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Use of the Australian Childhood Immunisation Register for vaccine safety data linkage

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ABSTRACT

We linked the Australian Childhood Immunisation Register (ACIR) to South Australian (SA) hospital outcome data in order to evaluate the association between Measles Mumps and Rubella (MMR) and Diphtheria Tetanus Pertussis (DTP) vaccines and convulsions. Linkage occurred using probabilistic matching and data was analysed using the self-controlled case series methodology. An increase in febrile convulsions 6–11 days post-MMR vaccination was demonstrated which equates to a vaccine-attributable risk of 1 convulsion per 6753 vaccines. This study confirms the known association between MMR vaccination and febrile convulsions and in doing so demonstrates the feasibility of using the ACIR for data linkage and vaccine safety surveillance.

1. Introduction

Despite the public health benefit of vaccination concern about the safety of vaccines may be the most important issue to affect immunisation coverage and the sustainability of an immunisation program [1]. There are a number of examples of how vaccine safety concerns, both in developed and developing countries, has affected vaccine coverage and resulted in a resurgence of vaccine preventable disease [2].

There is a limited capacity to evaluate all aspects of vaccine safety during pre-licensure clinical trials. This is because the safety evaluation of new vaccines takes place during clinical trials which usually include a limited number of healthy subjects and involves a short period of post-vaccination monitoring. This process does not identify adverse reactions which are rare, delayed, occur with specific vaccine combinations or in a sub-group of vaccinee's with co-morbid disorders [3,4]. Passive surveillance of adverse events following immunisation (AEFI) is used as the primary mechanism for safety surveillance following vaccine licensure. Passive surveillance also has limitations which include the underreporting of AEFI's and the inability to establish a causal relationship between immunisation and a specific adverse event.

Since the early 1990s data linkage has been used increasingly to assess vaccine safety. The most consistent application of this method occurs within the health maintenance organisations in the United States of America and is known as the Vaccine Safety Datalink (VSD) project [5]. VSD has been used successfully to examine a number of safety signals generated by passive surveillance such as vaccination with the rhesus re-assortment rotaviral vaccine (Rotashield®) and infantile intussusception [6–8]. Vaccine data linkage has also been used intermittently in the United Kingdom, Scandinavia and Vietnam [9–11]. Few countries use data linkage in an ongoing way to asses vaccine safety; however, it is increasingly being recognised that a global data linkage network needs to be established in order to develop the capacity to evaluate very rare safety signals. Developing the technical capacity in individual countries is essential if this goal of a global network is to be reached [12].

Data linkage for vaccine safety assessment has not been undertaken in Australia. Since 1996 all childhood immunisation records have been recorded on the Australian Childhood Immunisation Register (ACIR). The aim of this study was to assess the feasibility of using data linkage as a means of vaccine safety surveillance by linking immunisation records from the ACIR to hospital outcome data.

2. Methods

The study was performed in South Australia (SA), one of the eight states and territories of Australia, with a population of 1.6

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Table 1
Australian Standard Vaccine Schedule for children 12 months of age or less from November 1996 until September 2003 (note change in Schedule May 2000).

Age	Diseases	Vaccine combinations November 1996 to May 2000			Vaccine combinations June 2000 to September 2003		
Birth	Hepatitis B				Hepatitis B		
2 months	Diphtheria, Tetanus and Pertussis Poliomyelitis *Haemophilus Influenzae* type B Hepatitis B	DTPw or DTPa[a]	OPV (Sabin)	Hib (HbOC)[b]	DTPa-HepB	OPV (Sabin)	Hib (PRP-OMP)[c]
4 months	Diphtheria, Tetanus and Pertussis Poliomyelitis *Haemophilus Influenzae* type B Hepatitis B	DTPw or DTPa	OPV (Sabin)	Hib (HbOC)	DTPa-HepB	OPV (Sabin)	Hib (PRP-OMP)
6 months	Diphtheria, Tetanus and Pertussis Poliomyelitis *Haemophilus Influenzae* type B Hepatitis B	DTPw or DTPa	OPV (Sabin)	Hib (HbOC)	DTPa-HepB	OPV (Sabin)	
12 months	Measles Mumps Rubella *Haemophilus Influenzae* type B	MMR			MMR	Hib (PRP-OMP)	

[a] DTPa replaced DTPw in August 1998.
[b] HbOC – *Haemophilus Influenzae* type B vaccine antigen conjugated to Diphtheria CRM 197 protein.
[c] PRP-OMP – *Haemophilus Influenzae* type B vaccine antigen conjugated to meningococcal outer membrane protein.

million and a birth cohort of approximately 20,000 per year. Immunisation and health outcome data for children less than 7 years of age and between 1997 and 2002 was analysed. Between March 1999 and September 2000 the percentage of children who were fully immunised at 12 months of age (three doses of Diptheria Tetanus Pertussis (DTP), oral polio and *Haemophilus Influenzea type B* (HiB) vaccines) increased from 87% to 92% [13]. The Australian Standard Vaccine Schedule was changed during the study period as detailed in Table 1. Three DTP-containing vaccines were used during the study period and this included a whole cell DTP vaccine (Triple Antigen® Commonwealth Serum Laboratories, Melbourne), an acellular DTP vaccine (Infanrix® Glaxosmithkline) and a combination acellular DTPa-Hepatitis B vaccine (Infanrix-Hep B® Glaxosmithkline). The MMR vaccine (Priorix® – Glaxosmithkline) contained the attenuated measles virus (Schwarz strain), RIT 4385 strain of mumps virus (derived from the Jeryl Lynn strain) and the Wistar RA 27/3 rubella virus strain.

2.1. Data sets used in linkage analysis

Immunisation, hospital admission and Accident and Emergency (AE) attendance data was obtained for SA children, less than 7 years of age, from 1997 to 2002.

Immunisation data was obtained from the ACIR. The ACIR was established in 1996 as a national and central database to record all immunisations administered to children under 7 years. Approximately 98% of all newborns are registered on the database within 12 months [14]. Vaccine providers are funded to provide the register with vaccination details (name of child, date of birth, date of vaccination and vaccine antigens administered). Although the primary purpose of the ACIR is administrative, the register does provide an opportune source of data for linkage.

Health outcome data was obtained from the two major paediatric hospitals in SA – the Women's and Children's Hospital (WCH) and Flinders Medical Centre (FMC). Collectively these hospitals attract the majority of paediatric admissions and AE attendances. The data were derived from two sources; the Open Architecture Clinical Information System Clinical Reporting Repository (OACIS CRR), which contains hospital admissions data from WCH and FMC and AE department data from FMC, and the WCH AE Department database (WCH HAS-ED), which contains AE department data from WCH from 1998 to 2002.

2.2. Ascertainment of health outcome data

Convulsions and febrile convulsions were ascertained from the ICD-9 (780.3) and ICD-10 (R56.0 and R56.8) codes and idiopathic thrombocytopenia purpura (ITP) was ascertained from the ICD-9 (287.3) and ICD-10 (D69.3) codes in the primary diagnosis fields of the hospital admission records. Where primary diagnosis codes were missing for AE presentations, the complaint code was used. When neither of these was available an assessment of the descriptive text was undertaken and these records were then assigned as either cases or non-cases.

2.3. Linkage methods

The data linkage methodology closely followed that described by Kellman et al. [15]. The ACIR dataset was considered the primary data source since it contained the largest number of individuals. The demographic information on these patients (family name, first name, middle name, gender, date of birth and address) were matched with those on the other three datasets, WCH HAS-ED, OACIS and AEFI, using Linkage Wiz® probabilistic matching software.

Each variable was assigned a weight based on the level of agreement required to consider the records an acceptable match. The software then calculated an overall score for each match based on the weighted variables; any records scoring below the upper cut-off level (true matches) and above the lower cut-off level (true non-matches) were reviewed manually. In order to maintain the integrity of data privacy linkage was separated from data analysis. Hence, once all matched records were verified, a file listing only the unique identifiers of the matched records was created and sent to the data analysts.

A prospective log of data matches was kept and once the final linkage had occurred, the linkage process was replicated and the original log was compared with these results to ensure consistency.

2.4. Study hypotheses

The hypotheses tested were that there was no increase in the incidence of admissions to hospital and/or attendances at AE departments for convulsions within −1 to −14, 6–11 or 15–35 days of a Measles, Mumps and Rubella (MMR) vaccine or within −1 to −14, 0–3, 4–7 or 8–14 days of children receiving a DTP-containing vaccine or for ITP within 15–35 days of a MMR vaccine.

2.5. Statistical analysis

The relative incidence of events occurring recently before and after either MMR or DTP vaccination was estimated using the Self Controlled Case Series (SCCS) method [16]. Only individuals who were admitted to one of the chosen hospitals with convulsions and within one of the time periods of interest were included in the analysis. In this method, each individual is regarded as a fixed effect and only within-subject effects, i.e. the exposure periods of interest relative to the date of vaccination, and age (split into 3-month periods) were estimated. Incidence rate ratios (IRR) for the exposure periods and age groups were therefore obtained using a within-subjects Poisson regression model which accounts for the non-independent nature of multiple events that may occur for each individual. The partitioning of each individual's period of follow-up depended on the number of vaccinations received and their age at each vaccination. For MMR vaccinations only the first vaccination (which usually occurs between 1 and 2 years of age) was considered. For DTP vaccinations, the relevant exposure periods were defined according to all DTP vaccinations that occurred between 28 days and 1 year of age. This therefore included up to three DTP vaccinations for each individual. For each type of event a 2-week period prior to exposure was included in the partitioning of the follow-up time, since events during this period are likely to be reduced compared to other non-exposed periods, as scheduled vaccinations are often delayed immediately following such events. The remaining exposure periods or interest were defined according to risk periods identified from previous [16]. All analysis was performed using Stata version 9.2 (StataCorp, Texas).

2.6. Ethics approval, privacy and confidentiality

Approval was obtained from the SA Department of Health Human Research Ethics Committee (HREC), FMC HREC, WCH HREC, and the Commonwealth Department of Health and Ageing HREC. A delegate of the Commonwealth Department of Health and Ageing provided authorisation for disclosure of identified data from the ACIR. Lawful disclosure of the ACIR information, for research purposes, is allowed (under the Guidelines of the Privacy Act, Section 95) if public interest outweighs the privacy implications and a HREC approves the research proposal. The project adhered to the SA Department of Health Code of Fair information Practice and state acts governing the disclosure of information (Section 64 of the SA Health Commission Act 1976). Standardised protocols were used to ensure data privacy and confidentiality which included use of a stand alone computer, separate personnel who performed data linkage and analysis, confidentiality agreements and destruction of data at the completion of the study.

3. Results

3.1. Total number of individuals and vaccinations

A total of 195,544 children less than 7 years of age were included on ACIR, some individuals having up to 9 total vaccination dates between 1 January 1997 and 31 December 2002 for DTP-containing and MMR vaccines. There were a total of 185,495 MMR and 510,518 DTP-containing vaccinations administered.

3.2. Hospital and AE department data and coding

A total of 77,962 individuals were admitted to one or more of the hospitals of interest amongst the 195,544 individuals on ACIR included in the final analysis. Their total number of hospital admissions was 174,136. Amongst the 174,136 hospital admissions, there were 35,590 admissions (20.4%) without any ICD-codes or Complaint Codes (WCH AE admissions). Adverse events were carefully identified from the admission description text field using broad criteria for inclusion. This identified a further 188 febrile convulsions (20.3% of the total of 924) which were included in the MMR and multiple febrile convulsions analysis. Since this identified a very similar proportion of adverse events compared to the proportion of missing texts in the complete database, it is unlikely that we either underestimated or overestimated the number of true adverse events.

Table 2
Hospitalisation for convulsions post-MMR and DTP vaccination and following defined exposure periods (Self Controlled Case Series method, first events only).

Exposure period	IRR	SE (β)	p-Value	95% CI
MMR vaccine				
Baseline exposure	1.00			
−1 to −14 days	0.58	0.17	0.06	0.33–1.02
6 to 11 days	2.11	0.42	<0.001	1.43–3.10
15 to 35 days	0.90	0.15	0.54	0.65–1.25
DTP vaccine				
Baseline exposure	1.00			
−1 to −14 days	0.56	0.15	0.03	0.33–0.94
0 to 3 days	0.59	0.27	0.25	0.24–1.45
4 to 7 days	0.94	0.34	0.86	0.46–1.91
8 to 14 days	0.93	0.26	0.80	0.54–1.62

IRR: incidence rate ratio; SE: standard error; CI: confidence interval.

3.3. Quality of the linkage

The ACIR was regarded as the primary data set and this could be linked to 92.4% of the WCH (HAS-ED) records and 86.5% of the OACIS records.

3.4. Risk of convulsions with MMR vaccination

A total of 122,435 subjects received MMR vaccinations between the age of one and two years. There were 924 events that occurred amongst 789 subjects which included a total follow-up period of 759.3 person years. The results of the SCCS analysis are detailed in Table 2. There was a confirmed increased incidence rate of febrile convulsions 6–11 days post-MMR vaccination (IRR = 2.1, 95% CI = 1.43, 3.10; $p < 0.001$) and a confirmed decrease in the incidence of febrile convulsions in the 2-week period prior to vaccination (IRR = 0.58, 95% CI = 0.33, 1.02; $p = 0.048$). This equated to a post-MMR vaccine-attributable risk of convulsions of one per 6753 MMR vaccinations.

3.5. Risk of convulsions with DTP vaccination

A total of 125,560 subjects received DTP vaccinations between the age of 28 days and one year. There were 374 events that occurred amongst 323 subjects which included a total follow-up period of 293.2 person years. The results of the SCCS analysis are detailed in Table 2. Although there was a slight (but non-significant) reduction in events in the 2 weeks prior to vaccination (IRR = 0.56, 95% CI = 0.33, 0.94; $p = 0.03$), there was no increase in the incidence of febrile convulsions in the three exposure periods of interest. The risk of febrile convulsions was higher in the 9–12 month age group compared to the 1–3-month age group after adjusting for the effects of exposure to DTP vaccination (IRR = 2.4, 95% CI = 1.72, 3.35; $p < 0.001$).

3.6. Risk of ITP with MMR vaccine

Only one ITP event was identified within the 15–35-day risk period post-MMR vaccination. No further statistical analysis could be performed.

4. Discussions

This is the first study in Australia to examine the risk of convulsions following MMR and DTP vaccination using data linkage and the ACIR. The study was performed using data obtained from all SA children registered for immunisations over a 6-year period between 1997 and 2002. Although this cohort was relatively small (comprising 195,455 individuals) linkage was able to establish vaccine-attributable risks for adverse events with a prevalence of between approximately 1 in 1150 and 1 in 3000 [16,17]. This study confirmed the previously identified increased risk of febrile convulsion in the 6–11-day period following MMR vaccination, and a decrease in the risk of febrile convulsions in the 2-week period prior to MMR vaccination. The vaccine-attributable risk was lower (1 in 6753 vaccines) in our study compared with that of Farington and Barlow et al. (approximately 1 in 3000 vaccines) [16,17]. However, population based cohort studies show that the rate of convulsions within 2 weeks of a MMR vaccine, administered between 15 and 17 months of age, may be as high as 1.56 per 1000 children (95% CI, 1.44–1.68) [18]. No increase in convulsions were demonstrated between 15 and 35 days post-vaccination which is consistent with the experience of MMR vaccines which do not contain the Urabe strain of the attenuated mumps virus [19].

No increase in the vaccine-attributable risk of febrile convulsions post-DTP vaccination was demonstrated. Previous studies in the UK and the USA have found an increase in the vaccine-attributable risk of convulsions after the whole cell DTP vaccine [16,17]. The absence of risk after the DTP vaccine in SA is likely to reflect the introduction of the less reactogenic DTPa vaccine, which occurred in 1997, and the lower frequency of febrile convulsions occurring in the age group that receives this vaccine in South Australia (recommended at 2, 4 and 6 months of age).

This study was unable to detect a vaccine-attributable risk between MMR vaccination and ITP which has a risk of 1 event in 24,000 vaccinations [9]. This illustrates that for very rare events larger data sets are required and that for a country such as Australia (population 21 million) this can only be achieved through linkage of the ACIR to national health outcome data. This is likely to be challenging because Australia is a federation of states and territories that have different state based systems of electronic data collection and provisions which govern data privacy and access. These challenges may be similar in other countries and will be faced by any network wishing to establish data linkage within a global context. The development of strategies to maintain data privacy yet ensure the timely provision and analysis of data is required. Further research to understand community concern regarding use of data for linkage and measures to address these concerns are also clearly required.

A number of novel vaccines are being developed and some, such as the human papilloma virus vaccine and the H1N1 influenza A vaccine, have recently been introduced. It is predictable that a number of rare adverse events will be reported passively and that a rapid mechanism will be required to assess these events for a causal association. The ability of data linkage to be used for such an evaluation of a safety signal has already been established as part of the VSD project [20]. However, data linkage in the USA only includes the population enrolled in a number of Health Maintenance Organisations and this limits which vaccines can be evaluated. The attempt to assess the safety of pandemic influenza vaccines is informative because of the use of different vaccine formulations in different jurisdictions (adjuvanted vs. non-adjuvanted and cell vs. egg yolk culture based vaccines). This underlies the importance of developing local and regional systems for vaccine safety assessment which can contribute to a global safety network.

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References

[1] Chen R, Hibbs B. Vaccine safety: current and future challenges. Pediatr Ann 1998;27(7):445–55.
[2] Gangarosa E, Galazka A, Wolfe C, Phillips LM, Gangarosa RE, Miller E, et al. Impact of anti-vaccine movements on pertussis control: the untold story. Lancet 1998;351:356–61.
[3] Chen R. Commentary. Vaccine adverse events: causal or coincidental? Lancet 1998;351(9103):611.
[4] Jacobson R, Adegbenro A, Pankratz V, Poland GA. Adverse events and vaccination – the lack of power and predictability of infrequent events in pre-licensure study. Vaccine 2001;19:2428–33.
[5] Chen R, Glasser J, Rhodes P, Davis RL, Barlow WE, Thompson RS, et al. Vaccine Safety Datalink Project: a new tool for improving vaccine safety monitoring in the United States. Pediatrics 1997;99(6):765–73.
[6] Murphy T, Gargiullo P, Massuodi M, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusseption among infants given oral rotavirus vaccine. N Engl J Med 2001;344:564–72.
[7] Eriksen E, Perlman J, Miller A, Marcy SM, Lee H, Vadheim C, et al. Lack of association between hepatitis B birth immunization and neonatal death: a Population-Based Study from the Vaccine Safety Datalink Project. Pediatr Infect Dis J 2004;23(7):656–62.
[8] DeStefano F, Gu D, Kramarz P, Truman B, Lademarco MF, Mullooly JP, et al. Childhood vaccinations and risk of asthma. Pediatr Infect Dis J 2002;21:498–504.
[9] Miller E, Waight P, Farrington P, Andrews NJ. Idiopathic thrombocytopenia purpura and MMR vaccine. Arch Dis Child 2001;84:227–9.
[10] Mäkelä A, Nuorti JP, Peltola H. Neurologic disorders after measles–mumps–rubella vaccination. Pediatrics 2002;110(5):957–63.
[11] Ali M, Canh DG, Clemens JD, Park JK, von Seidlein L, Thiem VD, et al. The vaccines data link in Nha Trang, Vietnam: a progress report on the implementation of a database to detect adverse events related to vaccinations. Vaccine 2003;21:1681–6.
[12] Black S. Global Vaccine Safety DataNet meeting. Expert Rev Vacc 2008 Feb;7(1):15–20.
[13] O'Brien ED, Sam GA, Mead C. Methodology for measuring Australia's childhood immunisation coverage. Commun Dis Intell 1998;22:36–7.
[14] Lawrence G, Aratchige P, Boyd I, McIntyre P, Gold M. Annual report on surveillance of adverse events following immunisation in Australia 2006. Commun Dis Intell 2007;31:269–83.
[15] Kelman C, Bass A, Holman CD. Research use of linked health data – a best practice model. ANZJP 2002;26(3):222–51.
[16] Farrington P, Pugh S, Colville A, Flower A, Nash J, Morgan-Capner P, et al. A new method for active surveillance of diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. Lancet 1995;345:567–9.
[17] 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(August(9)):656–61.
[18] 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. J Am Med Assoc 2004;292(July(3)):351–7.
[19] Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Convulsion comparison: risks of convulsion and aseptic meningitis following measles–mumps–rubella vaccination in the United Kingdom. Am J Epidemiol 2007;165(March(6)):704–9 [Epub January 2007].
[20] Iskander J, Haber P, Herrera G. Monitoring vaccine safety during an influenza pandemic. Yale J Biol Med 2005;78(October(5)):265–75.