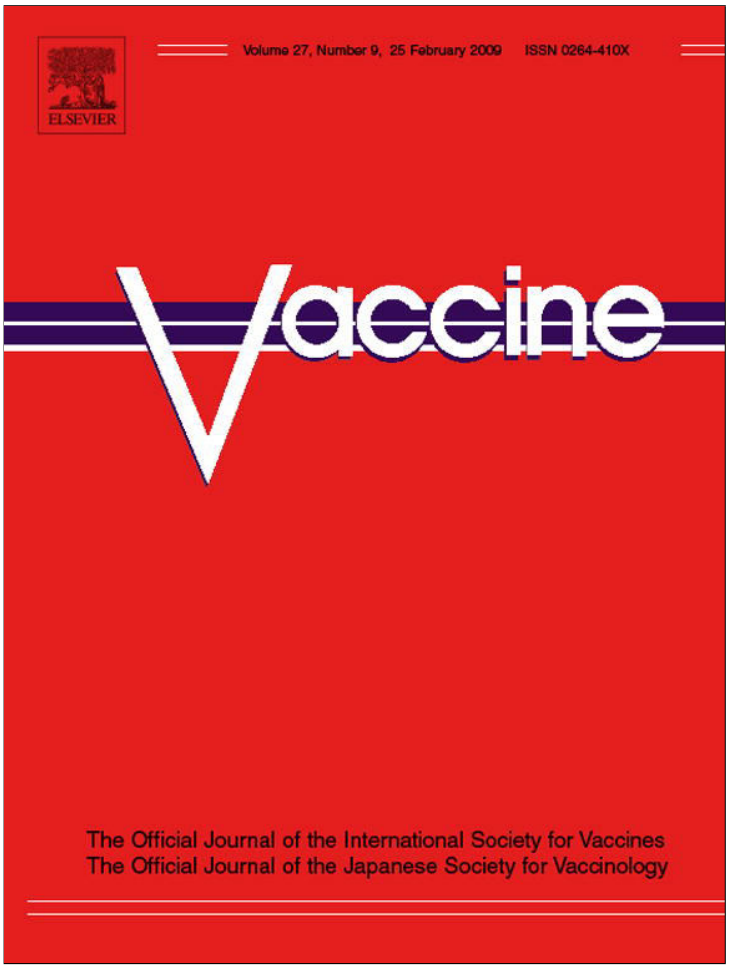
J. Stowe is funded from a grant from the Department of Health Policy Research Programs (grant number 039/0031).

The views expressed in the publication are those of the authors and not necessarily those of the Department of Health, UK.

References

[1] Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Risks of convulsion and aspectic meningits following measles–mumps–rubella vaccination in the United Kingdom. Am J Epidemiol 2007;165:704–9.
[2] Vestergaard M, Hviid A, Madsen KM, Wohlfahrt J, Thorsen P, Schendel D, et al. MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. JAMA 2004;292(July (3)):351–7.
[3] Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, et al. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. N Engl J Med 2001;345(9):656–61.
[4] Farrington P, Pugh S, Colville A, Flower A, Nash J, Morgan-Capner P, et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps rubella vaccine. Lancet 1995;345:567–9.
[5] Nick Andrews, Julia Stowe, Lesley Wise, Elizabeth Miller. Post licensure comparison of the safety profile of diphtheria/tetanus/whole cell pertussis/haemophilus influenza type b vaccine and a 5 in 1 diphtheria/tetanus/acellular pertussis/haemophilus influenza type b/polio vaccine in the United Kingdom. Vaccine 2010;28(Oct 18 (44)):7215–20 [Epub 2010 Aug 26].
[6] Le Saux N, Barrowman NJ, Moore DL, Whiting S, Scheifele D, Halperin S. Decrease in hospital admissions for febrile seizures and reports of hypotonic–hyporesponsive episodes presenting to hospital emergency departments since switching to acellular pertussis vaccine in Canada: a report from IMPACT. Pediatrics 2003;112(5):e348.
[7] Davis RL, Kolczak M, Lewis E, Nordin J, Goodman M, Shay D, et al. Active surveillance of vaccine safety: a system to detect early signs of adverse events. Epidemiology 2005;16:336–41.
[8] Waddington C, Andrews N, Hoschler K, Walker W, Oeser C, Reiner A, et al. Open-label, randomised, parallel-group, multicentre study to evaluate the safety, tolerability and immunogenicity of an AS03(B)/oil-in-water emulsion-adjuvanted (AS03(B)) split-virion versus non-adjuvanted whole-virion H1N1 influenza vaccine in UK children 6 months to 12 years of age. Health Technol Assess 2010;14(October (46)):1–130.
[9] The H1N1 swine flu vaccination programme 2009–2010 Chief Medical Officer Letter, Department of Health 15 October 2009 [http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_107169].
[10] A (H1N1) swine flu influenza: phase two of the vaccination programme; children over 6 months and under 5 years Chief Medical Officer Letter, Department of Health, 8 December 2009 [http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_109826].

[11] Hospital Episode Statistics. The Health and Social Care Information Centre [http://www.hesonline.org.uk].
[12] Skowronski DM, Strauss B, De Serres G, MacDonald D, Marion SA, Naus M, et al. Oculo-respiratory syndrome: a new influenza vaccine-associated adverse event? Clin Infect Dis 2003;36(March (6)):705–13 [Epub 2003 Mar 5].
[13] Andrews N, Waight P, Yung CF, Miller E. Age-specific effectiveness of an oil-in-water adjuvanted pandemic (H1N1) 2009 vaccine against confirmed infection in high risk groups in England. J Infect Dis 2011;203(January (1)):32–9.
[14] Bryan P, Seabroke S. No increased risk of febrile convulsions after seasonal. influenza immunisation in UK. Lancet 2011;377(March (9769)):904 [PubMed PMID: 21397766].
[15] MHRA Swine flu pandemic vaccines and antivirals: safety review Drug Safety Update—pandemic vaccines and antivirals: safety review October 2010 [www.mhra.gov.uk/swineflu].
[16] Australian Government. Department of Health and Ageing. Seasonal flu vaccine and young children. 23 April 2010. Media Release [available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-dept-dept230410.htm].
[17] Australian Government. Department of Health and Ageing Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination Status report as at 2 July 2010 [available from: http://www.tga.gov.au/alerts/medicines/fluvaccine-report100702.htm].
[18] Kelly H, Carcione D, Dowse G, Effler P. Quantifying benefits and risks of vaccinating Australian children aged six months to four years with trivalent inactivated seasonal influenza vaccine in 2010. Euro Surveill 2010;15(Sep 16; (37)), pii: 19661.
[19] Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine. Arch Dis Child 2001;84(March (3)):227–9.
[20] Stowe J, Andrews N, Wise L, Miller L. Investigation of the temporal association between Guillain–Barré syndrome and influenza vaccine and influenza-like illness using the UK General Practice Research Database. Am J Epidemiol 2009;169(February (3)):382–8.
[21] Stowe J, Andrews N, Taylor B, Miller E. No evidence of an increase of bacterial and viral infections following measles, mumps and rubella vaccine. Vaccine 2009;27(February (9)):1422–5.
[22] Chiu SS, Tse CY, Lau YL, Peiris M. Influenza A and infection is an important cause of febrile seizures. Pediatrics 2001;108(October (4)):E63.
[23] Kwong KL, Lam SY, Que TL, Wong SN. Influenza A and febrile seizures in childhood. Pediatr Neurol 2006;35(December (6)):395–9.
[24] Moore DL, Vaudry W, Scheifele DW, Halperin SA, Déry P, Ford-Jones E, et al. Surveillance for influenza admissions among children hospitalized in Canadian immunization monitoring program active centers, 2003–2004. Pediatrics 2006;118(September (3)):e610–9.
[25] Pandemic H1N1 (Swine) influenza vaccine uptake amongst patient groups in primary care in England Report commissioned by DH and written by Monica Sethi & Richard Pebody (HPA) October 2010 [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_121011].



Vaccine 27 (2009) 1422–1425

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

No evidence of an increase of bacterial and viral infections following Measles, Mumps and Rubella vaccine

Julia Stowe[a,c,*], Nick Andrews[b], Brent Taylor[c], Elizabeth Miller[a]

[a] Immunisation Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, United Kingdom
[b] Statistics, Modelling & Bioinformatics Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, United Kingdom
[c] General and Adolescent Paediatric Unit, UCL Institute of Child Health, 30 Guilford Street, London WC1N 3EH, United Kingdom

ARTICLE INFO

Article history:
Received 29 September 2008
Received in revised form 1 December 2008
Accepted 20 December 2008
Available online 13 January 2009

Keywords:
Immune overload
MMR
Measles
Mumps and Rubella
Vaccine-associated adverse events
Self-controlled case-series method

ABSTRACT

The suggestion that multi-antigen vaccines might overload the immune system has led to calls for single antigen vaccines. In 2003 we showed that rather than an increase there appeared to be a reduced risk of severe bacterial infection in the three months following Measles, Mumps and Rubella vaccine (MMR). The present analysis of illnesses in a general population is based on an additional 10 years of data for bacterial infections and also includes admissions with viral infections. Analyses were carried out using the self-controlled case-series method and separately for bacterial and viral infection cases, using risk periods of 0–30 days, 31–60 days and 61–90 days post MMR vaccine. An analysis was also carried out for those cases which were given MMR and Meningococcal serogroup C (MCC) vaccines concomitantly.

A reduced risk was seen in the 0–30-day period for both bacterial infection (relative incidence = 0.68, 95% CI 0.54–0.86) and viral infections (relative incidence = 0.68, 95% CI 0.49–0.93). There was no increased risk in any period when looking at combined viral or bacterial infections or for individual infections with the single exception of an increased risk in the 31–60 days post vaccination period for herpes infections (relative incidence = 1.69, 95% CI 1.06–2.70). For the children given Meningococcal group C vaccines concomitantly no significantly increased risk was seen in either the bacterial (relative incidence = 0.54, 95% CI 0.26–1.13) or viral cases (relative incidence = 0.46, 95% CI 0.11–1.93).

Our study confirms that the MMR vaccine does not increase the risk of invasive bacterial or viral infection in the 90 days after the vaccination and does not support the hypothesis that there is an induced immune deficiency due to overload from multi-antigen vaccines.

1. Background

Addition of a number of new vaccines to the infant vaccination programme in recent years has raised theoretical concerns about the possible adverse effects of multiple immunisations on the developing immune system [1]. One such concern relates to the potential for increasing susceptibility to other infections as a result of "immune overload". When reviewing this issue in 2002, the US Institute of Medicine concluded that the available epidemiological evidence favoured rejection of a causal association between multiple immunisations and an increased risk of heterologous infections [1]. However, most of the studies reviewed related to combined diphtheria/tetanus/pertussis (DTP) vaccines [2–6].

For combined Measles, Mumps,and Rubella (MMR) vaccine, a small number of epidemiological studies have also shown no evidence of increased risk of heterologous infection [7,2,8] but some parents remain concerned and uptake of MMR vaccine in the UK remains sub optimal [9]. This continuing concern has been fuelled by unsubstantiated allegations about a link between MMR and autism [10] and claims that administration of three live viral vaccines at the same time has adverse immunological effects [11].

We previously tested the hypothesis that the MMR vaccine induces significant immunosuppression with an increase in hospitalisations from bacterial infections in the three months following the vaccination and found no evidence of such an effect [7]. The following analysis provides an update for MMR vaccination, using the same methods and provides an additional 10 years of hospital admission data to encompass the move to ICD 10 coding, the inclusion of additional codes for viral infections and the concomitant administration of Meningococcal C conjugate (MCC) vaccine.

2. Methods

Children aged 12–23 months were identified from computerised hospital admission records from North, East and South London, Essex, East Anglia, Sussex and Kent, for the period 1st April 1995

* Corresponding author at: Immunisation Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, United Kingdom. Tel.: +20 8327 7485; fax: +20 8327 7404.
E-mail address: julia.stowe@hpa.org.uk (J. Stowe).

0264-410X/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2008.12.038

Table 1
Relative incidence (95% confidence intervals) [total cases in period] according to risk period after MMR vaccination and type of bacterial infection.

Risk period (days)	Lobar pneumonia code	Invasive bacterial code
−14 to −1	0.24 (0.13–0.46) [9]	0.33 (0.15–0.74) [6]
0 to 30	0.65 (0.48–0.86) [57]	0.75 (0.51–1.12) [30]
31 to 60	0.80 (0.61–1.05) [65]	1.03 (0.70–1.52) [34]
61 to 90	0.90 (0.69–1.18) [69]	0.92 (0.61–1.41) [27]
0 to 90	0.77 (0.64–0.93) [191]	0.89 (0.68–1.16) [91]

to 1st May 2005. Admissions were identified using ICD 9 and 10 codes for bacterial and viral infections (specific codes available on request). Each episode is coded with an ICD code which can be found in any of the seven diagnostic fields, with the first field being the primary diagnosis. Bacterial infections were categorised into either lobar pneumonia or invasive disease and the viral infections were categorised into those affecting the central nervous system (CNS), varicella zoster virus, and other herpes viruses, those causing viral pneumonia or a miscellaneous group. Varicella zoster was separated from other herpes viruses because of the known immunological interference between varicella and MMR vaccines when administered sequentially within a month of each other [12]. The analyses were performed for all bacterial and all viral infections as well as separately for each category.

The admissions were linked to the dates of independently collected MMR and co-administered MCC vaccination records held on computerised child health systems by sex, date of birth and full postcode or where available NHS number as previously described [7]. Sex, date of birth and full post code is a highly specific linking algorithm when used on these data sets [13]. Only successfully linked admissions were retained for the analysis as failure to link did not necessarily mean a child was unvaccinated.

Analysis was carried out using the self-controlled case-series method which only uses cases and automatically controls for fixed individual level confounding such as sex and socio-economic status [14]. When using this method the relative incidence is calculated by assigning person time from age 12–23months for each individual into vaccine and background risk periods and comparing the rate that outcome events (bacterial, viral infections) occur.

Adjustments for age (in 2-week period) and season (in calendar months) were made in the analysis. The risk periods examined were 0–30 days, 31–60 days and 61–90 days post MMR vaccine. The 14-day pre vaccination period was excluded from the background because vaccination might be delayed if the child had a study illness.

3. Results

A total of 2077 admissions in 2025 children were linked to an MMR record. An admission within 14 days of an earlier admission with the same condition was considered part of the same episode. Of these admissions, 871 were coded as lobar pneumonia and 449 as invasive bacterial infection. Of the children with more than one bacterial infection, 25 had 2 episodes, 3 had 3 episodes and 1 child had 8 episodes.

Of the viral infection admissions, 18 were coded as viral encephalitis/viral meningitis/CNS, 226 as herpes, 61 as pneumonia, 319 as varicella/zoster and 133 viral miscellaneous. Of the children with multiple episodes 11 had 2 viral episodes and 1 child had 4.

Of these linked cases, 1865 children (92.1%) received a dose of MMR within the age-range 11–23 months, with the remaining 160 children receiving their first dose later – often about the age the second dose is usually given. There were 90 admissions occurring in children who received MCC vaccine concomitantly with the MMR.

3.1. Bacterial infections

The relative incidence estimates in the 30-day period after MMR are shown in Table 1. In the first 30 days after vaccination, the relative incidence estimates were lowest, with a significant reduction seen for the lobar pneumonia analysis (the confidence interval does not contain 1.00). In the later periods there was no evidence of a significant reduction. When the whole 90-day period was combined, the reduction was only significant for lobar pneumonia. In the analysis where lobar pneumonia and invasive bacterial infection cases were combined, the results showed a significant reduction in the 0–30-day period (RI = 0.68, 95% CI 0.54–0.86) as well as in the overall 0–90-day period (RI = 0.81, 95% CI 0.70–0.95).

Figure 1 shows the number of admissions in 10-day interval around the time of vaccination. There were relatively few cases just prior to vaccination (because vaccination would usually be delayed if the child was ill). The reduced RI in the 30-day period after vaccination appears to be mainly due to low numbers during the initial 10 days post vaccination period.

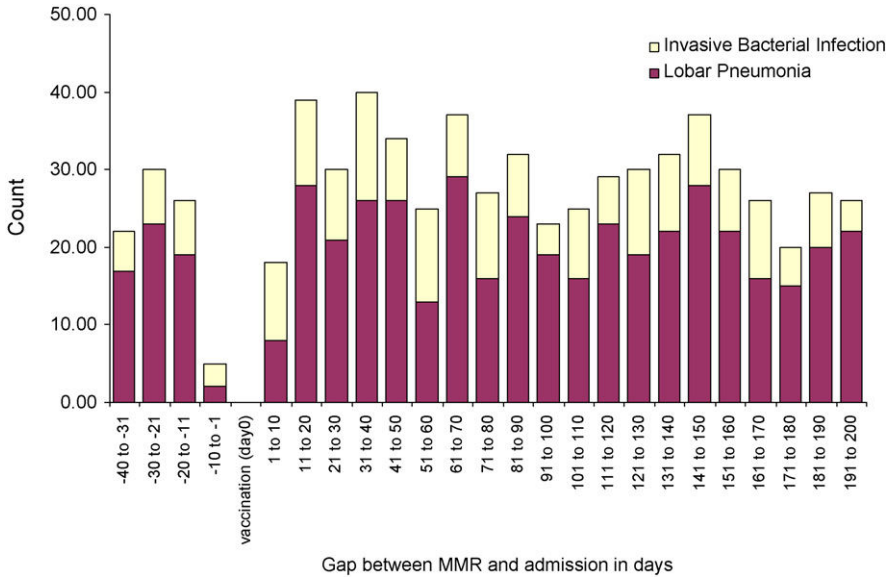


Fig. 1. Bacterial infections: Timing of infections relative to date of MMR vaccination in 10-day intervals.

Table 2
Relative incidence (95% confidence intervals) [total cases in period] according to risk period after MMR vaccination and type of viral infection.

Risk period (days)	Encephalitis, Meningitis, CNS	Herpes	Pneumonia	Varicella/zoster	Miscellaneous
−14 to −1	0 [0]	0.46 (0.15–1.45) [3]	0.69 (0.15–3.13) [2]	0.16 (0.04–0.56) [2]	0.60 (0.21–1.68) [4]
0 to 30	0.54 (0.06–4.83) [1]	1.00 (0.57–1.74) [16]	0 [0]	0.58 (0.34–0.99) [17]	0.71 (0.37–1.37)[12]
31 to 60	0.74 (0.07–7.47) [1]	1.69 (1.06–2.70) [25]	1.39 (0.49–3.90) [5]	1.23 (0.81–1.87) [32]	0.73 (0.37–1.14) [12]
61 to 90	1.46 (0.23–9.29) [2]	0.89 (0.50–1.59) [14]	1.27 (0.41–3.94) [4]	1.05 (0.66–1.67) [24]	0.61 (0.29–1.28) [9]
0 to 90	0.84 (0.20–3.49) [4]	1.17 (0.56–2.47) [55]	0.72 (0.33–1.62) [9]	0.93 (0.68–1.27) [73]	0.68 (0.43–1.09) [33]

An analysis of cases where MMR and Meningococcal group C vaccines were given concomitantly was carried out, with 64 bacterial cases identified – with 5 events in the 0–90-day risk period with a RI of 0.54 (95% CI 0.26–1.13).

3.2. Viral infections

The relative incidence estimates in the 30-day period after MMR are shown in Table 2. Similar to the bacterial infections, the overall relative incidence in the 0–30 day period after vaccination was the lowest at 0.68 (95% CI 0.49–0.93). When stratified by individual diagnostic groups only the RI for the varicella/zoster group remained significantly low within this period (0.58, 95% CI 0.34–0.99). The distribution of events relative to MMR appeared lowest during 11–20 days (Figure 2), unlike the bacterial infections, which appeared lowest in the first 10 days after vaccination. With the single exception of the herpes group which showed a significantly increased risk in 31–60 days after the MMR vaccine (RI 1.69, 95% CI 1.06–2.70) no other diagnostic group showed a significant increase within the 90 days risk period. There were 26 viral infections identified following the MMR and Meningococcal group C vaccines given concomitantly; of these three occurred in the 0–90 days risk period giving a RI of 0.46 (95% CI 0.11–1.93)

4. Discussion

Our results show that MMR vaccine administered in the second year of life, either alone or with concomitant MCC vaccine, does not increase the risk of severe infection, bacterial or viral, in various periods up to three months after vaccination. It therefore adds weight to the existing epidemiological evidence that multiple immunisations do not "overload" the immune system and increase susceptibility to heterologous infection [1]. Moreover, there is no scientific rationale for the hypothesis; young infants have an enormous capacity to respond to multiple vaccines, as well as to the many other antigenic challenges present in the environment, without demonstrated ill-effects. It has been estimated that an infant has the theoretical capacity to respond to some 10,000 immunogens and with advances in antigen vaccine production, particularly the change from whole cell to purified acellular pertussis vaccine, infants now receive fewer vaccine antigens than in the past, despite an increase in the number of vaccines given [15]. For measles containing vaccines, specific concerns have been raised because wild measles virus can have profound immunosuppressive effects but this has not been shown for attenuated vaccine virus [16].

Our results for bacterial infections, showed that both overall and in the lobar pneumonia group, there was a significant reduced risk in the 0–90 day period post-MMR vaccine. This was mainly due to the reduced risk in the 10 days after MMR vaccine and could suggest a healthy-vaccinee effect where individuals who are unwell but not (yet) hospitalised, have vaccination postponed. In our previous study [7] there was some evidence of a reduction in risk for lobar pneumonia in the 61–90 days post MMR with a RI 0.52 (95% CI 0.30–0.90). In this updated study we did not find such a reduction, although the present estimate we observed of 0.90 is still consistent with our previous estimate and its confidence interval.

In the viral infections analysis, the overall reduction in risk was significant in the 0–30 day period, but unlike the bacterial infection analysis the reduction appeared to be in the 11–20 day period not the 1–10 day period (Figures 1 and 2). When stratified by category (Table 2) only the varicella/zoster group showed a significantly reduced risk in the 0–30 day period. Misdiagnosis of hospitalised cases of chicken pox or zoster seems unlikely as does a healthy vaccinee-effect occurring this late after vaccination. Bias resulting from a reduced propensity to admit children to a hospital because they were vaccinated some weeks previously also seems unlikely while bias due to individual level confounders is also automatically controlled for in the self-controlled case-series method [14].

The reduced risk in late post-vaccination periods in our current and earlier study [7] may be chance findings, but others have also

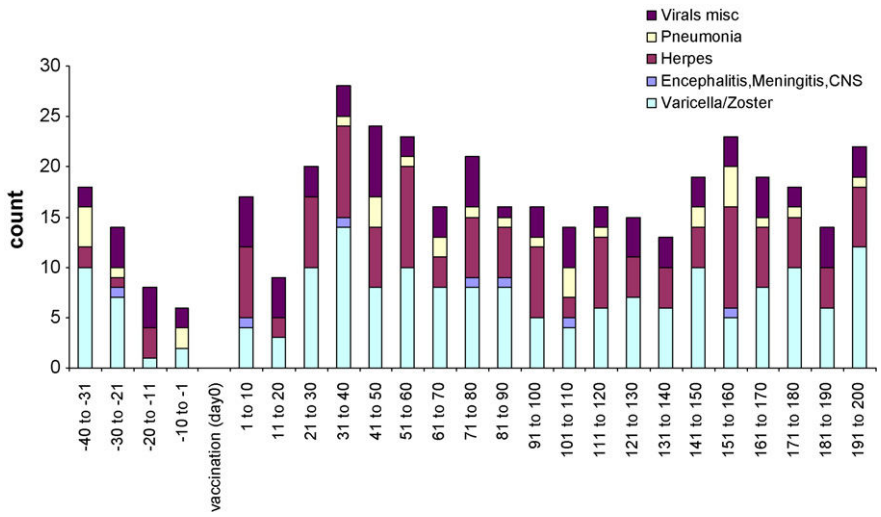


Fig. 2. Viral infections: Timing of infections relative to date of MMR vaccination in 10-day intervals.

reported reduced risks after DTP and MMR vaccination [8,2,5,6]. For example, Black et al. [2] using the case control approach found an odds ratio of 0.29 (95% CI 0.09 to 0.95) for an invasive bacterial infection 8–30 days after any dose of DTP, MMR or oral polio vaccine after controlling for confounders such as day care attendance and well care visits. While some of these apparent protective effects may be due to residual confounding, it is also possible that vaccination does provide a short-term protective effect by a non-specific stimulation of the immune system, for example by interleukin 2 induced enhancement of immunological activity or interferon production [5,17].

The only significantly increased relative incidence was in the herpes group where the RI was 1.69 (95% CI 1.06–2.70) 31–60 days post vaccination. There was no increased RI of herpes infections in the other risk periods and it is therefore most plausible that this is a chance finding due to the number of risk periods and categories being analysed.

Our study confirms that the MMR vaccine, with or without concomitantly administered MCC vaccine, does not increase the risk of bacterial infections, or severe viral infections in the 90 days after vaccination and does not support the hypothesis that there is an immune overload due to multi-antigen vaccines. It provides further evidence of a possible short-term protective effect of MMR vaccine against heterologous infection.

Acknowledgement

JS is supported by a Department of Health Research and Development Directorate grant 039/031.

References

[1] Stratton KR, Wilson CB, McCormick MC. Immunization safety review: Multiple Immunizations and Immune Dysfunction. Institute of Medicine. Washington, D.C: National Academy Press; 2002.

[2] Black SB, Cherry JD, Shinefield HR, Fireman B, Christenson P, Lampert D. Apparent decreased risk of invasive bacterial disease after heterologous childhood immunization. Am J Dis Child 1991;145(July (7)):746–9.

[3] Griffin MR, Taylor JA, Daugherty JR, Ray WA. No increased risk for invasive bacterial infection found following diphtheria-tetanus-pertussis immunization. Pediatrics 1992;89(April (4 Pt 1)):640–2.

[4] Davidson M, Letson GW, Ward JI, Ball A, Bulkow L, Christenson P, et al. DTP immunization and susceptibility to infectious diseases. Is there a relationship? Am J Dis Child 1991;145(July (7)):750–4.

[5] Otto S, Mahner B, Kadow I, Beck JF, Wiersbitzky SK, Bruns R. General non-specific morbidity is reduced after vaccination within the third month of life—the Greifswald study. J Infect 2000;41(September (2)):172–5.

[6] Burstein JL, Fleisher GR. Does recent vaccination increase the risk of occult bacteremia? Pediatr Emerg Care 1994;10(June (3)):138–40.

[7] Miller E, Andrews N, Waight P, Taylor B. Bacterial infections, immune overload, and MMR vaccine. Measles, mumps, and rubella. Arch Dis Child 2003;88(March (3)):222–3.

[8] Hviid A, Wohlfahrt J, Stellfeld M, Melbye M. Childhood vaccination and non-targeted infectious disease hospitalization. JAMA 2005;294(August (6)):699–705.

[9] The Information Centre for Health and Social Care. *Statistical Bulletin. NHS Immunisation Statistics, England: 2007-08*. http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles/immunisation.

[10] Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998;351(February (9103)):637–41.

[11] Wakefield AJ, Montgomery SM. Measles, mumps, rubella vaccine: through a glass, darkly. Adverse Drug React Toxicol Rev 2000;19(December (4)):265–83 [discussion 284–92].

[12] Mullooly J, Black S. Simultaneous administration of varicella vaccine and other recommended childhood vaccines—United States, 1995–9. MMWR 2001;50:1058–61.

[13] Nash JQ, Chandrakumar M, Farrington CP, Williamson S, Miller E, Nash, Farrington. Feasibility study for identifying adverse events attributable to vaccination by record linkage. Epidemiol Infect 1995;114(June (3)):475–80.

[14] Andrews N. Statistical assessment of the association between vaccination and rare adverse events post-licensure. Vaccine 2001;20:S49–50.

[15] Offit PA, Quarles J, Gerber MA, Hackett CJ, Marcuse EK, Kollman TR, et al. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? Pediatrics 2002;109:124–9.

[16] Okada H, Sato TA, Katayama A, Higuchi K, Shichijo K, Tsuchiya T, et al. Comparative analysis of host responses related to immunosuppression between measles patients and vaccine recipients with live attenuated measles vaccines. Arch Virol 2001;146(5):859–74.

[17] Petralli Jk, Merigan TC, Wilbur JR. Circulating interferon after measles vaccination. N Engl J Med 1965;273:198–201.

American Journal of Epidemiology Advance Access published January 20, 2009

American Journal of Epidemiology

DOI:10.1093/aje/kwn310

Original Contribution

Investigation of the Temporal Association of Guillain-Barré Syndrome With Influenza Vaccine and Influenzalike Illness Using the United Kingdom General Practice Research Database

Julia Stowe, Nick Andrews, Lesley Wise, and Elizabeth Miller

Initially submitted February 4, 2008; accepted for publication September 9, 2008.

In 1976, the national swine influenza vaccination program in the United States was suspended because of an increased risk of Guillain-Barré syndrome. Subsequent studies of seasonal influenza vaccine have given conflicting results. The authors used the self-controlled case series method to investigate the relation of Guillain-Barré syndrome with influenza vaccine and influenzalike illness using cases recorded in the General Practice Research Database from 1990 to 2005 in the United Kingdom. The relative incidence of Guillain-Barré syndrome within 90 days of vaccination was 0.76 (95% confidence interval: 0.41, 1.40). In contrast, the relative incidence of Guillain-Barré syndrome within 90 days of an influenzalike illness was 7.35 (95% confidence interval: 4.36, 12.38), with the greatest relative incidence (16.64, 95% confidence interval: 9.37, 29.54) within 30 days. The relative incidence was similar (0.89, 95% confidence interval: 0.42, 1.89) when the analysis was restricted to a subset of validated cases. The authors found no evidence of an increased risk of Guillain-Barré syndrome after seasonal influenza vaccine. The finding of a greatly increased risk after influenzalike illness is consistent with anecdotal reports of a preceding respiratory illness in Guillain-Barré syndrome and has important implications for the risk/benefit assessment that would be carried out should pandemic vaccines be deployed in the future.

association; Great Britain; Guillain-Barré syndrome; influenza, human; influenza vaccines; safety

Abbreviations: GPRD, General Practice Research Database; HES, Hospital Episode Statistics; VAERS, Vaccine Adverse Event Reporting System.

Guillain-Barré syndrome is an autoimmune disease often preceded by a respiratory or gastrointestinal illness. It is the commonest cause of acute neuromuscular paralysis in the United Kingdom, with an estimated annual incidence of 1.5/100,000 (95% confidence interval: 1.3, 1.8) (1). Clinical features include motor, sensory, and autonomic dysfunction such as limb weakness, severe pain, and sinus arrhythmia. Cases can present in any age group, but incidence increases with age, with an excess in males (2).

In 1976, the national influenza immunization program in the United States was suspended following an increased number of reports of Guillain-Barré syndrome after administration of swine influenza vaccine. A subsequent epidemiologic study showed relative risks of 4.0 and 7.6 for the 6- and 8-week postvaccination periods, respectively, with an attributable risk of just less than 1 case per 100,000 vaccinations (3). Studies with seasonal influenza vaccines over the period 1978–1988 showed no evidence of an increased risk of Guillain-Barré syndrome in the postvaccine period (4–6). However, following an increase in reports of vaccine-associated Guillain-Barré syndrome to the US national Vaccine Adverse Event Reporting System (VAERS), from 37 in 1992–1993 to 74 in 1993–1994, a further study was conducted (7). This study found no difference in risk between the 2 seasons, although there was an increased relative risk of 1.7 ($P = 0.04$) for the 2 seasons combined. Furthermore, a recent analysis of VAERS data (8) identified 2 features of influenza-vaccine-associated Guillain-Barré syndrome reports that suggested a possible causal association. First, the proportion of VAERS-reported cases with

Correspondence to Julia Stowe, Immunisation Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, United Kingdom (e-mail: julia.stowe@hpa.org.uk).

a preceding illness was lower than usually reported for non-vaccine-associated cases; second, there was an excess of VAERS cases with onset in the second week after vaccination.

These findings require further research to investigate the temporal association between influenza vaccine and Guillain-Barré syndrome. Cohort and case-control studies have traditionally been used for investigating putative vaccine-associated risks but pose problems when dealing with influenza vaccines. First, influenza vaccine is frequently given to individuals with specific clinical indications, thus raising the possibility of confounding by indication. Second, when the cohort approach is used, comprehensive population-based data are not usually available and person-time denominators inside and outside the risk period have been estimated from vaccination data obtained from small population samples (4, 5, 7). The self-controlled case series method (9) does not have these limitations. Based on a novel cases-only approach, this method automatically controls for individual-level confounders and requires only data on cases with their linked vaccination records.

We used the self-controlled case series method to investigate the temporal relation between influenza vaccine and Guillain-Barré syndrome. We also used this methodology to assess the risk of Guillain-Barré syndrome after influenza-like illness.

MATERIALS AND METHODS

We identified consultations for Guillain-Barré syndrome from the General Practice Research Database (GPRD), one of the world's largest primary care databases. It holds data on consultations, referrals, prescriptions, and vaccinations for more than 3 million active patients in practices throughout the United Kingdom (5.7% of the population). We selected any patient in the GPRD whose practice record had an ''acceptable'' status and listed an ''up-to-standard'' date earlier than the patient's first or new consultation for Guillain-Barré syndrome in the period 1990–2005. The up-to-standard date reflects when the practice complied with specific quality measures based on completeness, continuity, and plausibility in key areas. Acceptable status is given to a patient when certain data quality conditions have been met, such as no events recoded before the birth date, age less than 115 years, and a completed gender field. Consultations for Guillain-Barré syndrome were identified by using one of the following codes: READ F370000 (Guillian-Barré Syndrome), READ F370.00 (Acute Infective Polyneuritis), OXMIS 354 GB (Syndrome Guillian-Barré), or OXMIS 354 P (Polyneuritis). Influenza and influenzalike illness were identified by using any READ or OXMIS codes that included the terms ''influenza*'' or ''flu'' (a full list is available from the authors).

Two-stage validation of Guillain-Barré syndrome coding was carried out for just those individuals who received at least one dose of vaccine, since they contributed most of the power for looking at vaccine effects. First, the patient profile was reviewed to identify confirmatory clinical symptoms such as limb weakness at the time of diagnosis and to identify any cases with an earlier date of onset than the first coded diagnosis of Guillain-Barré syndrome. The patient profile is a summary of the whole patient record that includes dates and information on consultations, prescriptions, test results, referrals, and immunizations. Second, anonymized free-text comments were reviewed for 1 week before to 23 weeks after the date of the Guillain-Barré syndrome consultation to verify date of diagnosis and to identify supporting clinical information.

Analysis was carried out on all Guillain-Barré syndrome episodes, and, after review of the patient profile, just those episodes with supporting symptoms, and finally just those with supporting evidence and a confirmed earliest date of symptoms. The date that influenza vaccine was given was identified along with the date of any pneumococcal vaccine, which is recommended for the same age and clinical risk groups as influenza vaccine and, when given, is often administered at the same time as influenza vaccine.

The self-controlled case series method (6) was used to test the hypothesis of an increased risk of Guillain-Barré syndrome in the 3 risk periods of 0–30 days, 31–60 days, and 61–90 days after vaccination or influenzalike illness. Age was controlled for by using the 12 age periods of less than 8 years, 8–15 years, 16–23 years, 24–31 years, 32–39 years, 40–47 years, 48–55 years, 56–63 years, 64–71 years, 72–79 years, 80–87 years, and 88 years or older. Season was also controlled for in the analysis by using calendar month because influenza vaccine is given mainly between October and December. In this paper, relative incidence estimates are reported with 95% confidence intervals. A prevaccination low-risk period of 2 weeks was taken out of the background risk to allow for delayed vaccination because of Guillain-Barré syndrome. Repeat episodes with an interval of at least 6 months were counted as a separate episode.

To validate the recording of Guillain-Barré syndrome in a primary care setting, the GPRD consultation rate was compared with the admission rate from the Hospital Episode Statistics (HES) data set over the same period. HES holds details of discharge diagnoses for all National Health Service hospital admissions in England and, since April 1996, has used the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision, diagnosis codes. Annual HES admissions for the period 1997–2004 were extracted by using code G610 (Guillain-Barré syndrome) in the primary diagnosis field, with an additional admission within 6 months being classified as the same episode. Repeat episodes in the same patient were identified by using the unique identifier HES ID. The overall annual and average age-specific incidence over the period was calculated by using the Office of National Statistics population statistic for England as the denominator. The overall annual and age-specific incidence of GPRD recorded cases was estimated by using episodes recorded between 1997 and 2004 using the GPRD population statistic for each year.

RESULTS

A total of 989 episodes of Guillain-Barré syndrome within the study period were identified in the GPRD.

Seventeen episodes were excluded because the Guillain-Barré syndrome date was unknown, and one individual with 19 episodes of influenzalike illness was also excluded because no other individual experienced more than 3 episodes. Of the remainder, 196 episodes were excluded because they recurred within 6 months of a previous episode, which left 775 episodes for analysis. These 775 episodes occurred in 690 individuals; 372 were male and 318 female. The majority of individuals ($n = 625$, 91%) had only one episode recorded, 52 had 2 episodes, 9 had 3, 2 had 4, one had 5, and one had 6. Of these 775 GBS episodes in the analysis, 692 (89 percent) were coded as GBS and 83 (11 percent) as polyneuritis.

Of the 690 individuals, 169 had at least one influenza vaccine, 69 at least one pneumococcal vaccine, and 99 at least one influenzalike illness recorded. Although no minimum interval between influenzalike illness was prespecified, no repeat episodes within 4 months were identified. Table 1 shows the number of individuals and Guillain-Barré syndrome episodes according to the number of vaccine doses and influenzalike illness episodes. The ages of the individuals when the 775 separate episodes of Guillain-Barré syndrome occurred peaked in the group 56–63 years, whereas the ages in the subset of 199 with a linked influenza or pneumococcal vaccine record peaked in the group 64–71 years (Figure 1). The seasonal distribution of cases of Guillain-Barré syndrome showed an increase in January compared with the other months (chi-squared test $P < 0.001$) (Figure 2).

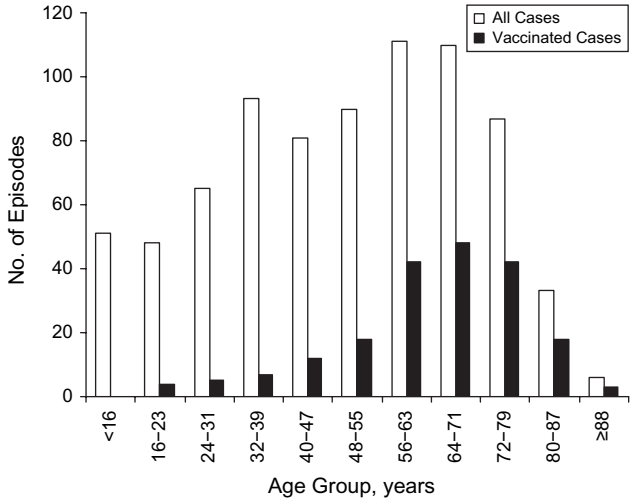


Figure 1. Age groups of individuals at onset of Guillain-Barré syndrome considering all episodes in the analysis ($n = 775$) and the subset with linked influenza or pneumococcal vaccination records ($n = 199$), United Kingdom, 1990–2005.

Table 1. Number of Individuals and Guillain-Barré Syndrome Episodes According to Number of Doses of Influenza and Pneumococcal Vaccines Received and Influenzalike Illness Episodes Recorded, United Kingdom, 1990–2005

Risk Factor	No. of Individuals ($n = 690$)	No. of Episodes ($n = 775$)
Influenza vaccination, no. of doses		
0	521	589
1	47	49
2	26	27
3	22	27
4	18	22
5	9	10
6	13	15
7	12	12
8–18	22	24
Pneumococcal vaccination, no. of doses		
0	621	698
1	67	75
2	2	2
Influenzalike illness, no. of episodes		
0	591	662
1	83	97
2	13	13
3	2	2
4	1	1

Vaccinations

We found no evidence of an increased risk of Guillain-Barré syndrome after pneumococcal vaccine or influenza vaccine, with relative incidence estimates for the 0–90-day period of 0.61 and 0.76, respectively (Table 2). An additional analysis was performed restricted to only those individuals who received at least one vaccination in case those without a recorded vaccination were missing vaccination

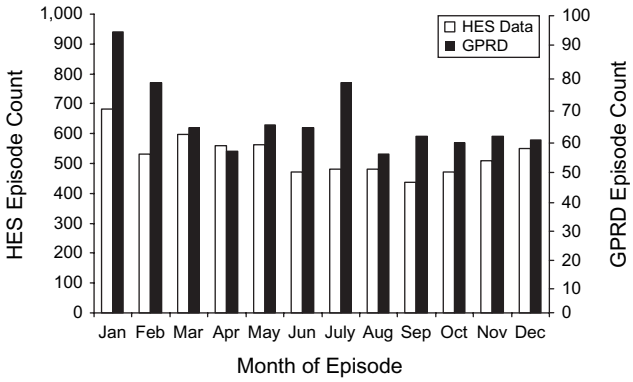


Figure 2. Number of Guillain-Barré syndrome episodes by month recorded in the General Practice Research Database (GPRD) and Hospital Episode Statistics (HES), United Kingdom, 1997–2004.

Table 2. Relative Incidence, 95% Confidence Interval, and Number of Episodes of Guillain-Barré Syndrome in Specified Intervals After Influenza and Pneumococcal Vaccines and a Consultation for Influenzalike Illness, United Kingdom, 1990–2005

Factor and Risk Period (Days)	RI[a]	95% CI	No. of Events
Influenza vaccination			
0–30	0.58	0.18, 1.86	3
31–60	0.39	0.10, 1.60	2
61–90	1.25	0.57, 2.73	7
0–90	0.76	0.41, 1.40	12
Pneumococcal vaccination			
0–90	0.61	0.08, 4.42	1
Influenzalike illness			
0–30	16.64	9.37, 29.54	15
31–60	4.70	1.70, 13.0	4
61–90	0		0
0–90	7.35	4.36, 12.38	19

Abbreviations: CI, confidence interval; RI, relative incidence.
[a] Adjusted for age and calendar month.

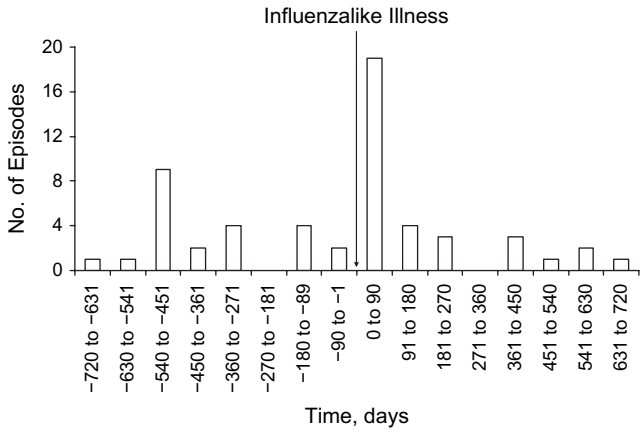


Figure 3. Distribution of Guillain-Barré syndrome episodes in 90-day intervals around the date of influenzalike illness, United Kingdom, 1990–2005.

information. In this analysis, the relative incidence in the 90 days after influenza vaccination was 0.81, with a 95% confidence interval of 0.44, 1.48. To further investigate the low relative incidence in the 90-day period and hence a possible protective effect, the postvaccination period was extended to 180 days. Doing so resulted in a relative incidence of 0.80 and a 95% confidence interval of 0.51, 1.27.

Influenzalike illness

An increased risk was seen following a consultation for influenzalike illness, with 19 events in the 0–90-day period and a relative incidence of 7.35 (95% confidence interval: 4.36, 12.38) (Table 2, Figure 3). Fifteen of the 19 episodes occurred in the 0–30-day period, with a relative incidence of 16.64 (95% confidence interval: 9.37, 29.54), with no episodes in the 61–90-day period. The number of Guillain-Barré syndrome events attributable to influenzalike illness was calculated to be 17.2, with an attributable fraction of 2.2%, assuming all influenzalike illness events were captured. An alternative calculation of the excess due to influenzalike illness is to compare the number of cases in January and February with the average from the other 10 months and attribute the excess to influenzalike illness. This comparison gives an estimated excess of 58.2, which is an attributable fraction of 7.5% of all cases.

Validation

After reviewing the patient profiles, 107 of the 199 episodes in individuals with a linked influenza vaccine record had information supporting the diagnosis of Guillain-Barré syndrome, such as leg weakness, a feeling of ''pins and needles,'' leg pain, or referral to the hospital. Of these 107, 47 had a date of first symptoms, for which 39 episodes had the symptom recorded prior to the Guillain-Barré syndrome date (23 within 30 days, 9 within 31–60 days, and 7 within more than 60 days). The relative incidence in the 90-day period when the analysis was restricted to the 107 cases with supporting evidence was 0.77 (95% confidence interval: 0.35, 1.69). When the analysis was restricted further to the 47 cases with a first recorded symptom, the relative incidence was 0.89 (95% confidence interval: 0.42, 1.89). This estimate is similar to the overall relative incidence of 0.76 (95% confidence interval: 0.41, 1.40) based on all episodes of Guillain-Barré syndrome.

Comparison with HES

A total of 6,340 admissions were found in the HES data set, which gave an overall incidence of 1.61/100,000 population, with a peak in admissions in January similar to that seen in the GPRD data set (Figure 2). There were 481 GPRD consultations over the same period, giving an overall incidence rate of 2.05/100,000 population. Age-specific incidence in HES and GPRD followed a similar pattern, with a peak in the age group 64–71 years (Figure 4).

DISCUSSION

This study found no evidence of an association between influenza vaccination and Guillain-Barré syndrome, with an upper end of the 95% confidence intervals excluding a relative incidence of 1.5. An increased risk of Guillain-Barré syndrome was seen in the period shortly after influenzalike illness, consistent with observations that Guillain-Barré syndrome is often preceded by a respiratory illness. A recent case-control study using the GPRD and restricted to cases of Guillain-Barré syndrome occurring between 1990 and 2001 also found evidence of an increased risk in the 2 months after an influenzalike illness (odds ratio = 18.64, 95% confidence interval: 7.49, 46.37) (10). The association with

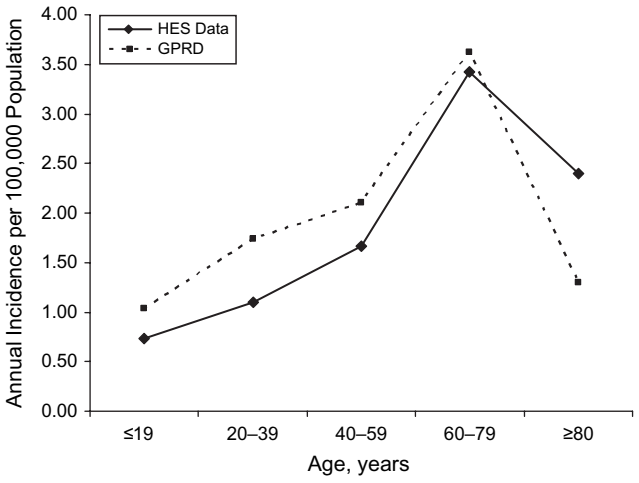


Figure 4. Average age-specific incidence of episodes of Guillain-Barré syndrome over the period 1997–2004 recorded in Hospital Episodes Statistics (HES) and the General Practice Research Database (GPRD), United Kingdom.

influenzalike illness may explain the seasonal pattern of Guillain-Barré syndrome, with an increase in cases during the influenza season that was evident in both the GPRD and HES data sets. Whether this association is specific to influenza virus infection or more generically with other respiratory pathogens that can present as influenzalike illness is difficult to discern since other respiratory infections also peak in the winter.

A time-series analysis investigating the short-term correlations between weekly laboratory-confirmed reports of putative triggering pathogens found a positive association between number of influenza reports in any week and hospital admissions for Guillain-Barré syndrome in the same week (11). The authors of this analysis suggested that absence of a lag period was consistent with a causal association with influenza vaccine rather than influenza infection, since the vaccine is usually administered some weeks before the influenza season begins. However, the correlation with other respiratory pathogens such as respiratory syncytial virus was not investigated. Since the winter peak of respiratory syncytial virus often precedes that of influenza (12), a causal relation between respiratory syncytial virus and Guillain-Barré syndrome is a plausible alternative explanation. Further work to explore the temporal relation between Guillain-Barré syndrome and the viruses known to contribute to the syndrome of influenzalike illness is in progress. The use of a clinical case definition of influenzalike illness as an indicator that influenza incidence has been studied extensively, and corresponding increases in viral positivity rates and general practice consultation rates, have been illustrated (13).

The increased risk of Guillain-Barré syndrome after influenzalike illness, if specific to infection with influenza virus, together with the absence of a causal association with influenza vaccine suggests that influenza vaccine should protect against Guillain-Barré syndrome. While the relative incidence in the 180 days after vaccination was 0.80, the 95% confidence interval spanned 1, so a significant protective effect was not demonstrated. However, a reduction of 20% is plausible given that the efficacy of seasonal influenza vaccine against influenzalike illness is approximately 15%–30% depending on the match between the vaccine and circulating strain (14). Tam et al. (10), using the case-control approach, reported an odds ratio of 0.16 for the risk of Guillain-Barré syndrome within 2 months of influenza vaccine. However, this reduction was not significant and the analysis was based on a total of 18 cases, only one of which occurred in the risk period. Furthermore, a protective effect of this magnitude against the nonspecific disease endpoint of influenzalike illness is not plausible.

The relation among Guillain-Barré syndrome, influenza vaccine, and influenza infection is relevant to the debate about the safety of pandemic influenza vaccines, for which Guillain-Barré syndrome has been identified as a potential adverse effect that requires enhanced surveillance. If such vaccines are protective against the pandemic strain, then, even if they are associated with a small risk of Guillain-Barré syndrome, the overall risk-benefit analysis for this outcome may be favorable. Clearly, in addition to establishing rapid systems for evaluating the risk of vaccine-associated adverse events such as Guillain-Barré syndrome, it will be equally important to evaluate the risk of such events from pandemic influenza and the degree of protection afforded by the vaccine in order to make an overall risk-benefit assessment.

Our finding of an increased risk of Guillain-Barré syndrome after influenzalike illness is also relevant to evaluating the robustness of the prior studies suggesting an increased risk after swine influenza or seasonal influenza vaccines. Any risk from influenzalike illness (or *Campylobacter*) would be a potential confounder in ecologic approaches as carried out with US Army data, where no increase in Guillain-Barré syndrome was seen after vaccination (6). A marginally significant increased relative risk of 1.7 (95% confidence interval: 1.0, 2.8) was reported with the seasonal vaccine by Lasky et al. (7) based on cases occurring in the 1992/1993 and 1993/1994 influenza seasons combined. These periods were chosen because passive reports to VAERS had shown a substantial rise in 1993/1994 compared with 1992/1993. However, when data were analyzed by individual season, the relative risk was not significantly different from 1 in the 1993/1994 season, with only the 1992/1993 season giving a signal (relative risk = 1.5, 95% confidence interval: 1.0, 4.3). This study used a cohort design in which person-time denominators were estimated from a population sample and did not take account of the effect of influenzalike illness.

Passive reporting systems such as VAERS also have major limitations when trying to assess causal associations. Evidence cited by Haber et al. (8) in support of a possible causal association with seasonal influenza vaccines was the lower-than-expected proportion of Guillain-Barré syndrome cases reported to VAERS who had a preceding illness. However, suspicion that a case of Guillain-Barré syndrome may be vaccine attributable is likely to be greater for those with

no other suspected cause, so this reasoning is not convincing. Neither is the apparent excess of VAERS reported cases with onset within the second week after vaccination, since it may also be affected by reporters' judgments regarding the likely interval for a causal association.

The advantage of the self-controlled case series method for assessing causal associations is that it should be free of the individual-level confounding that may affect cohort and case-control studies (9). An earlier study by Juurlink et al. (15) also used the self-controlled case series method to investigate the relation between seasonal influenza vaccine and Guillain-Barré syndrome, and it found a marginally increased relative incidence of 1.45 (95% confidence interval: 1.05, 1.99; $P = 0.02$) in the period 2–7 weeks after administration of influenza vaccine. However, information on the type of vaccine given was not available, and the analysis was restricted to adults who received a vaccine in October or November on the assumption that the majority of vaccines given in these months would be for influenza. Apart from the inherent uncertainty in this assumption, it did not incorporate seasonality, nor did it include influenzalike illness as a potential confounder. The results of this analysis should therefore be treated with caution.

Although our self-controlled case series analysis was not subject to these limitations, there may still be limitations in the GPRD data set that we used for this analysis. The date on which the first Guillain-Barré syndrome consultation is recorded may not be accurate and may reflect the date on which the patient was admitted or discharged from the hospital with the diagnosis. Thus, there may be a time lag between the onset of symptoms and recorded diagnosis. In addition, the coding of Guillain-Barré syndrome in the GPRD may not be accurate. Both these factors would lead to a reduced relative risk estimate. To assess this possibility, an analysis was performed on a vaccinated subset with additional supporting information on the date of onset and accuracy of diagnosis. Although only a relatively low proportion were validated, no significant difference in relative incidence was seen in this subset compared with that found by using all Guillain-Barré syndrome episodes. This finding suggests that a vaccine-attributable effect has not been missed. The finding of a 17-fold increased risk of Guillain-Barré syndrome in the month after an influenzalike illness provides further evidence that the GPRD data are suitable for detecting a vaccine-attributable effect. Further reassurance was provided by the similarity between the GPRD and HES data with respect to the age-specific and monthly incidence.

A further potential criticism of the GPRD data set is that not all influenza vaccine is given by general practitioners; a proportion is administered by occupational health practitioners, for example, to health care workers. However, loss of these data should not affect our results because the self-controlled case series method was also run confined to just those individuals with an influenza vaccine recorded, with similar results.

In conclusion, our study provides robust evidence that seasonal influenza vaccination does not cause Guillain-Barré syndrome. It also shows that patients presenting with influenzalike illness in general practice have a greatly increased risk of developing Guillain-Barré syndrome in the subsequent month. Our findings have implications for the risk assessment process that will need to be put in place to evaluate the utility of pandemic influenza vaccines. They also call into question the robustness of earlier studies that suggest a causal association of swine influenza and seasonal influenza vaccines with Guillain-Barré syndrome. Our study provides further evidence of the power of the self-controlled case series method for evaluating putative causal associations.

ACKNOWLEDGMENTS

Author affiliations: Immunisation Department, Health Protection Agency Centre for Infections, London, United Kingdom (Julia Stowe, Elizabeth Miller); Statistics, Modelling & Bioinformatics Department, Health Protection Agency Centre for Infections, London, United Kingdom (Nick Andrews); and Pharmacoepidemiology Research Team, Post Licensing Division, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom (Lesley Wise).

Support for the salary of J. Stowe was provided by a grant (121/7470) from the Department of Health Research and Development Division.

Conflict of interest: none declared.

REFERENCES

1. Rees JH, Thompson RD, Smeeton NC, et al. Epidemiological study of Guillain-Barré syndrome in south east England. *J Neurol Neurosurg Psychiatry.* 1998;64(1):74–77.
2. Seneviratne U. Guillain-Barré syndrome. *Postgrad Med J*. 2000;76(902):774–782.
3. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol*. 1979;110(2):105–123.
4. Hurwitz ES, Schonberger LB, Nelson DB, et al. Guillain-Barré syndrome and the 1978–1979 influenza vaccine. *N Engl J Med*. 1981;304(26):1557–1561.
5. Kaplan JE, Katona P, Hurwitz ES, et al. Guillain-Barré syndrome in the United States, 1979–80 and 1980–81. *JAMA*. 1982;248(6):698–700.
6. Roscelli JD, Bass JW, Pang L. Guillain-Barré syndrome and influenza vaccination in the US Army 1980–1988. *Am J Epidemiol*. 1991;133(9):952–955.
7. Lasky T, Terracciano DO, Magder L, et al. The Guillain-Barré syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *N Engl J Med*. 1998;339(25):1797–1802.
8. Haber P, DeStefano F, Angulo FJ, et al. Guillain-Barré syndrome following influenza vaccination. *JAMA*. 2004;292(20): 2478–2481.
9. Farrington P, Pugh S, Colville A, et al. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps rubella vaccine. *Lancet*. 1995; 345(8949):567–569.
10. Tam CC, O'Brien SJ, Petersen I, et al. Guillain-Barré syndrome and preceding infection with campylobacter, influenza,

and Epstein-Barr virus in the general practice research database [electronic article]. *PLoS ONE*. 2007;2(4):e344.
11. Tam CC, O'Brien SJ, Rodrigues LC. Influenza, campylobacter and mycoplasma infections, and hospital admissions for Guillain-Barré syndrome, England. *Emerg Infect Dis*. 2006; 12(12):1880–1887.
12. Pitman RJ, Melegaro A, Gelb D, et al. Assessing the burden of influenza and other respiratory infections in England and Wales. *J Infect*. 2007;54(6):530–538.
13. Goddard NL, Kyncl J, Watson JM. Appropriateness of thresholds currently used to describe influenza activity in England. *Commun Dis Public Health*. 2003;6(3):238–245.
14. Jefferson TO, Rivetti D, Di Pietrantonj C, et al. Vaccines for preventing influenza in healthy adults [electronic article]. *Cochrane Database Syst Rev.* 2007;(2):CD001269.
15. Juurlink DN, Stukel TA, Kwong J, et al. Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. *Arch Intern Med*. 2006;166(20):2217–2221.

was stopped now have their symptoms managed by combinations of paracetamol and mefenamic acid.

In our practice Depo-Provera is not currently used in these adolescents because of the concern over decreased acquisition of bone mineral density in conjunction with the use of anticonvulsants. Norethisterone is sometimes used to postpone menstruation if requested by the families or carers.

Most of the carers and families did not have specific concerns relating to menstrual management documented in the medical notes, however it is well recognised that many families and particularly mothers worry how their daughters with severe learning difficulties will manage menstruation. With appropriate support and advice, concerns appear to dissipate through time. The centre is devising an advice leaflet for families entitled ''Practical management of periods''. Two of the families had considered more definitive surgical management options in the past but are not currently pursuing this line of treatment.

We agree there is little evidence to guide clinicians' practice in this area and welcome your review in the first instance to stimulate debate and encourage further studies.

Mel McMahon, Margaret Huyton, Dan Hindley

David Lewis Centre, Warford, Alderley Edge, Cheshire, UK

Correspondence to: Mel McMahon, David Lewis Centre, Mill Lane, Warford, Alderley Edge, Cheshire SK9 7UD, UK; mel.mcmahon@bolton.nhs.uk

Competing interests: None declared.

Arch Dis Child 2008;**93**:181–182.
doi:10.1136/adc.2007.130328

REFERENCE

1. **Albanese A,** Hopper NW. Suppression of menstruation in adolescents with severe learning difficulties. *Arch Dis Child* 2007;**92**:629–32.

Idiopathic thrombocytopenic purpura and the second dose of MMR

An increase in idiopathic thrombocytopenic purpura (ITP) cases in the 6 weeks following the first dose of the measles, mumps and rubella (MMR) vaccine has been established, with absolute risks estimated as 1 in 22 300[1] and 1 in 21 000 vaccine doses,[2] with two in every three cases attributable to the vaccine. However, the risk after a second dose of MMR vaccine has not been investigated.

Hospital admissions for children aged from 3 to <6 years with a discharge diagnosis of ITP (ICD-code D693 in any diagnosis field) were identified from computerised hospital episode data from North, East and South London, Essex, East Anglia, Sussex and Kent for the period from 1 April 1997 to 31 December 2005. These admissions were then linked to second MMR dose records held on population-based child-health database systems. Only successfully linked admissions were used for the analysis.

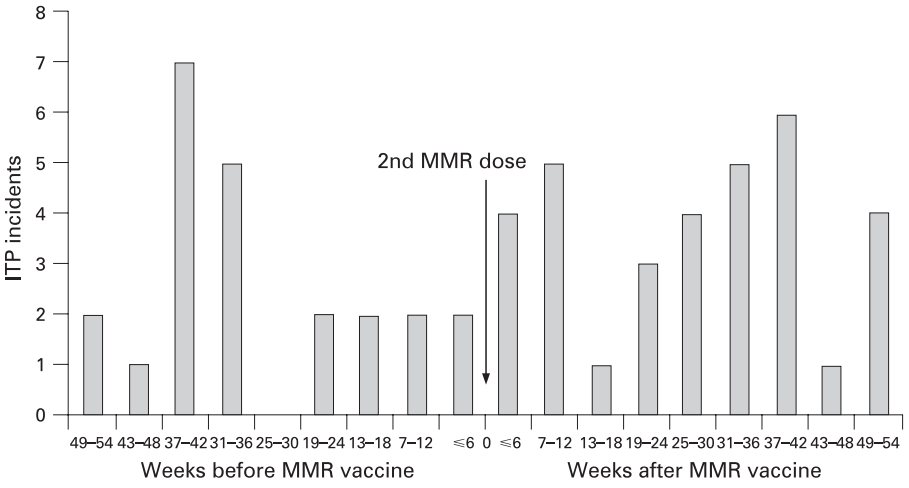


Figure 1 Episodes of ITP in children aged 3 to 6 years: interval from second mmR vaccination.

A re-admission for ITP within 10 days was classed as a continuation of the previous episode Validation of the coding was not undertaken because comprehensive validation in an earlier study using the same hospital discharge data set confirmed the diagnosis coding to be accurate.[1] Analysis was carried out using the self-controlled cases series method, which only uses cases and automatically controls for fixed individual level confounding.[3] The method enables us to estimate the relative incidence, which is the ratio of the rate of events in the 6 weeks after vaccination to the rate of events in the absence of this exposure, with adjustment for age.

A total of 106 ITP admissions in 78 individuals who had received a second dose of MMR vaccine were identified; 14 admissions were excluded because they occurred closer than 10 days to an earlier admission, leaving a total of 92 admissions satisfying the study criteria. Of these 92 admissions, four took place within the period of interest (fig 1). The relative incidence of an ITP episode during the 6-week post-vaccination period compared to the control period was estimated as 1.04 (95% CI 0.37 to 2.92). To identify the size of the risk excluded by this study the upper end of the 95% CI for the attributable risk was calculated as follows: the expected number of cases in the risk period is 4/1.04 = 3.85; the expected number attributable to MMR if the relative incidence is 2.92 is 3.85*(2.92−1) = 7.4; the attributable fraction of all cases is 7.4/92 = 8%; the annual incidence of ITP in 3–6 year olds in England is 14 per 100 000 (Hospital Episode data for the period April 1997 to March 2005); the upper 95% CI for the risk is therefore 0.08*14 = 1 per 100,000.

This study found no evidence of an increased risk of ITP within 6 weeks of the second dose of MMR and excludes risks of more than about 1 per 100 000. There have been isolated reports of ITP after both a first dose and second dose of a measles-containing vaccine [4 5] but we were unable to identify a cohort of children with ITP within 6 weeks of the first dose who then went on to receive the second dose. Indeed there may be few such children because it is recommended[6] that children who develop ITP within 6 weeks of the first dose are tested for antibodies and only receive the second dose if susceptible to one or more of the viruses. Of the 33 children who were admitted for ITP after the age of 3 years and before their second dose of MMR, none had a recurrence within 6 weeks of the second MMR.

In conclusion, our study provides reassurance that among children receiving a second dose of MMR vaccine there is no evidence of an increased risk of ITP.

Julia Stowe,[1] George Kafatos,[2] Nick Andrews,[2] Elizabeth Miller[1]

[1] Immunisation Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK; [2] Statistics, Modelling and Bioinformatics Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

Correspondence to: Professor Elizabeth Miller, Immunisation Department, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK; liz.miller@hpa.org.uk

Competing interests: Support for the salary of J Stowe was provided by a grant from the Department of Health Research and Development Division (grant number 121/7470). No other conflicts of interest.

Arch Dis Child 2008;**93**:182–183.
doi:10.1136/adc.2007.126003

REFERENCES

1. **Miller E,** Waight P, Farrington P, *et al*. Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child* 2001;**84**(3):227–9.
2. **Black C,** Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. *Brit J Clin Pharmacol* 2003;**55**:107–11.
3. **Farrington P,** Pugh S, Colville A, *et al*. A new method for active surveillance of adverse events from

diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* 1995;**345**:567–9.
4. **Vlacha V,** Forman EN, Miron D, *et al*. Recurrent thrombocytopenic purpura after repeated measles-mumps-rubella vaccination. *Pediatrics* 1996;**97**:738–9.
5. **Oski FA,** Naiman JL. Effect of live measles vaccine on the platelet count. *N Engl J Med* 1966;**275**:352–6.
6. . Joint Committee on Vaccine and Immunisation. *Immunisation against infectious disease*. Salisbury, D, Ramsay, M, Noakes, K, eds. DOH.London: Stationery Office, 2006.

Trial of naloxone imperative in children with unexplained reduced consciousness level

The recent Royal College of Paediatrics and Child Health (RCPCH) guideline on decreased conscious level in children[1] overlooks a treatable cause of coma. Opiates or benzodiazepines can cause coma following deliberate or accidental ingestion. The guideline advises considering drug ingestion and urine toxicology but fails to explicitly recommend naloxone or flumazenil as immediate therapy. These are harmless drugs and response is dramatic if intoxication is present.

History of drug ingestion might be withheld. Clinical signs such as pinpoint pupils are unreliable as pupils can dilate when oxygen saturations are low. Toxicology screens can take days to come back. In addition, opiates can cause hyperglycaemia, leading to diagnostic confusion.

High-profile cases have hit the news recently of child deaths following methadone overdose.

According to the 2006 British Crime Survey, 0.2% of adults use opiates,[2] and 4% of 15 year olds have used class A drugs.[3] In Scotland 21 000 people are on prescribed methadone. 7000 have children under 16 living with them. Studies suggest only half of patients store methadone safely.[4] A survey in Dublin found that a quarter of methadone users used babies' bottles for storage.

Thirteen cases of methadone overdose in children were reported in London in 1998. In the Whittington Hospital, North London, during a 9-month period, two patients were admitted following methadone overdoses.

In the absence of a cause for coma, a dose of naloxone (10 mcg/kg then 100 mcg/kg bolus followed by infusion at 5–20 mcg/kg/h) and flumazenil (10 mcg/kg) are essential. In obese patients prolonged naloxone infusion might be required because opiates are stored in fatty tissue.

Naloxone can be administered by paramedics without prescription. It is not enough simply to consider drug intoxication — opiate and benzodiazepine poisoning needs to be reliably excluded as a cause for unexplained reduced conscious level if further deaths are to be prevented.

Correspondence to: Rosemary Belderbos, St Mary's NHS Trust, Praed Street, London W2 1NY; rb@doctors.org.uk

Acknowledgements: Dr Andrew Robins, Whittington Hospital and Dr Ian Maconochie, St Mary's NHS Trust, Paddington, London.

Funding: None.

Competing interests: None.

Arch Dis Child 2008;**93**:183

REFERENCES

1. The Paediatric Accident and Emergency Research Group *The management of a child with decreased conscious level*. London, Royal College of Paediatrics and Child Health, 2005.
2. *British Crime Survey, 2005–2006*. London, Research, Development and Statistics Directorate, 2007.
3. **Fuller E,** Bates B, Blenkinsop S, *et al*. *Smoking, drinking and drug use among young people in England in 2004*. London, Department of Health, 2005.
4. **Calman L,** Finch E, Powis B, *et al*. Only half of patients store methadone in safe place. *BMJ* 1996;**313**:1481.

Asthma guidelines: are they implemented on discharge?

Asthma affects approximately 1 in 10 children in the UK.[1] The British Thoracic Soceity/Scottish Intercollegiate Guidelines Network algorithms[2] are widely used; however, personal experience suggested that their recommendations for patient education were not being used. We undertook a postal questionnaire to determine whether the guidelines were being implemented as recommended.

The questionnaire was sent to 150 randomly selected NHS hospitals in England, Scotland and Wales. Of 54 replies, six were excluded because the hospitals did not have inpatient paediatric facilities, leaving 48 responses (38 district general hospitals, seven teaching hospitals and three childrens hospitals). Forty-six hospitals have written asthma guidelines, of which 18 use the BTS guidelines and 28 use local guidelines. Of the 46, 39 hospitals guidelines (85%) specified that written advice should be provided on discharge. Of these, 29 hospitals use some form of asthma action plan to give the advice.

The BTS/SIGN guidelines suggest written information should be provided on the management of an acute attack including oral steroid use if indicated, use of preventative measures identification of triggers and check on inhaler technique.[2]

Of the 39 hospitals whose protocols included giving written advice on discharge, only 14 complied fully with the BTS guidelines. Thirteen of the remaining 25 had indicated that they use the BTS guideline as their protocol, despite 12 omitting information on triggers, seven omitting inhaler-technique check, five omitting information on acute attacks, five omitting use of oral steroids and two omitting the use of preventative measures. Evidently, using the BTS guideline does not guarantee its recommendations are followed.

Of units that responded, 27% failed to give written information on early recognition and management of an acute attack. Written advice on the use of preventers was not provided by 25%, and 27% fail to provide written advice on use of oral steroids. Omission of the need to check and document inhaler technique on discharge in 44% of responses is a concern. As triggers are often unavoidable in attacks in children, the absence of written avoidance advice in 65% is more understandable.

This failure to follow BTS recommendations is mirrored in a recent study looking at GP prescribing for children with asthma.[3] Over 120 000 prescriptions for bronchodilator syrups were issued in 2006, despite BTS guidelines advising against their use. It would be unthinkable to discharge a child with insulin-dependent diabetes mellitus without education, review and a support network. We still seem to be failing our asthmatic children.

Deborah Bird, Sheetal Bhojani, Selwyn D'Costa

Darent Valley Hospital, Darenth Wood Road, Dartford, Kent

Correspondence to: Deborah Bird, Specialist Registrar in Paediatrics, Darent Valley Hospital, Darenth Wood Road, Dartford, Kent; deborahbird@doctors.org.uk

Funding: None.

Competing interests: None.

Arch Dis Child 2008;**93**:183. doi:10.1136/adc.2007.131870

REFERENCES

1. **Asthma UK**. *Where do we stand? Asthma in the UK today* London: Asthma UK, 2005.
2. **British Thoracic Society/Scottish Intercollegiate Guidelines Network**. *British guideline on the management of asthma*. London'' Britisth Thoracic Society, 2005.
3. **Cohen SA,** Taitz J, Jaffe A. Paediatric prescribing of asthma drugs in the UK: are we sticking to the guidelines? *Arch Dis Child* 2007;92:847–9.

Oral rehydration therapy: a lesson from the developing world

Oral rehydration therapy (ORT) is the best treatment for rehydrating patients with acute infectious diarrhoea and its use has reduced childhood mortality worldwide.[1] Despite this, and despite better resources, success with oral rehydration is lower in developed countries, which have a higher frequency of intravenous fluid administration.[2] This may be either due to different aetiology or because we are worse at using oral rehydration effectively. The aim of our study was to assess current professional conventions and attitudes surrounding oral rehydration in England and identify any incorrect but easily remedied practices.

We conducted a telephone questionnaire study. A total of 109 units in England with acute admitting paediatric inpatient facilities were contacted and the most senior paediatric nurse available completed the questionnaire. The questions were based on the clinical scenario of a child below 2 years of age presenting with acute diarrhoea and moderate dehydration.

Idiopathic thrombocytopenic purpura and the second dose of MMR

Julia Stowe, George Kafatos, Nick Andrews and Elizabeth Miller

Arch Dis Child 2008 93: 182-183 originally published online October 25, 2007
doi: 10.1136/adc.2007.126003

Notes

[Human Vaccines 2:3, 110-112, May/June 2006]; ©2006 Landes Bioscience

Research Paper

Bell's Palsy and Parenteral Inactivated Influenza Vaccine

Julia Stowe[1]
Nick Andrews[2]
Lesley Wise[3]
Elizabeth Miller[1,*]

[1]Immunisation Department; [2]Statistics, Modelling & Bioinformatics Department; Health Protection Agency Centre for Infections; London, UK

[3]Pharmacoepidemiology Research Team; Post Licensing Division; Medicines and Healthcare products Regulatory Agency; London, UK

*Correspondence to: Elizabeth Miller; Immunization Department; Health Protection Agency Centre for Infections; 61 Colindale Avenue; London NW9 5EQ UK; Email: liz.miller@hpa.org.uk

Received 03/14/06; Accepted 04/11/06

Previously published online as a *Human Vaccines* E-publication: http://www.landesbioscience.com/journals/vaccines/abstract.php?id=2790

KEY WORDS

Bell's palsy, influenza vaccine, General Practice Research Database, vaccine associated adverse events, self-controlled case-series method

ABBREVIATIONS

GPRD	General Practice Research Database
SCCS	self-controlled case-series method
VAERS	Vaccine Adverse Event Reporting System

ACKNOWLEDGEMENTS

Support for the salary of J. Stowe was provided by a grant from the Department of Health Research and Development Division (grant number 121/7470).

ABSTRACT

Concern about a possible increased risk of Bell's palsy after parenteral inactivated influenza vaccine was raised following the publication in 2004 of a Swiss study in which there was an increased risk following the nasal inactivated formulation of the vaccine. When data from passive reporting systems in the United States and the United Kingdom were examined there was some evidence of increased reporting following the parenteral vaccine. A large population based study using the General Practice Research Database (GPRD) was therefore performed to test the hypothesis that there was an increased risk of Bell's palsy in the three months following parenteral inactivated influenza vaccine. The risk was also assessed for the same period following pneumococcal vaccine and was stratified into three age groups (<45, 45–64 and 65+ years). Relative incidence (RI) estimates were calculated using the self-controlled case-series method and showed no evidence of an increased risk in the three months following parenteral inactivated influenza vaccine RI 0.92 (95% confidence interval 0.78–1.08). There was also no evidence of an increased risk in any age group or following pneumococcal vaccine. A significant increase was seen on the day of vaccination (day 0) probably due to opportunistic recording of cases.

INTRODUCTION

Bell's palsy is an acute facial paralysis affecting the 7th facial nerve with no detectable cause. It has a reported incidence of about 25 cases per 100 000 population annually[1] and accounts for half of all paralyses affecting the face. Within 3 months 80% of cases recover but some people are affected permanently, 5–9% have a recurrence, with the average time span between episodes being 10 years.

Cases usually present in the community and it is thought that most people report to their GP. Incidence is similar in men and women and no seasonal variation is seen. An increase in incidence is seen with increased age.[2] Treatment is limited but steroids can be given within the first 24 hours of onset or acyclovir used in combination with steroids, although recent Cochrane reviews have shown limited evidence of effectiveness.[1]

An inactive nasal formulation of the influenza vaccine was introduced to the immunization campaign in Switzerland in October 2000. After this introduction an increased number of Bell's palsy cases were reported after vaccination. Mutsch et al carried out a case control study and an association between intranasal inactivated influenza vaccine and Bell's palsy was found, OR 84.0 (95% confidence interval (CI) 20.1–351.9). Self-controlled case-series analysis was also carried out within the risk periods of 1 to 30 days, 31 to 60 days and 61 to 91 days after vaccination. The highest risk was seen in the 31 to 60 day period, relative incidence 35.6 (95% CI 14.1–89.8).[3]

In the same study in Switzerland, Mutsch et al.[3] also looked at the risk with parenteral inactivated influenza vaccine but no causal association was found OR1.1 (95% CI 0.6–2.0). Although this study showed no association very few patients had received the parenteral vaccine and the study design had a number of limitations and biases that may have led to missing a true association.

Following the findings in the Swiss study, Zhou et al.[4] conducted an analysis of cases of suspected Bell's palsy following parenteral inactivated influenza vaccine using the Vaccine Adverse Event Reporting System (VAERS) in the US for the period 1991 to 2001, and found a 2 to 4 fold increased proportional reporting ratio in the 1–3 day and 1–30 day post vaccination periods. An increase of cases reported through the UK's Yellow Card Scheme has also been found and seems to support the US findings. Although the findings

from the passive reporting systems must be treated with caution they constitute a potential signal. It is therefore necessary to carry out a hypothesis testing study using population-based data.

It was proposed that the General Practice Research Database (GPRD) be used to investigate the signal indicated by the passive reporting systems and to test the hypothesis that there is an increased risk of Bell's palsy in the three risk periods 1 to 30 days, 31 to 60 days and 61 to 91 days post parenteral inactivated influenza vaccine.

METHODS

The General Practice Research Database is one of the largest primary care databases in the world. It holds data on consultations, referrals, prescriptions and vaccinations for over 3 million active patients in practices throughout the UK (5.7% of the population).

Patients were included in the study if they had a READ or OXMIS coded consultation for Bell's palsy between July 1st 1992 and June 30th 2005 and also received influenza vaccine in at least one of the 13 July–June influenza seasons. Data had to achieve GPRD up-to-standard status. All patients who had more than one dose of influenza vaccine recorded in the same flu season were dropped due to likely data entry errors, although it is possible that children under thirteen could have been given two doses in the first year they received the vaccine. Also for patients with more than one consultation of Bell's palsy any second consultation within 6 months of a previous one was regarded as part of the same episode. For each patient follow-up time was from July 1st 1992, or first registration in the practice if later, to the earliest of 30th June 2005, death, date patient left the practice and the date data were last obtained from the practice. In addition to follow-up dates, data obtained on each patient were year of birth, sex, date at each Bell's palsy episode, date of each influenza vaccine and date of each pneumoccoccal vaccine.

Validation of the diagnosis coding using the GPRD patient profile was carried out on a randomly selected sample of individual diagnoses. A diagnosis was confirmed if the patient was prescribed steroids, acyclovir or eye drops/ointments within a month of diagnosis and no other reason for the prescription was identified. In addition to this, free text comments were reviewed for episodes where the diagnosis could not be confirmed using the patient profile and for Bell's palsy events on the day of vaccination.

Analysis was carried out using the self-controlled case-series method (SCCS), which automatically controls for fixed individual level confounding.[5] The analysis was restricted to cases of Bell's palsy with one or more valid influenza vaccine dates. Age was adjusted for in 5-year age bands, and season and year were adjusted for by year and quarter.

In the 14 days prior to vaccination a reduced number of Bell's palsy episodes were expected due to delayed vaccination following an episode. Inclusion of this 'low risk' period in the background risk period can introduce bias so it was removed from the background by treating it as a separate risk period in the analysis. Opportunistic recording of episodes on the day of vaccination (day 0) was also anticipated so this day was also regarded as a separate risk period.

Relative incidence estimates were obtained for the entire 3-month (91 day) post vaccination period as well as in the 1–30, 31–60 and 61-91 day periods. Relative incidence was also calculated separately for three age groups (<45, 45–64 and 65+).

In a separate model the 3 month post vaccination relative incidence was estimated for both influenza and pneumoccocal vaccines—this allows for any potential confounding of one vaccine on the other. Finally the 3-month risk was calculated with day 0 included in the risk period. Relative incidence estimates are reported with 95% confidence intervals. The available sample size from GPRD of at least 2000 vaccinated individuals each with approximately 4 vaccine doses was estimated to have 90% power for detecting a relative incidence of 1.3 or greater at a 5% significance level.

RESULTS

A total of 2313 Bell's palsy episodes were identified in the study period with an interval of at least 6 months from any previous episode. READ code F310.00 Bell's (facial) palsy held the majority of the data (96%).

Fourty-six individuals (50 episodes), including one child aged under thirteen, were excluded because they were recorded as having had two flu vaccines in the same flu year. This left 2263 episodes that occurred in 1156 females and 972 males. 118 individuals had two episodes, 13 had three episodes, 2 had four and 2 had five. The age range was from 2 years to 95 years although most of the episodes were in those aged over 50 years (1905/2263, 84%). This is likely to be because this is the age most flu vaccine is given and we only included individuals with flu vaccine. Only 77 episodes were in individuals aged under 30 years, so this was taken as the youngest age group for analysis with age then increasing in five years steps to 85 years+. The total number of episodes in each month showed little variability (range 174 to 202). The number of episodes was also fairly constant over time by flu year (range 161 to 209) with the exception 2004/05 when the number of episodes was only 71. This is due to the fact that not all practices had reported data to the end of June 2005. The 2128 individuals were followed up for an average of 9.6 years and received a total of 8376 flu doses (average 3.9) and 724 pneumococcal vaccine doses (average 0.34). Over 50% (385/724) of

Table 1 **Age specific relative incidence (and 95% confidence intervals) of a general practice consultation for Bell's palsy within 91 days of influenza vaccine**

Risk Period	All ages [N=2263]	Age 0 to 44 [N=264]	Age 45 to 64 [N=766]	Age 65 + [N=1233]
-14 to -1	0.72 (0.48-1.07) [25]	1.25 (0.39-4.00) [3]	0.68 (0.32-1.43) [7]	0.70 (0.42-1.17) [15]
Day 0	4.38 (2.47-7.79) [11]	17.3 (5.4-55.5) [3]	2.76 (0.76-10.03) [2]	3.90 (1.80-8.45) [6]
1 to 91	0.92 (0.78-1.08) [212]	0.83 (0.47-1.48) [14]	0.84 (0.62-1.13) [56]	0.99 (0.80-1.21) [142]
1 to 30	0.99 (0.77-1.27) [75]	1.74 (0.85-3.57) [9]	0.58 (0.33-1.03) [13]	1.13 (0.83-1.54) [53]
31 to 60	0.91 (0.71-1.17) [69]	0.37 (0.09-1.50) [2]	1.08 (0.70-1.67) [24]	0.92 (0.66-1.27) [43]
61 to 91	0.86 (0.67-1.10) [68]	0.50 (0.16-1.57) [3]	0.84 (0.52-1.35) [19]	0.93 (0.68-1.27) [46]

Number of cases in each time interval in square brackets.

the pneumococcal vaccine doses were given at the same time as a Flu dose.

In the analysis looking at influenza vaccine alone in the whole 1 to 91 day period there was no evidence of a significantly increased relative incidence of Bell's palsy following flu vaccine within any of the age groups or overall (all ages) (Table 1).

When the risk period was divided into three 30-day periods and the relative incidence estimated in each of these, no significant increase in risk was seen in these periods either overall or in any of the three age groups (Table 1).

On day 0 a significant increase was seen in all ages overall and in each age group except the 45 to 64 year olds group. When overall analysis was carried out to include the day 0 episodes (i.e., day 0 to day 91) the relative incidence increased as expected but remained below one, RI 0.95 (95% CI 0.81–1.11).

When a model was fitted with a 1–91 day risk period following both influenza vaccine and pneumococcal vaccine neither showed a significant association with RI 0.97 (95% CI 0.84–1.13) for influenza vaccine and 0.67 (95% CI 0.38–1.17) for pneumococcal vaccine.

A total of 100 Bell's palsy episodes were randomly selected for validation. Diagnosis was confirmed using the patient profile for 69 episodes. A confirmation was defined as a prescription record for steroids, antiviral or eye drops/ointment within a month of the episode when no other reason for the prescription was identified.

For the remaining 31 episodes free text was sought for the 2 week period either side of the Bell's palsy episode. Free text was identified for 22 episodes; of these 8 episodes mentioned Bell's palsy, facial weakness or which side of the face was affected within the free text.

Free text was also sought for the 11 episodes that were recorded on the same day as the vaccine, 1 of which was included in the original 100 selected for validation. Of these 11 episodes 8 had free text available but none mentioned sudden onset of Bell's palsy on the day of vaccination. In two instances, the free text indicated that Bell's palsy was already present prior to vaccination but the diagnosis made at the earlier consultation had not been coded and in one instance the diagnosis of mild facial weakness of which the patient was unaware was made at the time of vaccination.

DISCUSSION

This study found no evidence of an increased risk of Bell's palsy in the three months following parenteral inactivated influenza vaccine using a self-controlled case-series analysis of cases with their vaccination history ascertained using GPRD. The observed increase in risk on the day of vaccination is unlikely to represent a causal association on grounds of biological plausibility and can be explained by opportunistic recording of cases at time of vaccination. For example, patients may have had their Bell's palsy diagnosed when presenting for the influenza vaccination or the vaccine was given opportunistically when the consultation was for Bell's palsy, as confirmed by the text comments for some patients. This opportunistic recording of events on the day of vaccination has been reported elsewhere[6] where no causal link between vaccine and diagnosis was recognized.

This validation exercise also demonstrated that many cases of Bell's palsy are not treated with medication and symptoms such as dry eyes are treated with eye drops and ointment only. Damage to the 7th nerve can often disrupt the closing of the eyelid and moisture conservation is important to protect the eye. As it is thought that less than 20% of cases of Bell's palsy are referred for specialist care[2] the strength of using the GPRD is that it allows for the identification of these non-hospitalized patients. As the analysis used only cases with an influenza vaccine history and this is mainly given to older patients, the sex ratio of 1156 females (54.3%) and 973 males (45.7%) was not unexpected.

Although there was no evidence of seasonality for Bell's palsy the analysis had to adjust for season due to the highly seasonal timing of influenza vaccination.

Our results concur with Mutsch et al.[3] who found no causal association in a small number of patients. This study suggests that the association seen with the inactivated intranasal influenza vaccine[3] may be specific to the administration of the intranasal vaccine and the association observed cannot be extrapolated to the parenteral inactivated vaccine. The importance of testing hypotheses raised by signals generated by passive adverse event reports is emphasized.

References

1. Shaw M, Nazir F, Bone I. Bell's palsy: A study of the treatment advice given by Neurologists. J Neurol Neurosurg Psychiatry 2005; 76:293-4.
2. Rowlands S, Hooper R, Hughes R, Burney P. The epidemiology and treatment of Bell's palsy in the UK. Eur J Neurol 2002; 9:63-7.
3. Mutsch M, Zhou W, Rhodes P, Bopp M, Chen RT, Linder T, Spyr C, Steffen R. Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland. N Engl J Med 2004; 350:896-903.
4. Zhou W, Pool V, DeStefano F, Iskander JK, Haber P, Chen RT, VAERS Working Group. 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; 13:505-10.
5. Farrington P, Pugh S, Colville, A, Flower A, Nash J, Morgan-Capner P, Rush M, Miller E. A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps rubella vaccine. Lancet 1995; 345:567-69.
6. Miller E, Andrews N, Grant A, Stowe J, Taylor B. No evidence of an association between MMR vaccine and gait disturbance. Arch Dis Child 2005; 90:292-6.

8. References

Allen, A. (2007) *Vaccine, The controversial Story of Medicine's Greatest Lifesaver.*: W.W. Norton & Company

Andrews, N. (2001) 'Statistical assessment of the association between vaccination and rare adverse events post-licensure.' *Vaccine*, 20 Suppl 1, Oct 15, pp. S49-53; discussion S45-48.

Andrews, N., Stowe. J, Miller. E and Taylor. B. (2007) 'Post-licensure safety of the meningococcal group C conjugate vaccine.' *Hum Vaccin*, 3(2), Mar-Apr, pp. 59-63.

Andrews, N., Stowe, J., Wise, L. and Miller, E. (2010) 'Post-licensure comparison of the safety profile of diphtheria/tetanus/whole cell pertussis/haemophilus influenza type b vaccine and a 5-in-1 diphtheria/tetanus/acellular pertussis/haemophilus influenza type b/polio vaccine in the United Kingdom.' *Vaccine*, 28(44), Oct 18, pp. 7215-7220.

Andrews, N., Stowe, J., Al-Shahi Salman, R. and Miller, E. (2011) 'Guillain-Barre syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: self-controlled case series.' *Vaccine*, 29(45), Oct 19, pp. 7878-7882.

Andrews, N., Miller, E., Taylor, B., Lingam, R., Simmons, A., Stowe, J. and Waight, P. (2002) 'Recall bias, MMR, and autism.' *Archive of diseases in childhood*, 87(6) pp. 493–494.

Andrews, N., Stowe, J., Miller, E., Svanstrom, H., Johansen, K., Bonhoeffer, J., Hviid, A. and consortium, T. V. (2012) 'A collaborative approach to investigating the risk of thrombocytopenic purpura after measles-mumps-rubella vaccination in England and Denmark.' *Vaccine*, 30(19), Apr 19, pp. 3042-3046.

Atchison, C. J., Stowe, J., Andrews, N., Collins, S., Allen, D. J., Nawaz, S., Brown, D., Ramsay, M. E. and Ladhani, S. N. (2016) 'Rapid Declines in Age Group-Specific Rotavirus Infection and Acute Gastroenteritis Among Vaccinated and Unvaccinated Individuals Within 1 Year of Rotavirus Vaccine Introduction in England and Wales.' *Journal of Infectious Diseases*, 213(2), Jan 15, pp. 243-249.

Baker, M. A., Nguyen, M., Cole, D. V., Lee, G. M. and Lieu, T. A. (2013) 'Post-licensure rapid immunization safety monitoring program (PRISM) data characterization.' *Vaccine*, 31 Suppl 10, Dec 30, pp. K98-112.

Banzhoff, A., Haertel, S. and Praus, M. (2011) 'Passive surveillance of adverse events of an MF59-adjuvanted H1N1v vaccine during the pandemic mass vaccinations.' *Hum Vaccin*, 7(5), May, pp. 539-548.

Bardage, C., Persson, I., Ortqvist, A., Bergman, U., Ludvigsson, J. F. and Granath, F. (2011) 'Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden.' *BMJ*, 343, Oct 12, p. d5956.

Bauchau, V., Van Holle, L., Mahaux, O., Holl, K., Sugiyama, K. and Buyse, H. (2015) 'Post-marketing monitoring of intussusception after rotavirus vaccination in Japan.' *Pharmacoepidemiol Drug Saf*, 24(7), Jul, pp. 765-770.

Bertuola, F., Morando, C., Menniti-Ippolito, F., Da Cas, R., Capuano, A., Perilongo, G. and Da Dalt, L. (2010) 'Association between drug and vaccine use and acute immune thrombocytopenia in childhood: a case-control study in Italy.' *Drug Saf*, 33(1), Jan 1, pp. 65-72.

Black, C., Kaye, J. A. and Jick, H. (2003) 'MMR vaccine and idiopathic thrombocytopaenic purpura.' *Br J Clin Pharmacol*, 55(1), Jan, pp. 107-111.

Black, D. (1982) 'Data for management: the Korner Report.' *Br Med J (Clin Res Ed)*, 285(6350), Oct 30, pp. 1227-1228.

Bonhoeffer, J., Kohl, K., Chen, R., Duclos, P., Heijbel, H., Heininger, U., Jefferson, T. and Loupi, E. (2002) 'The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI).' *Vaccine*, 21(3-4), Dec 13, pp. 298-302.

Brady, R. C., Hu, W., Houchin, V. G., Eder, F. S., Jackson, K. C., Hartel, G. F., Sawlwin, D. C., Albano, F. R. and Greenberg, M. (2014) 'Randomized trial to compare the safety and immunogenicity of CSL Limited's 2009 trivalent inactivated influenza vaccine to an established vaccine in United States children.' *Vaccine*, 32(52), Dec 12, pp. 7141-7147.

Brown, K. F., Long, S. J., Ramsay, M., Hudson, M. J., Green, J., Vincent, C. A., Kroll, J. S., Fraser, G. and Sevdalis, N. (2012) 'U.K. parents' decision-making about measles-mumps-rubella (MMR) vaccine 10 years after the MMR-autism controversy: a qualitative analysis.' *Vaccine*, 30(10), Feb 27, pp. 1855-1864.

Buttery, J. P., Danchin, M. H., Lee, K. J., Carlin, J. B., McIntyre, P. B., Elliott, E. J., Booy, R., Bines, J. E. and Group, P. A. S. (2011) 'Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia.' *Vaccine*, 29(16), Apr 5, pp. 3061-3066.

Carlin, J. B., Macartney, K. K., Lee, K. J., Quinn, H. E., Buttery, J., Lopert, R., Bines, J. and McIntyre, P. B. (2013) 'Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program.' *Clin Infect Dis*, 57(10), Nov, pp. 1427-1434.

Centers for Disease, C. and Prevention. (1999) 'Intussusception among recipients of rotavirus vaccine--United States, 1998-1999.' *MMWR Morb Mortal Wkly Rep*, 48(27), Jul 16, pp. 577-581.

Centers for Disease, C., Prevention and Advisory Committee on Immunization, P. (2008) 'Rotavirus vaccination coverage and adherence to the Advisory Committee on Immunization Practices (ACIP)-recommended vaccination schedule--United States, February 2006-May 2007.' *MMWR Morb Mortal Wkly Rep*, 57(15), Apr 18, pp. 398-401.

Centers for Disease Control and Prevention. (2016) *Vaccine Safety Datalink (VSD)*. [Online] [Accessed on 27/07/2016] http://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/

Chang, H. G., Smith, P. F., Ackelsberg, J., Morse, D. L. and Glass, R. I. (2001) 'Intussusception, rotavirus diarrhea, and rotavirus vaccine use among children in New York state.' *Pediatrics*, 108(1), Jul, pp. 54-60.

Chen, R. T., Mullen, S. C., Hayes, J. R., Cochi, S. W., Donlon, S. L. and Wassilak, J. A. (1994) 'The Vaccine Adverse Event Reporting System (VAERS).' *Vaccine*, 12(6), May, pp. 542-550.

Chiu, S. S., Tse, C. Y., Lau, Y. L. and Peiris, M. (2001) 'Influenza A infection is an important cause of febrile seizures.' *Pediatrics*, 108(4), Oct, p. E63.

Chou, C. H., Liou, W. P., Hu, K. I., Loh, C. H., Chou, C. C. and Chen, Y. H. (2007) 'Bell's palsy associated with influenza vaccination: two case reports.' *Vaccine*, 25(15), Apr 12, pp. 2839-2841.

Cimino, J. J. (1998) 'Desiderata for controlled medical vocabularies in the twenty-first century.' *Methods of Information in Medicine*, 37(4-5), Nov, pp. 394-403.

Dauvilliers, Y., Arnulf, I., Lecendreux, M., Monaca Charley, C., Franco, P., Drouot, X., d'Ortho, M. P., Launois, S., Lignot, S., Bourgin, P., Nogues, B., Rey, M., Bayard, S., Scholz, S., Lavault, S., Tubert-Bitter, P., Saussier, C., Pariente, A. and Narcoflu, V. F. s. g. (2013) 'Increased risk of narcolepsy in children and adults after pandemic H1N1 vaccination in France.' *Brain*, 136(Pt 8), Aug, pp. 2486-2496.

Department of Health. (2011) *Dismantling the NHS National Programme for IT*. [Online] [Accessed https://www.gov.uk/government/news/dismantling-the-nhs-national-programme-for-it

Department of Health. (2013a) *Payment by Results in the NHS: a simple guide*. Introduction to the system of Payment by Results (PbR) for healthcare providers,. [Online] [Accessed on 27/07/2016] https://www.gov.uk/government/publications/simple-guide-to-payment-by-results

Department of Health. (2013b) *Information: To Share or not to Share Government Response to the Caldicott Review*. Government response to the Caldicott review,. [Online] [Accessed on 27/07/2016] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/251750/9731-2901141-TSO-Caldicott-Government_Response_ACCESSIBLE.PDF

Dieleman, J., Romio, S., Johansen, K., Weibel, D., Bonhoeffer, J., Sturkenboom, M. and Group, V.-G. C.-C. S. (2011) 'Guillain-Barre syndrome and adjuvanted pandemic influenza A (H1N1) 2009 vaccine: multinational case-control study in Europe.' *BMJ*, 343 p. d3908.

Dodd, C. N., Romio, S. A., Black, S., Vellozzi, C., Andrews, N., Sturkenboom, M., Zuber, P., Hua, W., Bonhoeffer, J., Buttery, J., Crawford, N., Deceuninck, G., de Vries, C., De Wals, P., Gutierrez-Gimeno, M. V., Heijbel, H., Hughes, H., Hur, K., Hviid, A., Kelman, J., Kilpi, T., Chuang, S. K., Macartney, K., Rett,

M., Lopez-Callada, V. R., Salmon, D., Gimenez-Sanchez, F., Sanz, N., Silverman, B., Storsaeter, J., Thirugnanam, U., van der Maas, N., Yih, K., Zhang, T., Izurieta, H. and Global, H. N. G. B. S. C. (2013) 'International collaboration to assess the risk of Guillain Barre Syndrome following Influenza A (H1N1) 2009 monovalent vaccines.' *Vaccine*, 31(40), Sep 13, pp. 4448-4458.

Dourado, I., Cunha, S., Teixeira, M. G., Farrington, C. P., Melo, A., Lucena, R. and Barreto, M. L. (2000) 'Outbreak of aseptic meningitis associated with mass vaccination with a urabe-containing measles-mumps-rubella vaccine: implications for immunization programs.' *American Journal of Epidemiology*, 151(5), Mar 1, pp. 524-530.

Dubben, H. H. and Beck-Bornholdt, H. P. (2005) 'Systematic review of publication bias in studies on publication bias.' *British Medical Journal*, 331(7514), Aug 20, pp. 433-434.

Dunn, P. M. (2002) 'Dr William Farr of Shropshire (1807-1883): obstetric mortality and training.' *Archives of Diseases in Childhood, Fetal Neonatal Edition*, 87(1), Jul, pp. F67-69.

European Medicines Agency. 'EudraVigilance, http://eudravigilance.ema.europa.eu/human/index.asp.'

European Medicines Agency. (2016) *EudraVigilance*. [Online] [Accessed on 27/07/2016] http://eudravigilance.ema.europa.eu/human/index.asp

Farrington, C. P. (1993) 'Estimation of vaccine effectiveness using the screening method.' *Int J Epidemiol*, 22(4), Aug, pp. 742-746.

Farrington, C. P. (2004) 'Control without separate controls: evaluation of vaccine safety using case-only methods.' *Vaccine*, 22(15-16), May 7, pp. 2064-2070.

Farrington, C. P., Whitaker, H. J. and Hocine, M. N. (2009) 'Case series analysis for censored, perturbed, or curtailed post-event exposures.' *Biostatistics*, 10(1), Jan, pp. 3-16.

Farrington, C. P., Pugh, S., Colville, A., Flower, A., Nash, J., Morgan-Capner, P., Rush, M. and Miller, E. (1995) 'A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines.' *Lancet*, 345(8949), Mar 4, pp. 567-569.

Great Britain. (1998) *Data Protection Act* London: The Stationary Office.

Greater Manchester Academic Health Science Network. (2016) *DataWell exchange*. [Online] [Accessed on 27/07/2016] http://www.gmahsn.org/en/datawell

Haber, P., Parashar, U. D., Haber, M. and DeStefano, F. (2015) 'Intussusception after monovalent rotavirus vaccine-United States, Vaccine Adverse Event Reporting System (VAERS), 2008-2014.' *Vaccine*, 33(38), Sep 11, pp. 4873-4877.

Haber, P., DeStefano, F., Angulo, F. J., Iskander, J., Shadomy, S. V., Weintraub, E. and Chen, R. T. (2004) 'Guillain-Barre syndrome following influenza vaccination.' *JAMA*, 292(20), Nov 24, pp. 2478-2481.

Halliday, S. (2000) 'William Farr: campaigning statistician.' *Journal of Medical Biography*, 8(4), Nov, pp. 220-227.

Health and Social Care Information Centre. (2016a) *Hospital Episode Statistics*. [Online] [Accessed on 27/07/2016] http://www.hscic.gov.uk/hes

Health and Social Care Information Centre. (2016b) *Read codes*. [Online] [Accessed on 28/07/2016] http://systems.hscic.gov.uk/data/uktc/readcodes

Health and Social Care Information Centre. (2016c) *Care Information Choices, England*. [Online] [Accessed on 11/08/2016] http://digital.nhs.uk/catalogue/PUB21163/Care-Information-Choices-Jul-2016.pdf

Health Research Authority. (2016) *National Research Ethics Service (NRES)*. National Health Service. [Online] [Accessed on 27/07/2016] http://www.hra.nhs.uk/

Hilton, S., Petticrew, M. and Hunt, K. (2006) ''Combined vaccines are like a sudden onslaught to the body's immune system': parental concerns about vaccine 'overload' and 'immune-vulnerability'.' *Vaccine*, 24(20), May 15, pp. 4321-4327.

Hviid, A. (2006) 'Postlicensure epidemiology of childhood vaccination: the Danish experience.' *Expert Review of Vaccines*, 5(5), Oct, pp. 641-649.

Izurieta, H. S., Haber, P., Wise, R. P., Iskander, J., Pratt, D., Mink, C., Chang, S., Braun, M. M. and Ball, R. (2005) 'Adverse events reported following live, cold-adapted, intranasal influenza vaccine.' *JAMA*, 294(21), Dec 7, pp. 2720-2725.

Jackson, M. L. and Nelson, J. C. (2013) 'The test-negative design for estimating influenza vaccine effectiveness.' *Vaccine*, 31(17), Apr 19, pp. 2165-2168.

Juurlink, D. N., Stukel, T. A., Kwong, J., Kopp, A., McGeer, A., Upshur, R. E., Manuel, D. G., Moineddin, R. and Wilson, K. (2006) 'Guillain-Barre syndrome after influenza vaccination in adults: a population-based study.' *Arch Intern Med*, 166(20), Nov 13, pp. 2217-2221.

Kaplan, J. E., Katona, P., Hurwitz, E. S. and Schonberger, L. B. (1982) 'Guillain-Barre syndrome in the United States, 1979-1980 and 1980-1981. Lack of an association with influenza vaccination.' *JAMA*, 248(6), Aug 13, pp. 698-700.

Kramarz, P., France, E. K., Destefano, F., Black, S. B., Shinefield, H., Ward, J. I., Chang, E. J., Chen, R. T., Shatin, D., Hill, J., Lieu, T. and Ogren, J. M. (2001) 'Population-based study of rotavirus vaccination and intussusception.' *Pediatr Infect Dis J*, 20(4), Apr, pp. 410-416.

Kwong, J., Vasa, P. P., Campitelli, M. A., Hawken, S., Wilson, K., Rosella, L. C., Stukel, T. A., Crowcroft, N. S., McGeer, A. J., Zinman, L. and Deeks, S. L. (2013) 'Risk of Guillain-Barre syndrome after seasonal influenza vaccination and influenza health-care encounters: a self-controlled study.' *Lancet Infect Dis*, 13(9), Sep, pp. 769-776.

Kwong, K., Lam, S., Que, T. and Wong, S. (2006) 'Influenza A and febrile seizures in childhood.' *Pediatr Neurol*, 35(6), Dec, pp. 395-399.

Lasky, T., Terracciano, G. J., Magder, L., Koski, C. L., Ballesteros, M., Nash, D., Clark, S., Haber, P., Stolley, P. D., Schonberger, L. B. and Chen, R. T. (1998) 'The Guillain-Barre syndrome and the 1992-1993 and 1993-1994 influenza vaccines.' *N Engl J Med*, 339(25), Dec 17, pp. 1797-1802.

Lee, G. M., Greene, S. K., Weintraub, E. S., Baggs, J., Kulldorff, M., Fireman, B. H., Baxter, R., Jacobsen, S. J., Irving, S., Daley, M. F., Yin, R., Naleway, A., Nordin, J. D., Li, L., McCarthy, N., Vellozzi, C., Destefano, F., Lieu, T. A. and Vaccine Safety Datalink, P. (2011) 'H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project.' *Am J Prev Med*, 41(2), Aug, pp. 121-128.

Leite, A., Andrews, N. J. and Thomas, S. L. (2016) 'Near real-time vaccine safety surveillance using electronic health records-a systematic review of the application of statistical methods.' *Pharmacoepidemiology Drug Safety*, 25(3), Mar, pp. 225-237.

Lewis, D. J., Huo, Z., Barnett, S., Kromann, I., Giemza, R., Galiza, E., Woodrow, M., Thierry-Carstensen, B., Andersen, P., Novicki, D., Del Giudice, G. and Rappuoli, R. (2009) 'Transient facial nerve paralysis (Bell's palsy) following intranasal delivery of a genetically detoxified mutant of Escherichia coli heat labile toxin.' *PLoS One*, 4(9), Sep 16, p. e6999.

Lindquist, L. (2008) 'VigiBase, the WHO Global ICSR Database System: Basic Facts.' *Drug Information Journal*, 42 pp. 409-419.

Maclure, M. (1991) 'The case-crossover design: a method for studying transient effects on the risk of acute events.' *Am J Epidemiol*, 133(2), Jan 15, pp. 144-153.

Medicine and Healthcare Regulatory Agency. (2016) *MHRA Yellow card scheme*. [Online] [Accessed on 27/07/2016] https://yellowcard.mhra.gov.uk/

Miller, E. and Stowe, J. (2012) 'Vaccine Safety Surveillance.' *In* Talbot and Aronson (ed.) *Stephens' Detection and Evaluation of Adverse Drug Reactions*. 6th ed.: Wiley-Blackwell,

Miller, E., Waight, P., Farrington, P., Andrews, N., Stowe, J. and Taylor, B. (2001a) 'Idiopathic thrombocytopenic purpura and MMR vaccine.' *Archives of Diseases in Childhood*, 84 pp. 227–229.

Miller, E., Waight, P., Farrington, C. P., Andrews, N., Stowe, J. and Taylor, B. (2001b) 'Idiopathic thrombocytopenic purpura and MMR vaccine.' *Arch Dis Child*, 84(3), Mar, pp. 227-229.

Miller, E., Andrews, N., Stowe, J., Grant, A., Waight, P. and Taylor, B. (2007) 'Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom.' *American Journal of Epidemiology*, 165(6), Mar 15, pp. 704-709.

Miller, E., Andrews, N., Stellitano, L., Stowe, J., Winstone, A. M., Shneerson, J. and Verity, C. (2013) 'Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis.' *British Medical Journal*, 346 p. f794.

Moore, D. L., Vaudry, W., Scheifele, D. W., Halperin, S. A., Dery, P., Ford-Jones, E., Arishi, H. M., Law, B. J., Lebel, M., Le Saux, N., Grimsrud, K. and Tam, T. (2006) 'Surveillance for influenza admissions among children hospitalized in Canadian immunization monitoring program active centers, 2003-2004.' *Pediatrics*, 118(3), Sep, pp. e610-619.

Morabia, A. (2013) 'Epidemiology's 350th Anniversary: 1662-2012.' *Epidemiology*, 24(2), Mar, pp. 179-183.

Murphy, T. V., Gargiullo, P. M., Massoudi, M. S., Nelson, D. B., Jumaan, A. O., Okoro, C. A., Zanardi, L. R., Setia, S., Fair, E., LeBaron, C. W., Wharton, M., Livengood, J. R. and Team, R. I. I. (2001) 'Intussusception among infants given an oral rotavirus vaccine.' *New England Journal of Medicine*, 344(8), Feb 22, pp. 564-572.

Mutsch, M., Zhou, W., R, hodes, P., Bopp, M., Chen, R. T., Linder, T., Spyr, C. and Steffen, R. (2004) 'Use of the inactivated intranasal influenza vaccine and the risk of Bell's palsy in Switzerland.' *New England Journal of Medicine*, 350(9), Feb 26, pp. 896-903.

Nash, J. Q., Chandrakumar, M., Farrington, C. P., Williamson, S. and Miller, E. (1995) 'Feasibility study for identifying adverse events attributable to vaccination by record linkage.' *Epidemiology and Infection*, (114) pp. 475-480.

NHS England. (2015) *Child Health Information Services (CHIS) Provider Service Specification*. [Online] [Accessed on 27/07/2016] https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/05/chis-provider-service-spec.pdf

NHS England. (2016) *The care.data programme – collecting information for the health of the nation*. [Online] [Accessed on 27/07/2016] https://www.england.nhs.uk/ourwork/tsd/care-data/

NHS/DHSS. (1982) *Korner Report- use of information in management of patients 1987. National Health Service and Department of Health and Social Security Steering Group on Health Services Information. First Report,.* London.

O'Leary, S. T., Glanz, J. M., McClure, D. L., Akhtar, A., Daley, M. F., Nakasato, C., Baxter, R., Davis, R. L., Izurieta, H. S., Lieu, T. A. and Ball, R. (2012) 'The risk of immune thrombocytopenic purpura after vaccination in children and adolescents.' *Pediatrics*, 129(2), Feb, pp. 248-255.

Offit, P. A., Davis, R. L. and Gust, D. (2013) 'Vaccine Safety.' *In* Plotkin S.A., Orenstein, W. A. and Offit P.A. (eds.) *Vaccines*. 6th ed., Edinburgh: Elsevier/Saunders,

Owatanapanich, S., Wanlapakorn, N., Tangsiri, R. and Poovorawan, Y. (2014) 'Measles-mumps-rubella vaccination induced thrombocytopenia: a case report and review of the literature.' *Southeast Asian J Trop Med Public Health*, 45(5), Sep, pp. 1053-1057.

Patel, M. M., López-Collada, V. R., Bulhões, M. M., De Oliveira, L., Bautista Márquez, A., Flannery, B., Esparza-Aguilar, M., Montenegro Renoiner, E. I., Luna-Cruz, M. E., Sato, H. K., Hernández-Hernández., Ldel, C., Toledo-Cortina, G., Cerón-Rodríguez, M., Osnaya-Romero, N., Martínez-Alcazar, M., Aguinaga-Villasenor, R. G., Plascencia-Hernández, A., Fojaco-González, F., Hernández-Peredo Rezk, G., Gutierrez-Ramírez, S. F., Dorame-Castillo, R., Tinajero-Pizano, R., Mercado-Villegas, B., Barbosa, M. R., Maluf, E. M., Ferreira, L. B., de Carvalho, F. M., dos Santos, A. R., Cesar, E. D., de Oliveira, M. E., Silva, C. L., de Los Angeles Cortes, M., Ruiz Matus, C., Tate, J., Gargiullo, P. and Parashar, U. D. (2011) 'Intussusception risk and health benefits of rotavirus vaccination in

Mexico and Brazil. .' *New England Journal of Medicine*, 364 pp. 2283–2292.

Peeraully, R., Henderson, K. and Davies, B. (2016) 'Emergency readmissions to paediatric surgery and urology: The impact of inappropriate coding.' *Ann R Coll Surg Engl*, 98(4), Apr, pp. 250-253.

Perez-Vargas, J., Isa, P., Lopez, S. and Arias, C. F. (2006) 'Rotavirus vaccine: early introduction in Latin America-risks and benefits.' *Arch Med Res*, 37(1), Jan, pp. 1-10.

Perez-Vilar, S., Diez-Domingo, J., Puig-Barbera, J., Gil-Prieto, R. and Romio, S. (2015) 'Intussusception following rotavirus vaccination in the Valencia Region, Spain.' *Hum Vaccin Immunother*, 11(7) pp. 1848-1852.

Persson, I., Granath, F., Askling, J., Ludvigsson, J. F., Olsson, T. and Feltelius, N. (2014) 'Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up.' *J Intern Med*, 275(2), Feb, pp. 172-190.

Petousis-Harris, H., Poole, T., Booy, R. and Turner, N. (2011) 'Fever following administration of two inactivated influenza vaccines--a survey of parents of New Zealand infants and children 5 years of age and under.' *Vaccine*, 29(16), Apr 5, pp. 2933-2937.

Petousis-Harris, H., Poole, T., Turner, N. and Reynolds, G. (2012) 'Febrile events including convulsions following the administration of four brands of 2010 and 2011 inactivated seasonal influenza vaccine in NZ infants and children: the importance of routine active safety surveillance.' *Vaccine*, 30(33), Jul 13, pp. 4945-4952.

Plotkin, S. L. and Plokin, S. A. (2013) 'A Short History of vaccination.' *In* Plotkin, S. A., Orenstein, W. A. and Offit, P. A. (eds.) *Vaccines*. 6th ed., Edinburgh: Elsevier/Saunders,

Posfay-Barbe, K. M., Heininger, U., Aebi, C., Desgrandchamps, D., Vaudaux, B. and Siegrist, C. A. (2005) 'How do physicians immunize their own children? Differences among pediatricians and nonpediatricians.' *Pediatrics*, 116(5), Nov, pp. e623-633.

Postila, V. and Kilpi, T. (2004) 'Use of vaccine surveillance data in the evaluation of safety of vaccines.' *Vaccine*, 22(15-16), May 7, pp. 2076-2079.

Prestel, J., Volkers, P., Mentzer, D., Lehmann, H. C., Hartung, H. P., Keller-Stanislawski, B. and Group, G. B. S. S. (2014) 'Risk of Guillain-Barre syndrome following pandemic influenza A(H1N1) 2009 vaccination in Germany.' *Pharmacoepidemiol Drug Saf*, 23(11), Nov, pp. 1192-1204.

Public Health England. (2006) *Immunisation against infectious disease: Influenza: the green book*. [Online] [Accessed on 28/07/2016] https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book

Rajantie, J., Zeller, B., Treutiger, I., Rosthoj, S., group, N. I. w. and five national study, g. (2007) 'Vaccination associated thrombocytopenic purpura in children.' *Vaccine*, 25(10), Feb 26, pp. 1838-1840.

Roscelli, J. D., Bass, J. W. and Pang, L. (1991) 'Guillain-Barre syndrome and influenza vaccination in the US Army, 1980-1988.' *Am J Epidemiol*, 133(9), May 1, pp. 952-955.

Ruiz-Palacios, G. M., Perez-Schael, I., Velazquez, F. R., Abate, H., Breuer, T., Clemens, S. C., Cheuvart, B., Espinoza, F., Gillard, P., Innis, B. L., Cervantes, Y., Linhares, A. C., Lopez, P., Macias-Parra, M., Ortega-Barria, E., Richardson, V., Rivera-Medina, D. M., Rivera, L., Salinas, B., Pavia-Ruz, N., Salmeron, J., Ruttimann, R., Tinoco, J. C., Rubio, P., Nunez, E., Guerrero, M. L., Yarzabal, J. P., Damaso, S., Tornieporth, N., Saez-Llorens, X., Vergara, R. F., Vesikari, T., Bouckenooghe, A., Clemens, R., De Vos, B., O'Ryan, M. and Human Rotavirus Vaccine Study, G. (2006) 'Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis.' *N Engl J Med*, 354(1), Jan 5, pp. 11-22.

Saez-Llorens, X. and Guevara, J. N. (2004) 'Intussusception and rotavirus vaccines: what is the background risk?' *Pediatr Infect Dis J*, 23(4), Apr, pp. 363-365.

Schonberger, L. B., Bregman, D. J., Sullivan-Bolyai, J. Z., Keenlyside, R. A., Ziegler, D. W., Retailliau, H. F., Eddins, D. L. and Bryan, J. A. (1979) 'Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976--1977.' *Am J Epidemiol*, 110(2), Aug, pp. 105-123.

National Health Service, E. a. W. (2002) *The Health Service (Control of Patient Information) Regulations 2002.* 1438, (Secretary of State for Health Report)

Sorup, S., Benn, C. S., Poulsen, A., Krause, T. G., Aaby, P. and Ravn, H. (2014) 'Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections.' *JAMA*, 311(8), Feb 26, pp. 826-835.

Stowe, J., Andrews, N., Wise, L. and Miller, E. (2006) 'Bell's Palsy and Parenteral Inactivated Influenza Vaccine.' *Human Vaccines*, 2 (3), May-June, pp. 110-112.

Stowe, J., Kafatos, G., Andrews, N. and Miller, E. (2008) 'Idiopathic thrombocytopenic purpura and the second dose of MMR.' *Archives of Diseases in Childhood*, 93(2), Feb, pp. 182-183.

Stowe, J., Andrews, N., Wise, L. and Miller, E. (2009a) 'Investigation of the temporal association of Guillain-Barre syndrome with influenza vaccine and influenzalike illness using the United Kingdom General Practice Research Database.' *American Journal of Epidemiology*, 169(3), Feb 1, pp. 382-388.

Stowe, J., Andrews, N., Taylor, B. and Miller, E. (2009b) 'No evidence of an increase of bacterial and viral infections following Measles, Mumps and Rubella vaccine.' *Vaccine*, 27(9), Feb 25, pp. 1422-1425.

Stowe, J., Andrews, N., Wise, L. and Miller, E. (2009c) '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*, 169(3), Feb 1, pp. 382-388.

Stowe, J., Andrews, N., Ladhani, S. and Miller, E. (2016a) 'The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation.' *Vaccine*, 34(32), Jul 12, pp. 3684-3689.

Stowe, J., Andrews, N., Bryan, P., Seabroke, S. and Miller, E. (2011) 'Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: a database study.' *Vaccine*, 29(51), Nov 28, pp. 9467-9472.

Stowe, J., Andrews, N., Kosky, C., Dennis, G., Eriksson, S., Hall, A., Leschziner, G., Reading, P., Shneerson, J. M., Donegan, K. and Miller, E. (2016b) 'Risk of Narcolepsy after AS03 Adjuvanted Pandemic A/H1N1 2009 Influenza Vaccine in Adults: A Case-Coverage Study in England.' *Sleep*, 39(5) pp. 1051-1057.

Svanstrom, H., Callreus, T. and Hviid, A. (2010) 'Temporal data mining for adverse events following immunization in nationwide Danish healthcare databases.' *Drug Saf*, 33(11), Nov 1, pp. 1015-1025.

The Stationary Office. (2012) *Health and Social Care Act 2012, Chapter 7*. [Online] [Accessed on 27/07/2016] http://www.legislation.gov.uk/ukpga/2012/7/pdfs/ukpga_20120007_en.pdf

United States National Library of Medicine. (January 1996) *PubMed*. [Online] [Accessed on 15/11/2016] www.ncbi.nlm.nih.gov/pubmed/

VAESCO. *Narcolepsy in association with pandemic influenza vaccination – a multi-country European epidemiological investigation*. [Online] [Accessed on 20/09/2016] http://vaesco.net/vaesco/results.html

Velazquez, F. R., Colindres, R. E., Grajales, C., Hernandez, M. T., Mercadillo, M. G., Torres, F. J., Cervantes-Apolinar, M., DeAntonio-Suarez, R., Ortega-Barria, E., Blum, M., Breuer, T. and Verstraeten, T. (2012) 'Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico.' *Pediatr Infect Dis J*, 31(7), Jul, pp. 736-744.

Vesikari, T., Matson, D. O., Dennehy, P., Van Damme, P., Santosham, M., Rodriguez, Z., Dallas, M. J., Heyse, J. F., Goveia, M. G., Black, S. B., Shinefield, H. R., Christie, C. D., Ylitalo, S., Itzler, R. F., Coia, M. L., Onorato, M. T., Adeyi, B. A., Marshall, G. S., Gothefors, L., Campens, D., Karvonen, A., Watt, J. P., O'Brien, K. L., DiNubile, M. J., Clark, H. F., Boslego, J. W., Offit, P. A., Heaton, P. M., Rotavirus, E. and Safety Trial Study, T. (2006) 'Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine.' *N Engl J Med*, 354(1), Jan 5, pp. 23-33.

Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M., Berelowitz, M., Dhillon, A. P., Thomson, M. A., Harvey, P., Valentine, A., Davies, S. E. and Walker-Smith, J. A. (1998) 'RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children.' *The Lancet*, 351(9103) pp. 637-641.

Weintraub, E. S., Baggs, J., Duffy, J., Vellozzi, C., Belongia, E. A., Irving, S., Klein, N. P., Glanz, J. M., Jacobsen, S. J., Naleway, A., Jackson, L. A. and DeStefano, F. (2014) 'Risk of intussusception after monovalent rotavirus vaccination.' *N Engl J Med*, 370(6), Feb 6, pp. 513-519.

World Health Organization. (2010) *International Statistical Classification of Diseases and Related Health Problems*. [Online] [Accessed on 27/07/2016] http://www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf

World Health Organization. (2012) *Global vaccine safety blueprint*. [Online] [Accessed on 09/09/216] http://extranet.who.int/iris/restricted/bitstream/10665/70919/1/WHO_IVB_12.07_eng.pdf?ua=1

World Health Organization. (2013) *Causality assessment of an adverse event following immunization (AEFI). User manual for the revised WHO AEFI causality assessment classification*. [Online] [Accessed http://www.who.int/vaccine_safety/publications/gvs_aefi/en/

Yih, W. K., Lieu, T. A., Kulldorff, M., Martin, D., McMahill-Walraven, C. N., Platt, R., Selvam, N., Selvan, M., Lee, G. M. and Nguyen, M. (2014) 'Intussusception risk after rotavirus vaccination in U.S. infants.' *N Engl J Med*, 370(6), Feb 6, pp. 503-512.

Yung, C. F., Chan, S. P., Soh, S., Tan, A. and Thoon, K. C. (2015) 'Intussusception and Monovalent Rotavirus Vaccination in Singapore: Self-Controlled Case Series and Risk-Benefit Study.' *J Pediatr*, 167(1), Jul, pp. 163-168 e161.

Zhou, W., Pool, V., DeStefano, F., Iskander, J. K., Haber, P., Chen, R. T. and Group, V. W. (2004) 'A potential signal of Bell's palsy after parenteral inactivated influenza vaccines: reports to the Vaccine

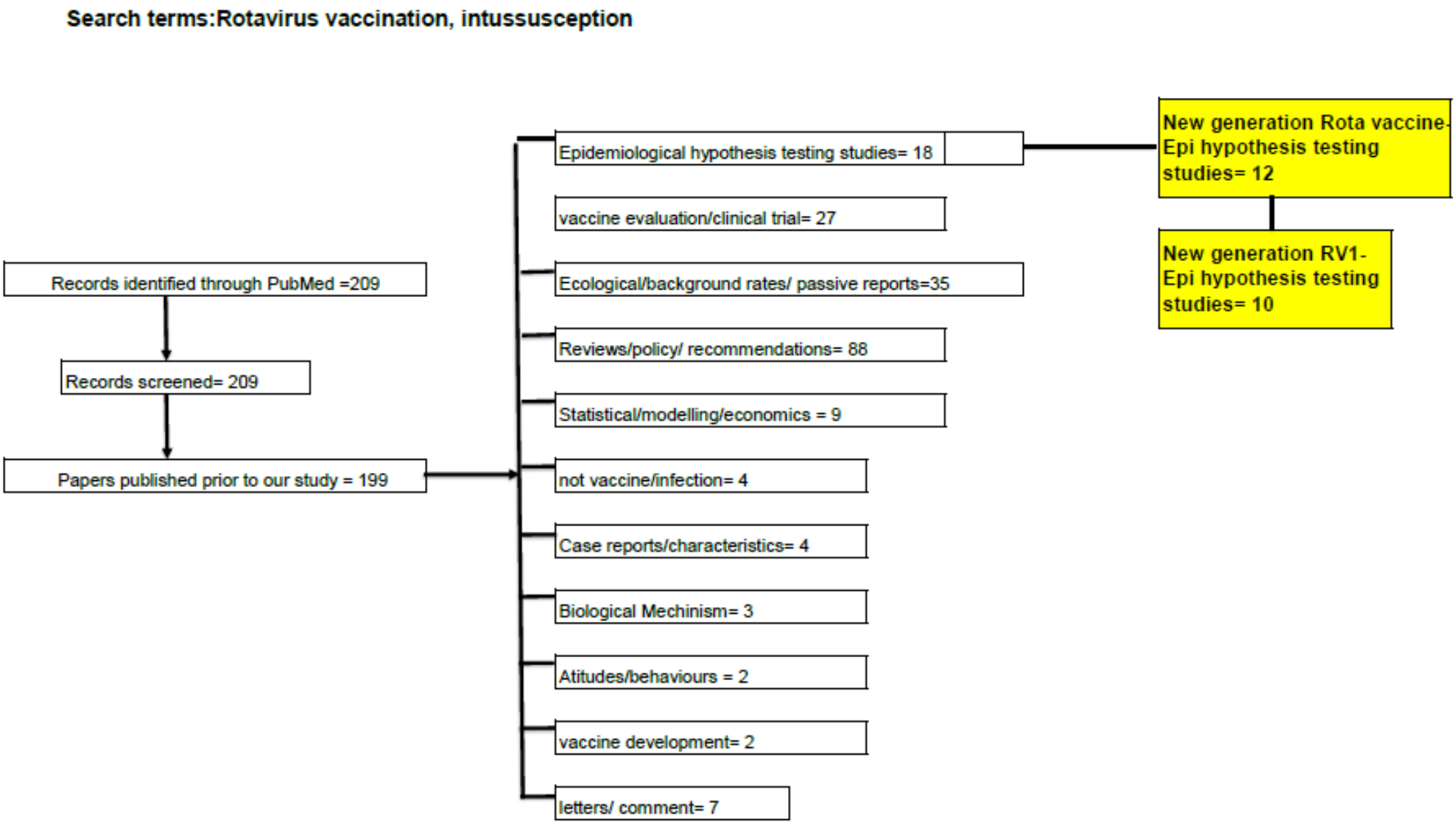
Adverse Event Reporting System (VAERS)--United States, 1991-2001.' *Pharmacoepidemiol Drug Saf*, 13(8), Aug, pp. 505-510.

9. Table:

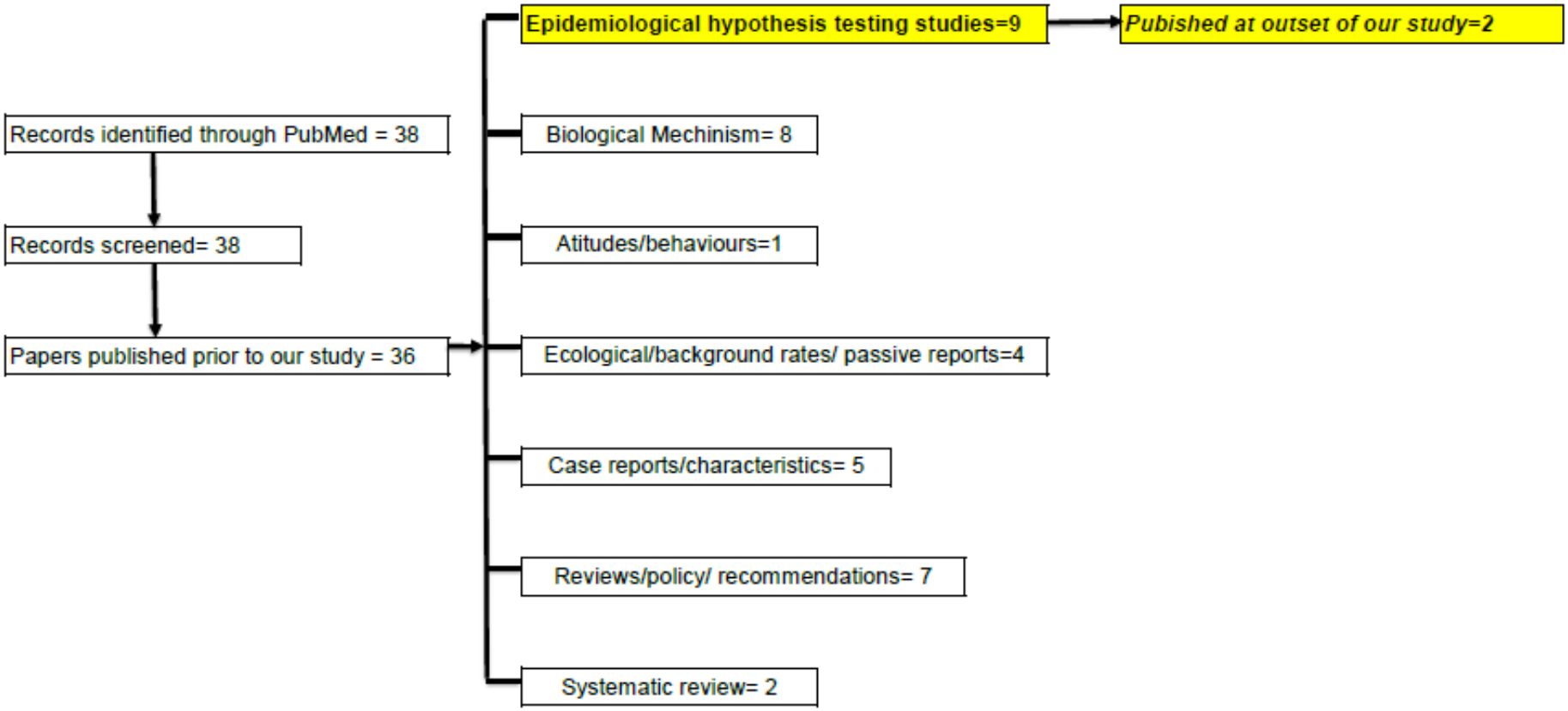
Table 2: Health data systems and coding

Level of care	Area of NHS	Name System	Population covered	Type of coded data	name of coding system	computer system name:
Primary	General Practice	The Health Improvement Network (THIN)	6% of UK population	clinical, procedures, prescriptions, vaccinations, referrals	READ/CTV2/3 SNOWMED	VISION
Primary	General Practice	Clinical Practice Research Database (formally GPRD)	9% of UK population	clinical, procedures, prescriptions, vaccinations, referrals-linked to secondary care for a subset	READ/CTV2/SNOWMED	VISION/EMIS
Primary	General Practice	Royal College of General Practioners (RCGP)	1.5% of English population - 107 practices	clinical, procedures, prescriptions, vaccinations, referrals	READ/CTV2/3 SNOWMED	Covers a number of systems
Primary	General Practice	Qresearch	1000 practices in UK	clinical, procedures, prescriptions, vaccinations, referrals-links to secondary care	READ/CTV2/3 SNOWMED	EMIS
Primary	Child Health Information Systems	TPP	46% of Local Authorities	immunisation, screening,	non-standard- specific to database	
Primary	Child Health Information Systems	Health Solution Wales	18% of Local Authorities	immunisation, screening,	non-standard- specific to database	
Primary	Child Health Information Systems	CarePlus (McKesson)	16% of Local Authorities	immunisation, screening,	nonstandard- specific to database	
Primary	Child Health Information Systems	RIO	12% of Local Authorities	immunisation, screening,	non-standard- specific to database	
Secondary	Hospital Inpatient	Hospital Episode Statistics	All NHS hospital in England	clinical & procedures	ICD10/OPCS-4	Patient administration systems
Secondary	Hospital Outpatient	Hospital Episode Statistics	All NHS hospital in England	none		Patient administration systems
Secondary	Hospital Accident and Emergency	Hospital Episode Statistics	All NHS hospital in England	none		Patient administration systems

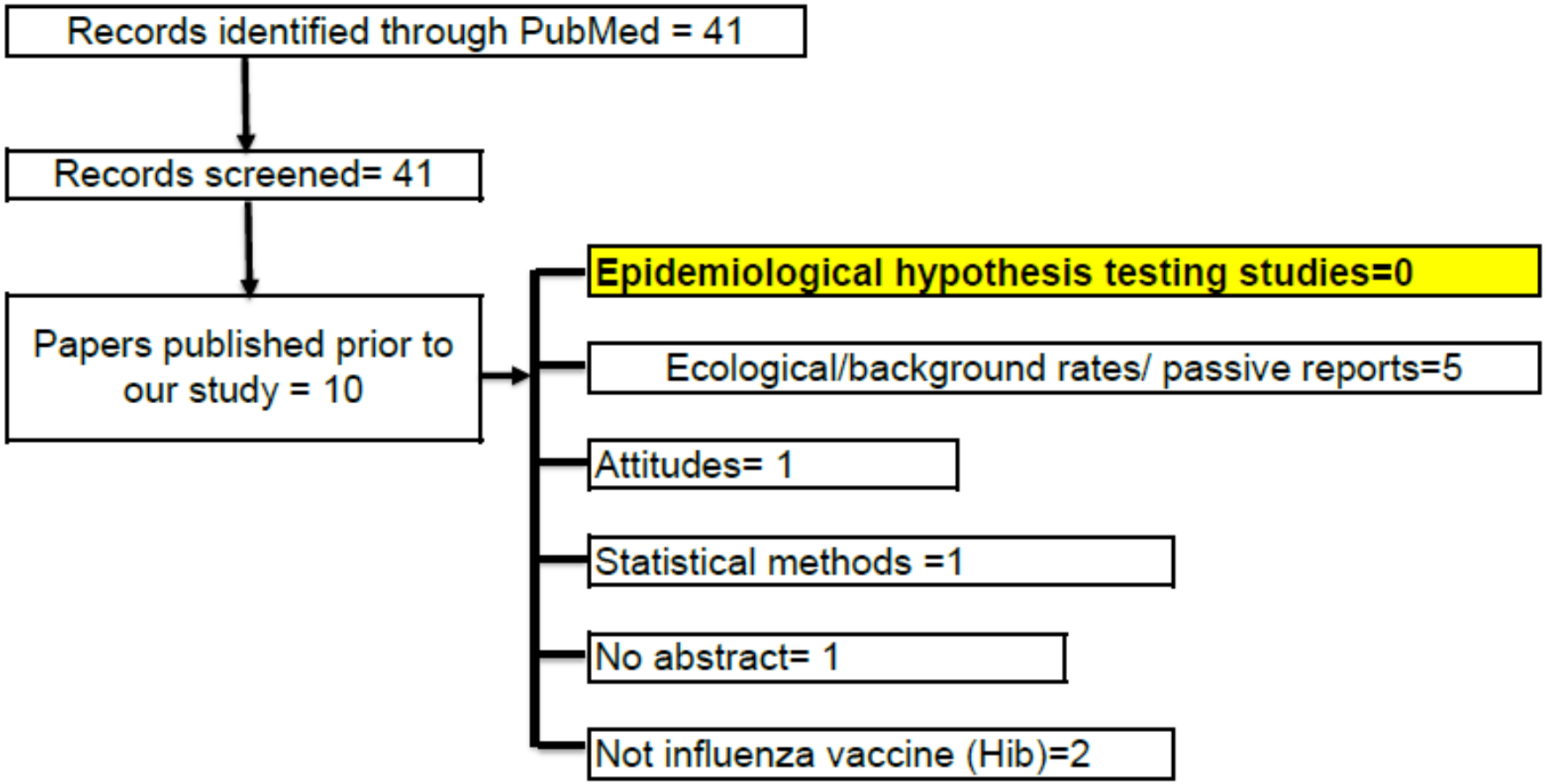
10. Appendix 1- Systematic reviews



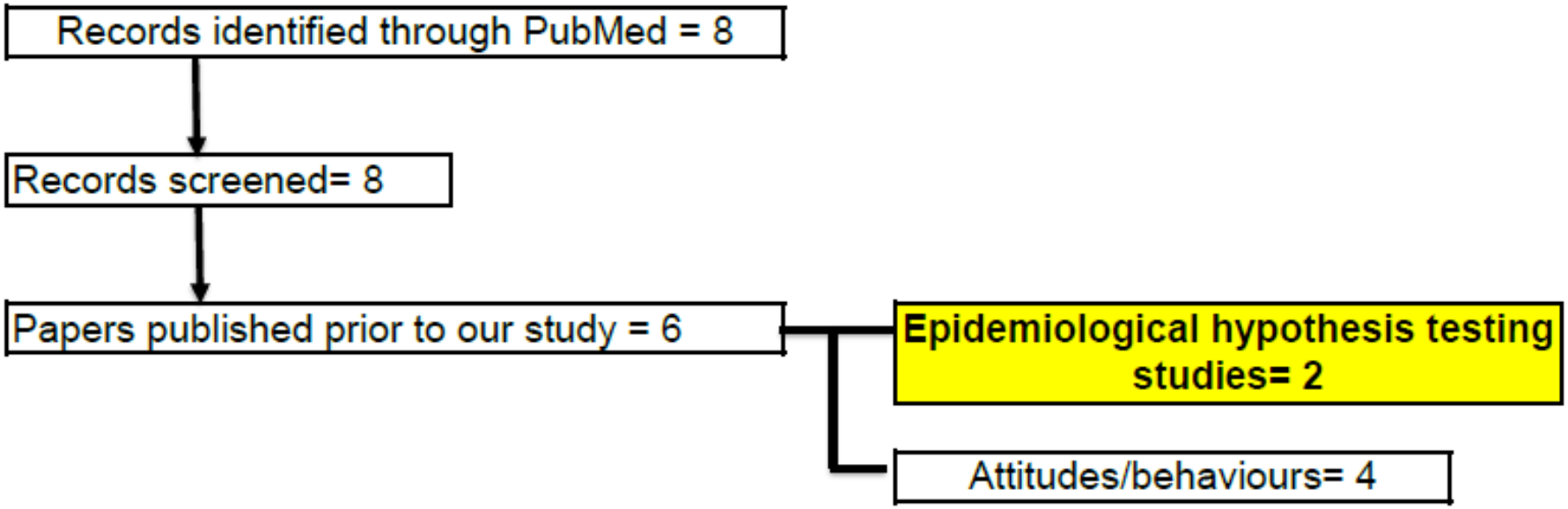
Search terms:narcolepsy, influenza, vaccine, adults



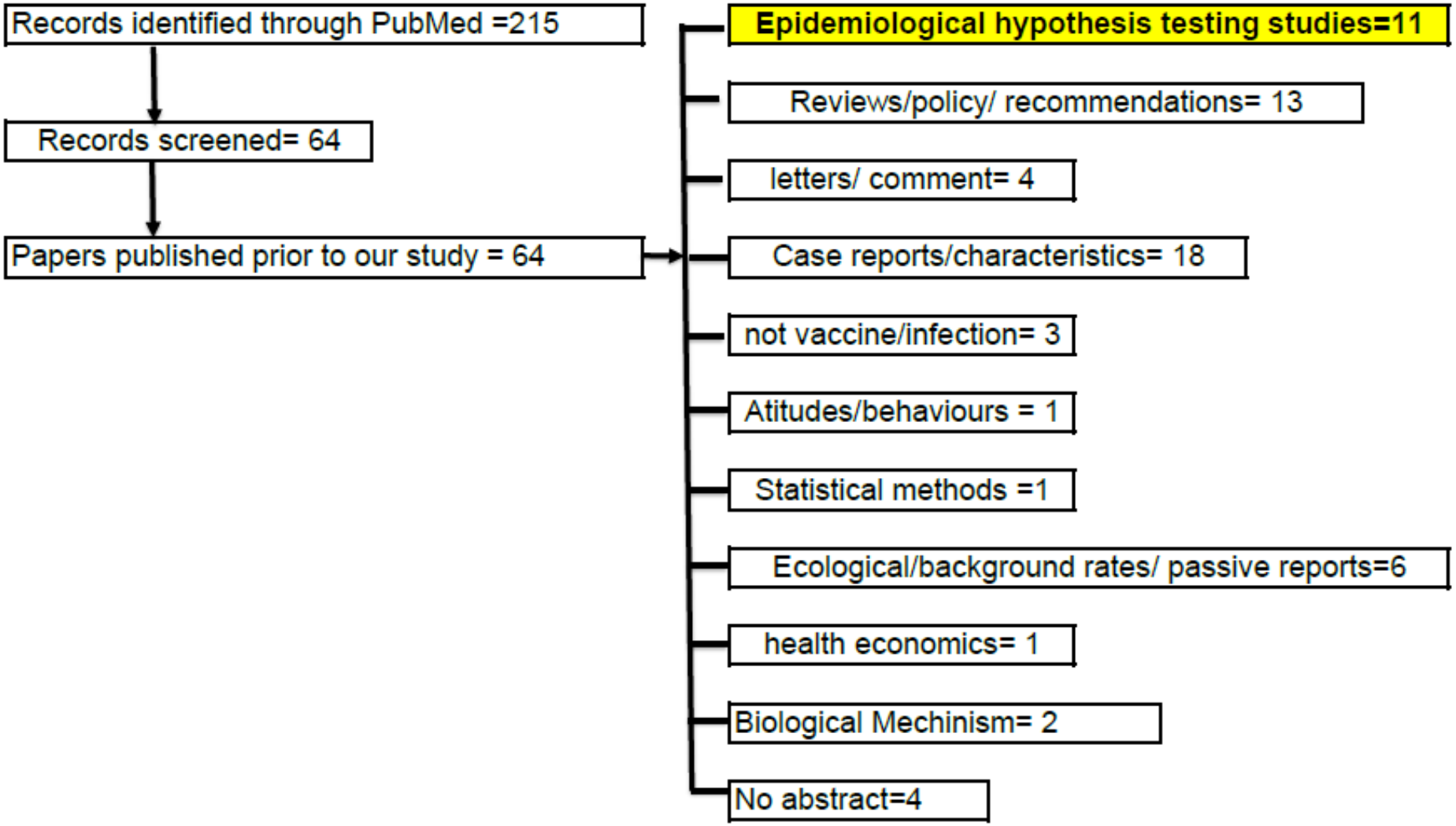
Search terms:safety, influenza vaccination, convulsions



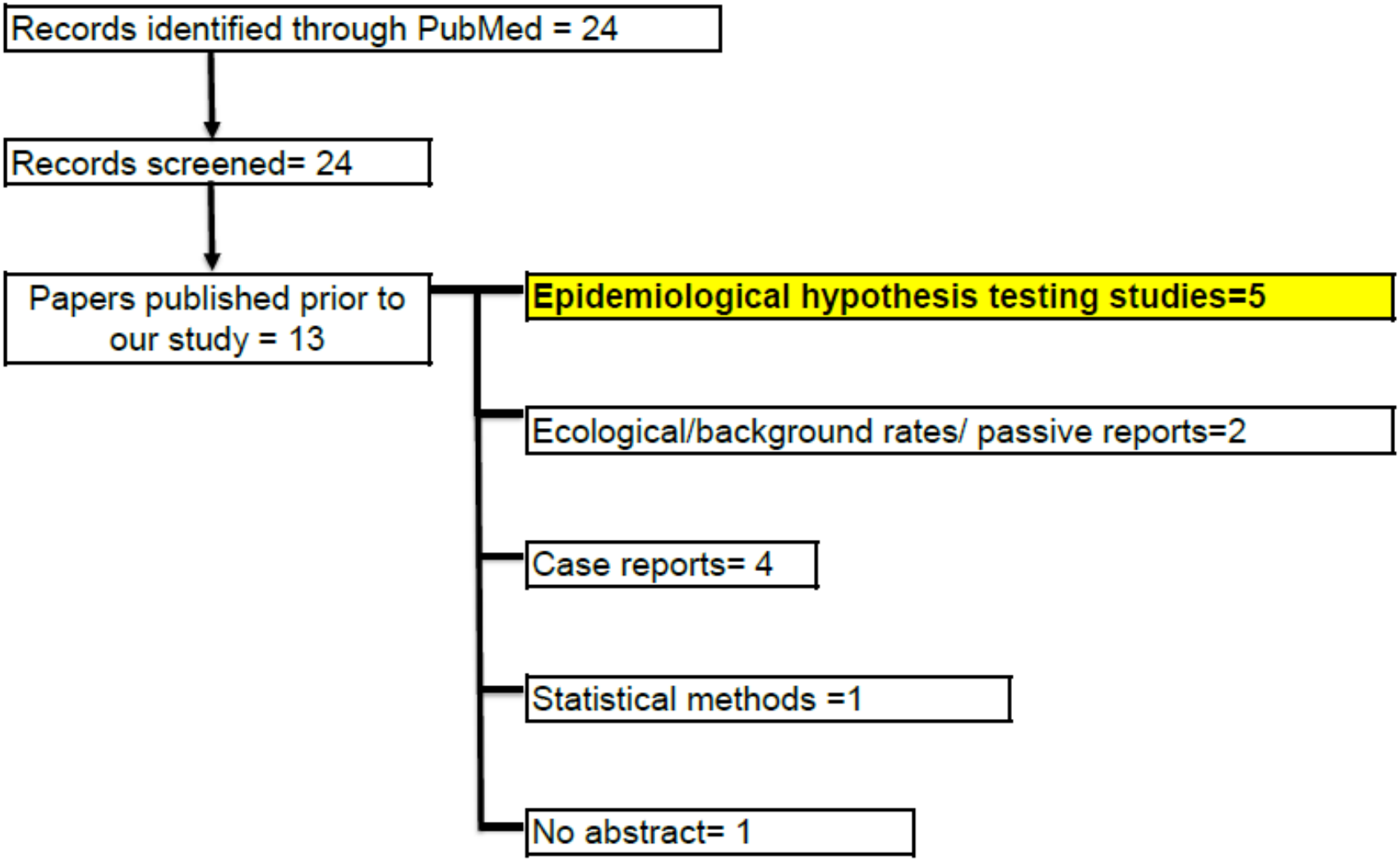
Search terms:immune overload, measles, mumps, rubella



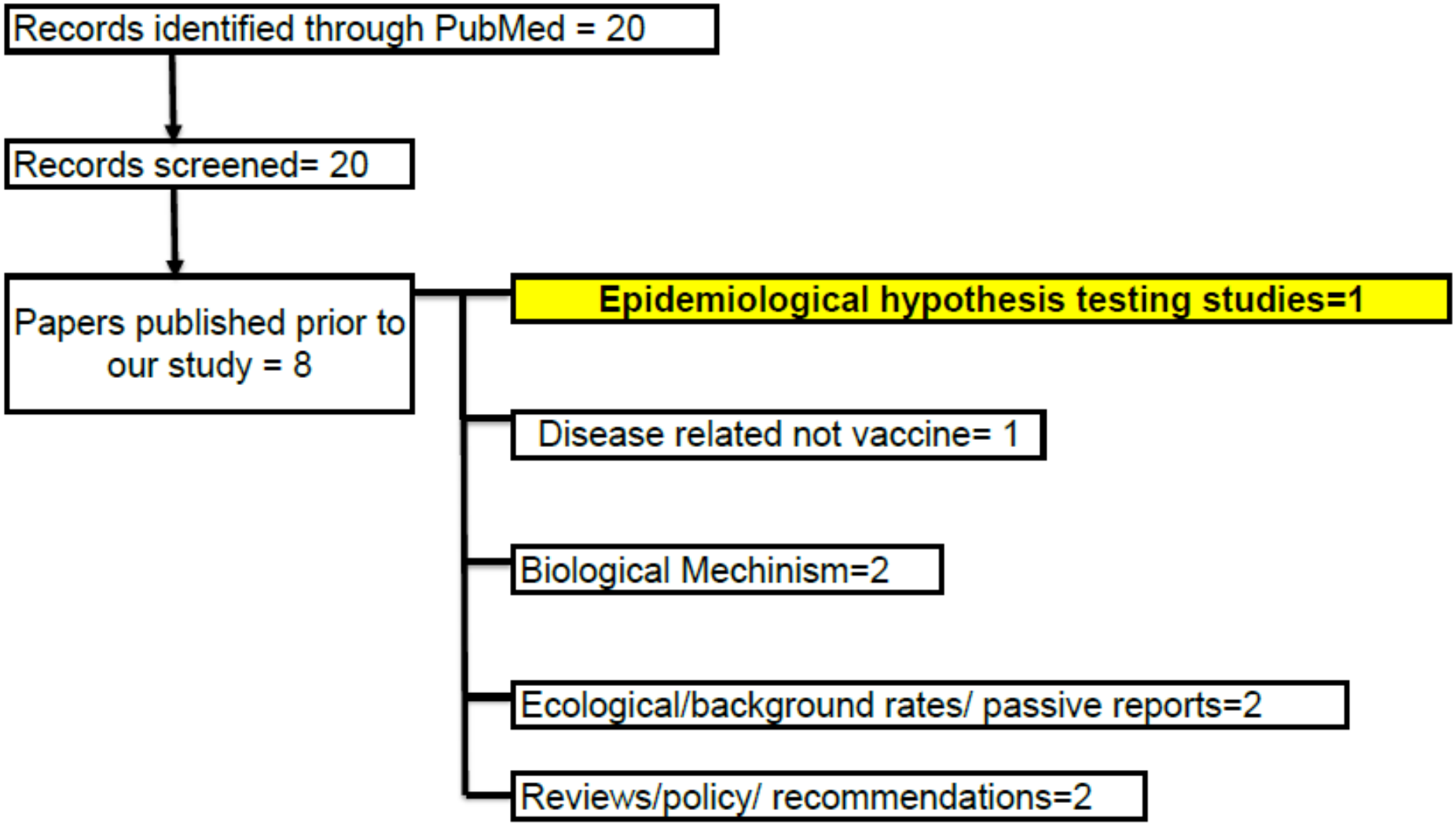
Search terms:Guillain-Barre syndrome, Influenza Vaccination



Search terms: idiopathic thrombocytopenia purpura, measles, mumps, rubella, vaccine



Search terms:Bells palsy, influenza vaccine



Appendix II- Full list of publication in vaccine safety field

1. Stowe J, Andrews N, Ladhani S, Miller E.
   The risk of intussusception following monovalent rotavirus vaccination in England: a self-controlled case-series evaluation. Vaccine. 2016 Jul 12;34(32):3684-9.

2. Stowe J, Miller E, Andrews N, Kosky C, Leschziner G, Shneerson JM, Hall A, Eriksson S, Reading P, Dennis G, Donegan K.
   Risk of Narcolepsy after AS03 Adjuvanted Pandemic A/H1N1 2009 Influenza Vaccine in Adults: A Case-Coverage Study in England. SLEEP 2016 May 1;39(5):1051-7. doi: 10.5665/sleep.5752

3. Winstone AM, Stellitano L, Verity C, Andrews N, Miller E, Stowe J, Shneerson J.
   Clinical features of narcolepsy in children vaccinated with AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine in England. Dev Med Child Neurol. 2014 Jul 10. doi: 10.1111/dmcn.12522

4. Verity C, Stellitano L, Winstone AM, Stowe J, Andrews N, Miller E.
   Pandemic A/H1N1 2009 influenza vaccination, preceding infections and clinical findings in UK children with Guillain-Barre syndrome. Arch Dis Child. 2014 Feb 28. doi: 10.1136/archdischild-2013-304475.

5. Miller E, Andrews N, Stellitano L, Stowe J, Winstone AM, Shneerson J, Verity C.
   Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. BMJ. 2013 Feb 26;346:f794. doi: 10.1136/bmj.f794.

6. Verity C, Stellitano L, Winstone AM, Andrews N, Stowe J, Miller E . Guillain-Barré syndrome and pandemic H1N1 (swine) influenza vaccination in UK children. Correspondence in Lancet. 2011 Oct 29;378(9802):1545-6

7. Stowe J, Andrews N, Bryan P, Seabroke S, Miller E.
   Risk of convulsions in children after monovalent H1N1 (2009) and trivalent influenza vaccines: (a database study). Vaccine. 2011 Nov 28;29(51):9467-72..

8. Andrews N, Stowe J, Al-Shahi Salman R, Miller E.
   Guillain-Barré syndrome and H1N1 (2009) pandemic influenza vaccination using an AS03 adjuvanted vaccine in the United Kingdom: Self-controlled case series. Vaccine. 2011 Oct 19;29(45):7878-82. Epub 2011 Aug 27

9. Andrews N, Stowe J, Miller E, Svanström H, Hviid A.
   A collaborative approach to investigate the risk of idiopathic thrombocytopenic

purpura after measles, mumps, rubella vaccination in England and Demark. Vaccine. 2012 Apr 19;30(19):3042-6. doi: 10.1016/j.vaccine.2011.06.009.

10. Andrews N, Stowe J, Wise L, Miller E.

Post licensure comparison of the safety profile of diphtheria/ tetanus/ whole cell pertussis/ haemophilus influenza type b vaccine and a 5 in 1 diphtheria/ tetanus/ acellular pertussis/ haemophilus influenza type b/ polio vaccine in the United Kingdom. Vaccine. 2010 Oct 18;28(44):7215-20. Epub 2010 Aug 26.

11. Black S, Eskola J, Siegrist CA, Halsey N, Macdonald N, Law B, Miller E, Andrews N, Stowe J, Salmon D, Vannice K, Izurieta HS, Akhtar A, Gold M, Oselka G, Zuber P, Pfeifer D, Vellozzi C. 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. Stowe J , Andrews N, Taylor B, Miller E.

No evidence of an increase of bacterial and viral infections following Measles, Mumps and Rubella vaccine Vaccine. 2009 Feb 25;27(9):1422-5.

13. Stowe J , Andrews N , Wise L, Miller E.

Investigation of the temporal association between Guillain-Barré syndrome and influenza vaccine and influenza-like illness using the UK General Practice Research Database. Am J Epidemiol. 2009 Feb 1;169(3):382-8

14. Stowe J, Kafatos G, Andrews NJ, Miller E.

Idiopathic Thrombocytopenic Purpura and the second dose of MMR. A short report. Arch Dis Child. 2008 Feb;93(2):182-3.

15. Taylor B, Andrews N, Stowe J, Hamidi-Manesh L, Miller E

No increased risk of relapse after meningococcal C conjugate vaccine in nephrotic syndrome Arch Dis Child 2007; 92: 887-889

16. Andrews N, Stowe J, Miller E, Taylor B

Post-Licensure Safety of the Meningococcal Group C Conjugate Vaccine Hum Vaccin. 2007 Mar-Apr;3(2):59-63.PubMed PMID: 17312400.

17. Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B.

Risks of Convulsion and Aseptic Meningitis following Measles-Mumps-Rubella Vaccination in the United Kingdom Am J Epidemiol 2007; 165:704-709

18. Stowe J, Andrews N, Wise L, Miller E.

Bell's Palsy and Parenteral Inactivated Influenza Vaccine
Human Vaccines 2006 Vol:2;3:110-112

19. Miller E, Andrews N, Grant A, Stowe J, Taylor B.

No evidence of an association between MMR vaccine and gait disturbance. Arch Dis Child. 2005 Mar; 90:292-296.

20. Andrews N, Miller E, Grant A, Stowe J, Osbourne V, Taylor B
Thiomersal exposure in infants and developmental disorders: A retrospective cohort study in the United Kingdom does not support a causal association. Pediatrics 2004;114;584-591

21. Lingam R, Simmons A, Andrews N, Miller E, Stowe J, Taylor B
Prevalence of autism and parentally reported triggers in a North East London population. Arch Dis Child 2003;88:666-670

22. Andrews N, Miller E, Taylor B, Lingam R, , Simmons A, Stowe J. Waight P. Recall bias, MMR and Autism. Arch Dis Child. 2002;87:493-494

23. Taylor B, Lingam R, Simmons A, Stowe J, Miller E, Andrews N. Autism and MMR vaccination in North London; no causal relationship. Mol Psychiatry. 2002;7 Suppl 2:S7-8.

24. Andrews N, Miller E, Waight P, Farrington P, Crowcroft N, Stowe J, Taylor B. Does oral polio vaccine cause intussusception in infants? Evidence from a sequence of three self-controlled cases series studies in the United Kingdom. Eur J Epidemiol. 2002;17(8):701-6.

25. Taylor B, Miller E, Lingam R, Andrews N, Simmons A, Stowe J.
Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study.
BMJ. 2002 Feb 16;324(7334):393-6.

26. Miller E, Waight P, Farrington CP, Andrews N, Stowe J, Taylor B.
Idiopathic thrombocytopenic purpura and MMR vaccine.
Arch Dis Child. 2001 Mar;84(3):227-9.PubMed PMID: 11207170; PubMed Central PMCID: PMC1718684.

Book Chapter

E. Miller and J. Stowe.
Chapter 14: Vaccine Safety
Stephens' Detection and Evaluation of Adverse Drug Reactions Sixth Edition.
Editors Talbot Waller.
Wiley-Blackwell; 6th Edition (9 Dec 2011) ISBN-13**:** 978-0470986349