Vaccine 29 (2011) 3746–3752

Contents lists available at ScienceDirect

Vaccine

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

Patterns of emergency room visits, admissions and death following recommended pediatric vaccinations—A population based study of 969,519 vaccination events☆

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ARTICLE INFO

Article history:
Received 17 December 2010
Received in revised form 15 February 2011
Accepted 11 March 2011
Available online 8 April 2011

Keywords:
Immunization
Surveillance
Patient safety
Pediatric
Health services research

ABSTRACT

Background: The risk of immediate adverse events due to the inflammation created by a vaccine is a potential concern for pediatric vaccine programs.
Methods: We analyzed data on children born between March 2006 and March 2009 in the province of Ontario. Using the self-controlled case series design, we examined the risk of the combined endpoint of emergency room visit and hospital admission in the immediate 3 days post vaccination to a control period 9–18 days after vaccination. We examined the end points of emergency room visits, hospital admissions and death separately as secondary outcomes.
Results: We examined 969,519 separate vaccination events. The relative incidence of our combined end point was 0.85 (0.80–0.90) for vaccination at age 2 months, 0.74 (0.69–0.79) at age 4 months and 0.68 (0.63–0.72) at age 6 months. The relative incidence was reduced for the individual endpoints of emergency room visits, admissions and death. There were 5 or fewer deaths in the risk interval of all 969,519 vaccination events. In a post hoc analysis we observed a large reduction in events in the immediate 3 days prior to vaccination suggesting a large healthy vaccinee effect.
Conclusion: There was no increased incidence of the combined end point of emergency room visits and hospitalizations in the 3-day period immediately following vaccination, nor for individual endpoints or death. The health vaccinee effect could create the perception of worsening health following vaccines in the absence of any vaccine adverse effect and could also mask an effect in the immediate post-vaccination period.

The standards for pediatric vaccine safety are higher than for other pharmaceuticals for several reasons. A high percentage of the population is exposed to many pediatric vaccines, which are also typically administered to healthy individuals. While phase 3 vaccine clinical trials can rule out adverse event rates of 1:10,000 or greater, events occurring at lower rates can have important population level consequences [1]. Therefore, ensuring vaccine safety on an ongoing basis through effective post-market surveillance is a key priority of any mass pediatric immunization program.

There have been many widely discredited theories of vaccine adverse events and the association of vaccines with specific diseases. One aspect of vaccine safety that has been considered credible is the possibility of adverse events resulting from the immune response and the ensuing inflammation created by a vaccine [2]. These concerns were highlighted in relation

Abbreviations: ER, Emergency room; CIHI, Canadian Institute for Health Information; DAD, Discharge abstract database; NACRS, National ambulatory care reporting system.

☆ The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred.

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doi:10.1016/j.vaccine.2011.03.044

to the whole cell pertussis vaccine and its high rate of febrile reactions—ultimately leading to the replacement of the vaccine with a safer acellular form [3,4]. In more severe cases, these inflammation based adverse events could potentially lead to emergency room presentations or hospital admissions.

In the province of Ontario, Canada, standard 2-, 4- and 6-month vaccines consist of diphtheria, pertussis, tetanus, polio, haemophilus influenzae type b (Hib) and pneumococcus. The objective of our study is to examine patterns of emergency department visits, admission to hospital, or death following vaccination and, in particular, in the immediate post-vaccination period. Using the self-controlled case series design and administrative databases in the province of Ontario, we examine for temporal clustering of these events in specified time periods following routine childhood immunizations [5,6,7].

1. Methods

1.1. Design

The overall goal of this study was to examine patterns of emergency room (ER) visits, hospital admissions and death in all children vaccinated in Ontario at 2, 4 and 6 months of age with standard pediatric vaccines and to determine if events clustered in the immediate post-vaccination period. This was measured by identifying the risk of these events in the immediate 3-day post-vaccination period compared to a later control period. This analysis was conducted on a 3-year cohort of children from the years 2006 to 2009. Previous analyses have examined the risk of specific adverse events following this vaccine. We sought to determine if the inflammation based adverse events would result in a general increase in health service utilization which may not have been identified in the previous studies.

Our primary analysis of the composite risk of ER visits or hospitalizations was conducted using the self-controlled case-series design, described by Farrington and associates [6,7]. A fundamental premise in our study was that an ER visit, hospital admission, or death attributable to the inflammation from the vaccine would occur immediately after an exposure and should be identifiable within 3 days. This is supported by the physiological effects of non-live vaccines and is distinct from live vaccines which can cause reactions 1–2 weeks removed from the date of vaccination. We analyzed events following the 2-, 4- and 6-month vaccinations separately. Ethics approval was obtained from the Ottawa Hospital Research Institute's research ethics board.

1.2. Data

This study was completed as a component of the Vaccine and Immunization Surveillance in Ontario (VISION) system. The study included all children in the Newborn Screening Ontario data set between March 2006 and March 2009 and who had at least 12 months of outcome data. The Newborn Screening Ontario data set contains information on all children screened for a group of mainly metabolic disorders in the province of Ontario. Since uptake of the screening program is near 100%, this data set includes virtually every birth in the province. Our exposure of interest, pediatric vaccination, was identified using the Ontario Health Insurance Plan database. We used codes for general vaccination in the first year of life. To identify the 2-, 4- and 6-month vaccinations separately, we identified vaccination occurring on exactly the scheduled dates (62, 124 and 186 days, respectively—scheduling systems tended to work with 31-day months) as well as any vaccinations within 30 days before and 30 days after the scheduled date. The decision about the window to include was based on examination of the frequency distribution of the timing of vaccinations, as well as clinical expertise.

The Canadian Institute for Health Information's (CIHI) Discharge Abstract Database (DAD) was used to ascertain hospital admission and discharge date. The DAD captures all hospital admissions, including children in both tertiary and community hospitals. CIHI's National Ambulatory Care Reporting System (NACRS) was used to ascertain emergency department visits. All emergency departments in Ontario participate in NACRS. The Registered Persons Database was used to ascertain death.

All datasets needed for this study were housed at the Institute for Clinical Evaluative Sciences (ICES), where the data were individually linked and accessed. Linkage was to the Ontario Registered Persons Database, a patient registry that includes Ontario residents with provincially funded health care insurance (Ontario Health Insurance Program)—virtually all Ontario residents. Within the ICES secure computing environment, patient level data can be linked across multiple ICES databases for analysis using the encrypted individual identifier (known as the ICES Key Number or IKN).

1.3. Analysis

In the self-controlled case series model, the date of vaccination served as the index date for exposure for each patient. For analytical purposes, we divided each individual follow-up period into 2 distinct intervals after the vaccination date: an initial 3-day interval classified as exposed, followed by days 9–18 classified as unexposed with a washout period in between the exposed and unexposed periods (Fig. 1). Our choice of the control period was based on the fact that it would be highly unlikely that acute inflammation from the vaccine would result in health service increases this far removed from the date of vaccination. Further we did not want to choose a control period so far removed from the vaccination that it could be influenced by the subsequent vaccination event. The relative incidence rate of the composite end point of ER visit or hospitalization during the exposed period compared with the unexposed period was analyzed using a fixed effects Poisson regression model that included a term for exposure period and a term for patient, allowing each individual to serve as his or her own control, while accounting for intra-individual correlation. An offset term was also included in the model to account for the differing durations of the exposed and unexposed periods. To address the correlation of multiple events close together in time (e.g. an ER visit leading to an admission, or serial ER visits), the occurrence of events were classified as "one or more events" or "no events" in each of the risk and control periods. For example, if a subject had one event or multiple events in a risk or control period, they would be coded as event = 1, and if they had no events they would be coded as event = 0.

A 3-day period was selected as the risk interval based on the understanding that inflammation and anorexia would result in immediate illness [8]. Where multiple events occurred for a given individual, the first occurrence of the composite outcome of ER visit, hospitalization, or death in each of the exposed and unexposed post-vaccination periods was used. Subjects who died before or during the study observation window were excluded from the analysis of emergency room visits and hospitalization, due to the fact that deaths would inappropriately truncate the followup time in the SCCS analysis. Instead, a separate descriptive analysis of death was performed. We conducted separate analyses for the 2-, 4- and 6-month vaccination period. In addition to our primary analysis, we also conducted 3 sensitivity analyses. In the first two analyses, we used a later control period and pre-vaccination control period. In the third sensitivity analysis, we used a shorter risk period. We also conducted secondary analyses to determine if there is an association of vaccination with ER visits, hospital admissions or deaths

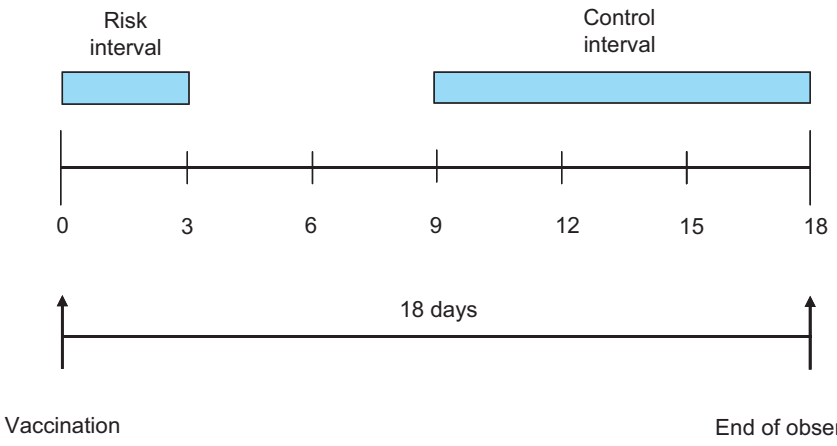

Fig. 1. Illustration of the self-controlled case series design. The observation period for each patient begins with pediatric vaccination date (leftmost upward arrow) and continues for a total of 18 days. In the primary analyses, the first 3 days post vaccination is the *risk interval*, and days 9–18 comprise the *control interval*. The intervening days represent the wash-out period. In the sensitivity analyses we used a shorter risk interval and a later control period and a pre-vaccination control period.

separately. We examined the risk of our combined end-point in the immediate 3 days prior to vaccination in a post-hoc analysis. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

2. Results

At least 1 year of clinical administrative follow-up data was available for 413,957 children born between March 2006 and March 2009. In total, we analyzed data on 969,519 separate vaccination events in these children that occurred at 2, 4 or 6 months plus or minus 30 days (Fig. 2). We present the events versus days pre and post vaccination graphically for the 2-, 4- and 6-month vaccinations (Figs. 3–5).

2.1. 2-Month analysis

333,244 children received a vaccination at 62 days of age ±30 days, 86% of which were within a ±10 days window. Of these, 1388 experienced one of the combined end-points during the immediate 3 days post vaccination, compared to 4893 in the 9-day control period for our primary analysis. The relative incidence of an event was 0.85 (0.80–0.90). The reduced relative incidence was present in all sensitivity analyses (Table 1). The relative incidence of an event in the immediate 3 days prior to vaccination compared to the control period was 0.74 (0.69–0.78).

2.2. 4-Month analysis

323,580 children received a vaccination at 124 ± 30 days, 78% of which were within a ±10 days window. Of these, 1066 experienced one of the combined end-points during the immediate 3 days post vaccination, compared to 4313 in the 9-day control period for our primary analysis. The relative incidence of an event was 0.74 (0.69–0.79). The reduced relative incidence was present in all sensitivity analyses (Table 2). The relative incidence of an event in the immediate 3 days prior to vaccination compared to the control period was 0.57 (0.53–0.61).

2.3. 6-Month analysis

312,695 children received a vaccination at 186 ± 30 days, 72% of which were within a ±10 days window. Of these, 1070 experienced one of the combined end-points during the immediate 3 days post vaccination, compared to 4743 in the 9-day control period for our primary analysis. The relative incidence of an event was 0.68 (0.63–0.72). The reduced relative incidence was present in all sensitivity analyses (Table 3). The relative incidence of an event in the immediate 3 days prior to vaccination compared to the control period was 0.50 (0.46–0.54).

2.4. Individual end-point analysis

When examined separately, there was no increase in the relative incidence of any of the individual end-points of emergency room visits, hospital admission or death in the 3-day post vaccination risk interval compared to the control period 9–18 days post vaccination. The combined number of deaths in the 3 days immediate post vaccination period for all 3 vaccination periods was 5 or fewer and the relative incidence was less than the rate in the control period (Table 4).

3. Discussion

Vaccines, while continually demonstrated to be safe, have the potential to cause immediate adverse events through their mechanism of action. In order to create immunity, vaccines need to create some level of inflammation in the vaccinated individual. Such a process is often mediated through the introduction of both the inactive or attenuated antigen and the use of an adjuvant to enhance the immune response [9,10]. This process can create local inflammation and fever. It is conceivable that in some individuals the response could produce more serious outcomes which could manifest as emergency room visits, hospital admissions or death. The use of the whole cell pertussis vaccine was often associated with a strong immune response including increased risk of anorexia and high fevers. The switch to the acellular form of the vaccine substantially reduced this risk [4].

Our study found no increased incidence of the combined end point of emergency room visits or hospitalizations in the 3-day period immediately following 2-, 4- and 6-month pediatric vaccination compared to a control period 9–18 days after vaccination. Nor was an increased incidence of death evident in the risk period. In contrast there was an apparent protective effect. These findings persisted when we used a shorter post vaccination event period and when we used a later and a pre-vaccination control period. When we examined the end points of emergency room visits and hospital admissions separately we found similar results.

These findings suggest that acute inflammation caused by standard 2-, 4- and 6-month pediatric vaccines is not of a magnitude

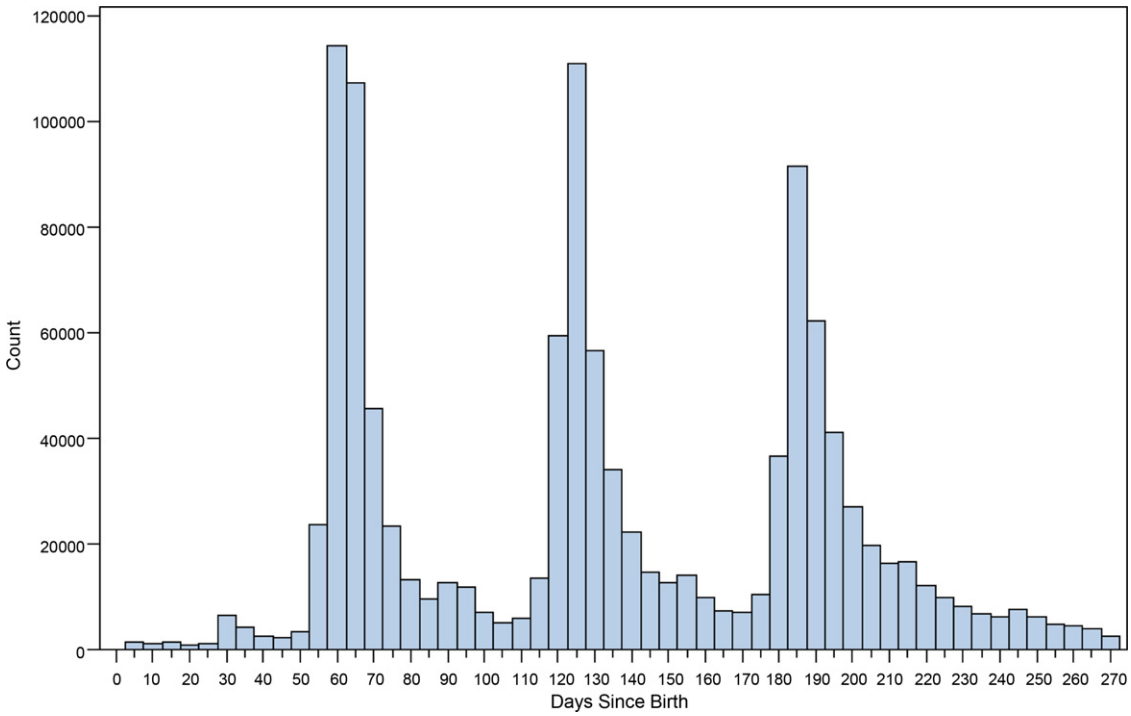

Fig. 2. Vaccination events by days since birth up to 270 days.

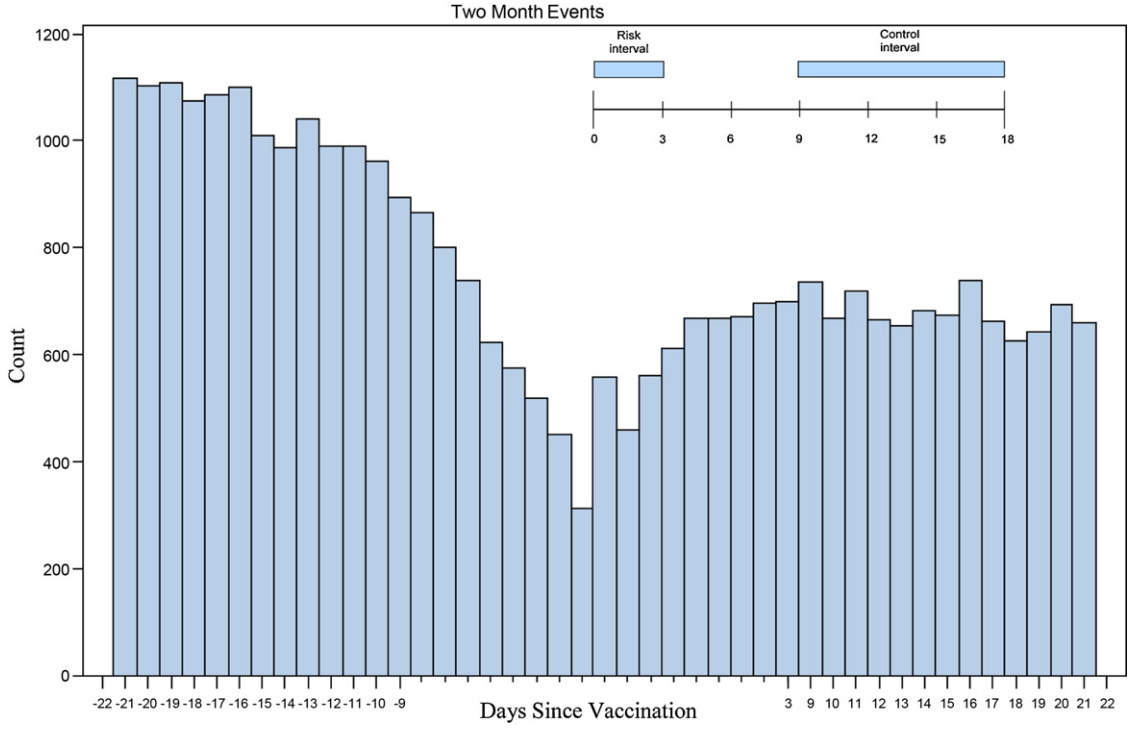

Fig. 3. Number of combined endpoints versus days before/after 2 month. Count = number of combined endpoints of emergency room visit, hospitalization and death. Days = number of days before or after vaccination, day 0 being the day of vaccination.

Table 1
Relative incidence of combined end-point (hospital admission, emergency room visit or death following 2-month vaccination).

Analysis	Risk interval*	End-points during risk interval (*n*)	Control interval*	End-points during control interval (*n*)	Relative incidence (95% CI)
Primary	Days 1–3	1388	Days 9–18	4893	0.85 (0.80,0.90)
Secondary	Days 1–3	1390	Days −18 to −9	6972	0.60 (0.56,0.63)
	Days 1–3	1388	Days 19–27	4716	0.88 (0.83,0.94)
	Days 1–2	913	Days 9–18	4893	0.84 (0.78,0.90)

* Risk and control intervals expressed as days following vaccination.
Subjects who died before or during the observation window are excluded from this analysis.

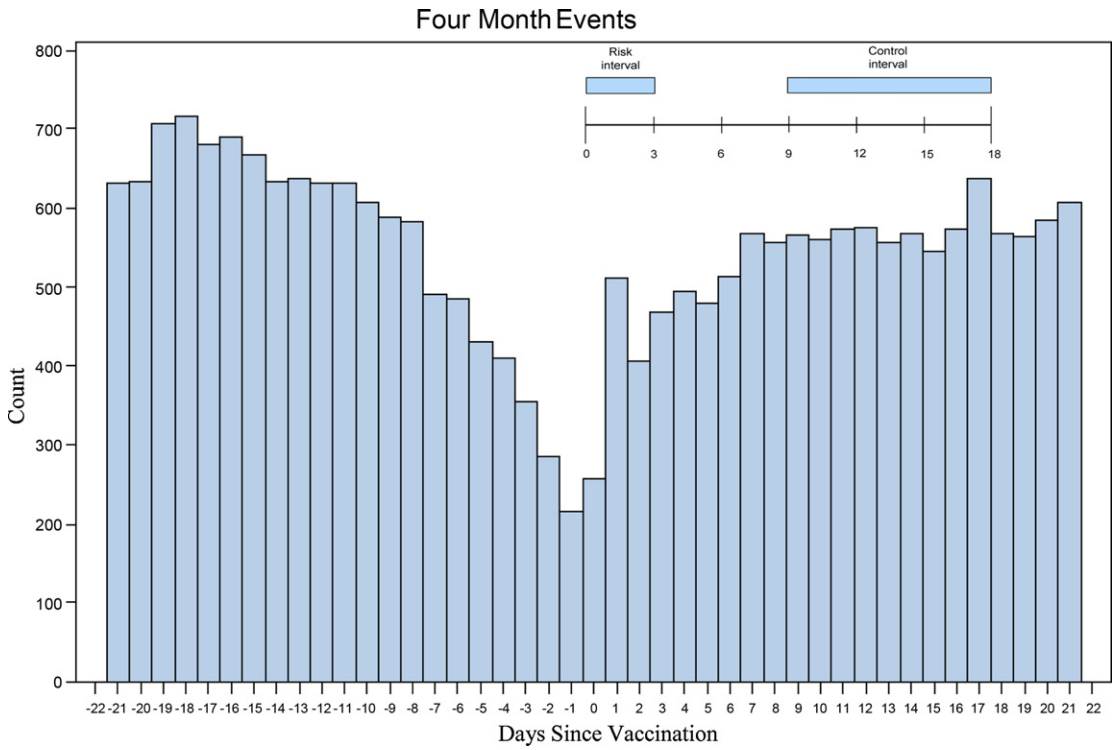

Fig. 4. Number of combined endpoint versus days before/after 4 month. Count = number of combined endpoints of emergency room visit, hospitalization and death. Days = number of days before or after vaccination, day 0 being the day of vaccination.

that it would cause a detectable increase in emergency room visits or admissions to hospital in the immediate post-vaccination period. However, our study also identified a large healthy user/healthy vaccinee effect that likely produced the apparent protective effect from vaccines. Children who are vaccinated are those who are less likely to have had a hospital admission or ER visit in the preceding days, likely due to deferral of vaccination among children who are acutely ill. In our analysis, the immediate pre-vaccination period was the lowest risk period for our combined end-point. Due to this selection bias, the time of vaccination is therefore one of the healthier

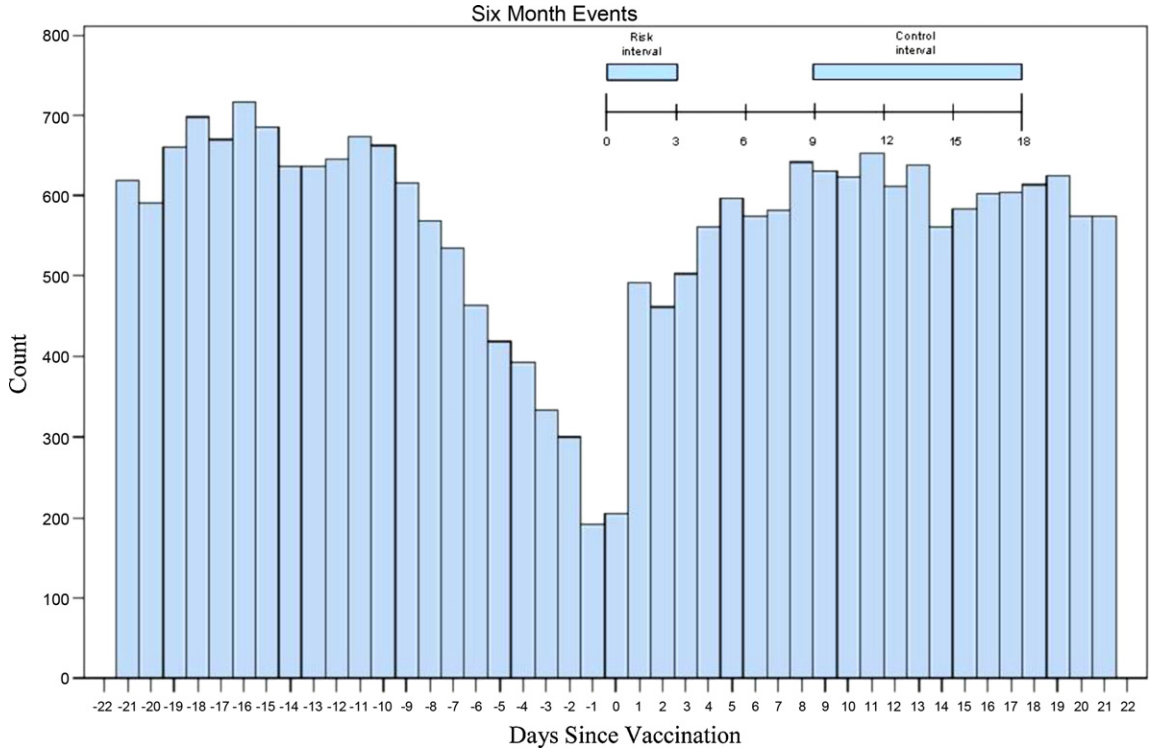

Fig. 5. Number of combined endpoint versus days before/after 6 month. Count = number of combined endpoints of emergency room visit, hospitalization and death. Days = number of days before or after vaccination, day 0 being the day of vaccination.

Table 2
Relative incidence of combined end-point (hospital admission, emergency room visit or death following 4-month vaccination).

Analysis	Risk interval*	End-points during risk interval (*n*)	Control interval*	End-points during control interval (*n*)	Relative incidence (95% CI)
Primary	Days 1–3	1066	Days 9–18	4313	0.74 (0.69, 0.79)
Secondary	Days 1–3	1066	Days −18 to −9	4807	0.67 (0.62, 0.71)
	Days 1–3	1066	Days 19–27	4473	0.71 (0.67, 0.76)
	Days 1–2	706	Days 9–18	4313	0.74 (0.68, 0.80)

* Risk and control intervals expressed as days following vaccination.
Subjects who died before or during the observation window are excluded from this analysis.

Table 3
Relative incidence of combined end-point (hospital admission, emergency room visit or death following 6-month vaccination).

Analysis	Risk interval*	End-points during risk interval (n)	Control interval*	End-points during control interval (n)	Relative incidence (95% CI)
Primary	Days 1–3	1070	Days 9–18	4743	0.68 (0.63, 0.72)
Secondary	Days 1–3	1070	Days −18 to −9	5050	0.64 (0.59, 0.68)
	Days 1–3	1070	Days 19–27	4724	0.68 (0.64, 0.73)
	Days 1–2	654	Days 9–18	4743	0.62 (0.57, 0.67)

* Risk and control intervals expressed as days following vaccination.
Subjects who died before or during the observation window are excluded from this analysis.

periods in the first year of a child life, as measured by the use of health services data. These same children would thus be expected to have a lower incidence of these same events in the immediate days following vaccination, assuming no harmful effects from the vaccination itself. It is conceivable that such a bias may have masked a small increased in our composite endpoint immediately post vaccination. The healthy vaccine effect in combination with the use of the aggregate outcome measures such as ER visits and hospitalization could have also masked increases in disease specific end-points, such as febrile seizures.

A primary strength of this study is the sample size. To the best of our knowledge this is the largest study examining this specific question. By examining 3 entire birth cohorts we had the capability of detecting even small changes in our end points. Another strength of the study is the use of the self-controlled case series design. This increasingly used study design to examine for vaccine adverse events has several advantages over other observational studies [11–16]. By using individuals as their own controls this study design avoids the bias introduced by using unvaccinated controls who are likely systematically different from vaccinated children [11].

Apart from the healthy vaccinee effect other potential limitations of this study include missing an effect in a vulnerable subset of children. By examining the entire population the effect in the healthy population could mask an effect in vulnerable subgroups. Future studies should examine whether children with specific disorders or low birth weight or premature children do not have an increase in adverse events post vaccination. It is also possible that the immediate adverse events from vaccination may occur later than the 3-day interval we examined. However the risk of immediate adverse events produced by inflammation from the vaccine is described as happening within 24 to 48 h and usually resolves by 72 h after vaccination with non-live vaccines [8]. Furthermore, we did not identify any spikes in events in subsequent periods post vaccination as shown in Figs. 3–5.

There are important implications of the results of this study. First, standard 2-, 4- and 6-month pediatric vaccinations administered in the province of Ontario do not appear to result in an increase in hospitalizations, emergency room visits or death in the immediate post vaccination period. This further supports research demonstrating the safety of the acellular pertussis vaccine [4,17,18]. This should be reassuring to parents, health care workers who administer vaccines and public health officials. It is particularly reassuring that in our examination of nearly 1,000,000 vaccination events there were 5 or fewer deaths that occurred in the 3-day post vaccination period. Second, a large healthy vaccinee effect is evident in our study demonstrating that children who receive vaccines were less likely to have been admitted to hospital or visit an emergency room in the days prior to the vaccination. This observation is consistent with those of previous studies, however, our study clearly demonstrates the magnitude of the effect before vaccination (Fig. 3) [19–21]. For example, children vaccinated at 4 and 6 months are half as likely to experience the combined end point in the immediate 3 days prior to vaccination as the control period, which is an estimate of their baseline risk. The belief among some that children fall ill following the vaccine is perhaps largely driven by the presence of this bias and the normal return to a baseline state of health following immunization. This bias also has important implications for future studies which seek to compare vaccinated and unvaccinated children as the vaccinated children reflect a selected population at a healthier period in their childhood. Third, the methodology we used can be utilized to monitor the safety of vaccines on an ongoing basis. As new vaccines are introduced into the pediatric schedule or when new additives are added to current vaccines, the relative incidence emergency room visits, hospitalizations and death can be compared to historical controls. Such a system, which examines aggregate, all cause health service utilization end points as a non-specific marker of adverse events, can work synergistically with existing post-market surveillance systems which look at specific adverse events such as the US

Table 4
Relative incidences of individual end-points (emergency room visit, hospital admission, or death following 2-, 4- and 6-month vaccination).

Outcome	2 months	Events (risk/control)	4 months	Events (risk/control)	6 months	Events (risk/control)
Emergency visits	0.86 (0.81–0.91)	1349/4718	0.76 (0.71–0.81)	1054/4159	0.69 (0.64–0.73)	1055/4619
Admissions	0.55 (0.47–0.65)	161/881	0.45 (0.36–0.57)	82/542	0.45 (0.35–0.59)	65/429
Deaths*	–	≤5/9	–	≤5/≤5	–	≤5/≤5
	$P > 0.05$					

For privacy reasons actual OR and/or counts could not be presented in some blocks.
Subjects who died before or during the observation window are excluded from the emergency room visits, and admissions analyses.

Vaccine Safety Datalink program and Canada's IMPACT (Immunization Monitoring Program Active) system [22–24].

Acknowledgements

Dr. Kwong is supported by a Career Scientist award from the Ontario Ministry of Health and Long-Term Care and a Clinician Scientist award from the Department of Family and Community Medicine, University of Toronto. Professor Keelan is supported by a Career Scientist award from the Ontario Ministry of Health and Long-Term Care. Dr. Wilson holds the Canada Research Chair in Public Health Policy. Dr. Manuel holds the CIHR Chair in Applied Public Health.

Financial disclosure and ethics statement: This study received ethics approval from the Ottawa Hospital Research Institute's Research Ethics Board.

Source of funding/support: This study was supported by the Canadian Foundation for Innovation and by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC).

References

[1] Fritzell B. Detection of adverse events: what are the current sensitivity limits during clinical development? Vaccine 2001;20(Suppl. 1):S47–8.
[2] Centres for Disease Control and Prevention. Possible Side-effects from Vaccines. http://www.cdc.gov/vaccines/vac-gen/side-effects.htm#dtap.
[3] Stratton K, Almario DA, Wizemann TM, McCormick MC, editors. Immunization safety review: vaccinations and sudden unexpected death in infancy. Washington, D.C: The National Academies Press; 2003.
[4] Pertussis vaccination: use of acellular pertussis vaccines among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1997;46(RR-7):1–25.
[5] Glanz JM, McClure DL, Xu S, Hambidge SJ, Lee M, Kolczak MS, et al. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. J Clin Epidemiol 2006;59(8):808–18.
[6] 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 vaccines. Lancet 1995;345(8949):567–9.
[7] Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. Stat Med 2006;25(10):1768–97.
[8] Siegrist CA. Mechanisms underlying adverse reactions to vaccines. J Comp Pathol 2007;137Suppl1:S46–50.
[9] Mastelic B, Ahmed S, Egan WM, Del Giudice G, Golding H, Gust I, et al. Mode of action of adjuvants: implications for vaccine safety and design. Biologicals 2010;38(5):594–601.
[10] Aguilar JC, Rodriguez EG. Vaccine adjuvants revisited. Vaccine 2007;25(19):3752–62.
[11] Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. Am J Epidemiol 1996;143(11):1165–73.
[12] Farrington CP, Miller E, Taylor B. MMR and autism: further evidence against a causal association. Vaccine 2001;19(27):3632–5.
[13] Taylor B, Miller E, Farrington CP, Petropulos MC, Favot-Mayaud I, Li J, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet 1999;353(9169):2026–9.
[14] 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(3):292–6.
[15] Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351(25):2611–8.
[16] Juurlink DN, Stukel TA, Kwong J, Kopp A, McGeer A, Upshur RE, et al. Guillain–Barre syndrome after influenza vaccination in adults: a population-based study. Arch Intern Med 2006;166(20):2217–21.
[17] Decker MD, Edwards KM, Steinhoff MC, Rennels MB, Pichichero ME, Englund JA, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics 1995;96(3 Pt 2):557–66.
[18] Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med 1996;334(6):349–55.
[19] Virtanen M, Peltola H, Paunio M, Heinonen OP. Day-to-day reactogenicity and the healthy vaccinee effect of measles–mumps–rubella vaccination. Pediatrics 2000;106(5):E62.
[20] Fine PE, Chen RT. Confounding in studies of adverse reactions to vaccines. Am J Epidemiol 1992;136(2):121–35.
[21] Davis RL, Marcuse E, Black S, Shinefield H, Givens B, Schwalbe J, et al. MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the Vaccine Safety Datalink Project. The Vaccine Safety Datalink Team. Pediatrics 1997;100(5):767–71.
[22] Chen RT, DeStefano F, Davis RL, Jackson LA, Thompson RS, Mullooly JP, et al. The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA. Bull World Health Organ 2000;78(2):186–94.
[23] Chen RT, Glasser JW, Rhodes PH, Davis RL, Barlow WE, Thompson RS, et al. Vaccine Safety Datalink Project: a new tool for improving vaccine safety monitoring in the United States. The Vaccine Safety Datalink Team. Pediatrics 1997;99(6):765–73.
[24] Scheifele DW, Halperin SA. Immunization Monitoring Program, Active: a model of active surveillance of vaccine safety. Semin Pediatr Infect Dis 2003;14(3):213–9.