The population-level safety benefits of the acellular pertussis vaccine may have been underestimated because only specific adverse events were considered, not overall impact on health services utilization. Using the Vaccine and Immunization Surveillance in Ontario (VISION) system, the authors analyzed data on 567,378 children born between April 1994 and March 1996 (before introduction of acellular pertussis vaccine) and between April 1998 and March 2000 (after introduction of acellular pertussis vaccine) in Ontario, Canada. Using the self-controlled case series study design, they examined emergency room visits and hospital admissions occurring after routine pediatric vaccinations. The authors determined the relative incidence of events taking place before introduction of the acellular vaccine versus after introduction by calculating relative incidence ratios (RIRs). The observed RIRs demonstrated a highly statistically significant reduction in relative incidence after introduction of the acellular vaccine. RIRs for vaccine administered at ages 2, 4, 6, and 18 months were 1.82 (95% confidence interval (CI): 1.64, 2.01), 1.91 (95% CI: 1.71, 2.13), 1.54 (95% CI: 1.38, 1.72), and 1.51 (95% CI: 1.34, 1.69), respectively, comparing event rates before the introduction of acellular vaccine with those after introduction. The authors estimated that approximately 90 emergency room visits and 9 admissions per month were avoided by switching to the acellular vaccine, which is a 38-fold higher impact than when they considered only admissions for febrile and afebrile convulsions. Future analyses comparing vaccines for safety should examine specific endpoints and general health services utilization.

One of the primary objectives of postmarketing surveillance of vaccines is to monitor populations for rare adverse events following immunization which would not be identified in clinical trials. In some cases, this surveillance will target specific adverse events—for example, intussusception following rotavirus vaccination or Guillain-Barré syndrome following influenza vaccination (1–3). However, changes in general measures of health services utilization may provide signals that could be missed by looking for specific outcomes.

Pertussis is a highly infectious respiratory tract infection caused by the bacterium *Bordetella pertussis* and is one of the most frequently reported vaccine-preventable diseases in Canada (4). In addition to persistent cough lasting for weeks if left untreated, pertussis can lead to complications such as pneumonia, febrile and afebrile convulsions,
encephalopathy, and death, especially in young infants. A whole-cell pertussis vaccine was introduced in Canada in 1943, leading to a substantial (~90%) decrease in pertussis incidence during the subsequent 4 decades (5). However, the vaccine was associated with relatively high rates of adverse reactions (e.g., fever, erythema, tenderness, irritability) and, of more concern, adverse neurologic events such as convulsions and hypotonic-hyporesponsive episodes (6–15). Consequently, between July 1997 and April 1998, an acellular pertussis vaccine was adopted by all Canadian provinces and territories. Acellular vaccines have been shown to have an improved safety profile in clinical trials (14, 16) and in a recent Cochrane review (15). Hospital admissions and emergency room (ER) visits for febrile and afebrile convulsions and hypotonic-hyporesponsive episodes decreased significantly in Canada after the introduction of the acellular vaccine (17). Additionally, as Andrews et al. (18) demonstrated using a large primary-care database in the United Kingdom, milder adverse events such as persistent crying, fever, and irritability also decreased significantly after introduction of the acellular vaccine.

Studies focusing only on specific adverse events following vaccination may have underestimated the safety benefits of the acellular vaccine. In this investigation, we examined health services utilization (total acute-care hospital admissions and ER visits for any reason) when the whole-cell pertussis vaccine was used and after the acellular vaccine was introduced, using health administrative data from Ontario, Canada.

MATERIALS AND METHODS

Data

Both the whole-cell (previously) and acellular (currently) pertussis vaccines were administered in Ontario as part of a combination vaccine, which also includes diphtheria, tetanus, poliomyelitis, and Haemophilus influenzae type b. This pentavalent vaccine is the only vaccine administered at 2, 4, and 6 months of age in Ontario, with a booster at 18 months of age. The whole-cell formulation in use before the transition was Penta (Aventis Pasteur, Toronto, Ontario, Canada), and the acellular formulation in use after the transition was Pentacel (Aventis Pasteur) (17).

Using the Vaccine and Immunization Surveillance in Ontario (VISION) system, which is based on health administrative data held at the Institute for Clinical Evaluative Sciences (ICES), we examined vaccinations at ages 2, 4, 6, and 18 months in Ontario children who were eligible for coverage by the Ontario Health Insurance Plan (OHIP) between April 1994 and March 1996 (when the whole-cell pertussis vaccine was in use) and between April 1998 and March 2000 (when the acellular pertussis vaccine was in use). All data sets required for this study were housed at ICES, and all of these databases were linked by encrypted health card number. ICES data include Ontario residents covered by OHIP, encompassing virtually all people living in the province, but may exclude recent immigrants. Pediatric vaccinations were identified using physician billing claims data from OHIP. We used OHIP billing codes for general vaccination during this time period. To identify the 2-, 4-, 6-, and 18-month vaccinations, we identified vaccinations occurring exactly on the due date (61, 122, 183, and 549 days, assuming an average month length of 30.5 days), as well as any vaccinations occurring up to 14 days before the due date and up to 40 days after the due date to allow for variations in scheduling. The Canadian Institute for Health Information’s Discharge Abstract Database was used to identify all acute-care admissions to tertiary and community hospitals for any reason. OHIP billing data were used to ascertain all ER visits made for any reason during the study period.

Statistical methods

Vaccine-specific analysis. We examined hospital admissions and ER visits in the immediate postvaccination period. To conduct this analysis, we utilized the self-controlled case series study design (11, 19). This design requires only data for vaccinated children who experienced events. The design allows individual children to serve as their own controls, whereby the rate of events in an “at-risk” period is compared with the rate of events in 1 or more control periods temporally removed from the time period of vaccination, such that it is unlikely that vaccination could have caused the outcome. For the 2-, 4-, 6-, and 18-month analyses, the at-risk period was defined as the 3 days immediately following vaccination, since an acute reaction to the vaccine would most likely occur within 48 hours, leading to an admission or ER visit within 3 days of vaccination (20). We divided each individual subject’s follow-up period into an initial 3-day interval classified as exposed, followed by a 6-day washout period and then an unexposed period 9–18 days postvaccination (Appendix Figure 1). The unexposed period was carefully defined so that it was far enough removed from the vaccination that the event rate had returned to the baseline rate and was unlikely to be influenced by the vaccination, but not far enough that it would overlap with the next vaccination period. If a child had undergone more than 1 vaccination in the database during the allowable window for each of the scheduled vaccines, the first vaccination was used as the index vaccination. If another vaccination occurred within the observation period (0–18 days after the index vaccination) for a given child, that child was excluded from the analysis.

Where multiple events occurred for a given individual, the first occurrence of the composite outcome of ER visit or hospitalization in each of the exposed and unexposed postvaccination periods was used. Only subjects with both vaccinations and events in the observation period contributed to the self-controlled case series analysis.

In our study, we employed the self-controlled case series design to calculate the relative incidence of adverse events in the exposed periods versus the unexposed periods. The relative incidence is the ratio of the rate of events in the 3-day risk period to the rate of events in the 9-day control period (19). The relative incidence of the composite endpoint of ER visit or hospitalization was analyzed using a fixed-effects Poisson regression model that included terms.
for exposure periods and a term for individual subject, allowing each child to serve as his or her own control, implicitly adjusting for all fixed covariates. We also included an offset term in the model to account for the differing durations of the exposed and unexposed periods (19). We repeated this analysis for the specific endpoint of convulsions based on International Classification of Diseases, Ninth Revision, codes for all 4 vaccinations.

Comparative analysis. To compare the relative incidences of admissions and ER visits after the introduction of acellular vaccine as compared with relative incidences for whole-cell pertussis vaccine, we fitted a model including

vaccinations from before and after the transition and included an interaction term for whole-cell period versus the acellular period. A likelihood ratio test was used to assess the statistical significance of the pre-versus post-interaction. The parameter estimate for the interaction term estimated the relative incidence ratio (RIR) for the acellular period versus the whole-cell period. In secondary analyses, we examined ER visits and hospital admissions separately. All analyses were conducted using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

**Sensitivity analysis.** For comparison, we analyzed the 12-month vaccination, in which only the measles-mumps-rubella vaccine was administered during both the 1994–1996 and 1998–2000 periods and thus we would not expect differences in adverse event rates between the periods. For the purposes of the 12-month analysis, follow-up was broken into a 9-day risk period from day 4 to day 12 and a 9-day control period from day 20 to day 28. The measles-mumps-rubella vaccine is a live attenuated vaccine, and adverse events are expected to occur approximately 1 week following vaccination. We have shown in previous work that rates of ER visits and hospital admissions are elevated on days 4–12 following measles-mumps-rubella vaccination (21).

Ethics approval for this study was obtained from the Ottawa Hospital Research Ethics Board.

**RESULTS**

**2-, 4-, 6-, and 18-month vaccinations**

There were a total of 567,378 OHIP-eligible children available for study in ICES health administrative data: 297,043 from April 1994 to March 1996 and 270,335 from April 1998 to March 2000. Figure 1 shows the frequency of primary adverse events (ER visit or hospital admission) from –7 days to +30 days relative to the index vaccination events for all of the children included in the 2-month vaccination analysis, separately for each of the whole-cell and acellular vaccine periods. For the 2-month vaccination, from 1994 to 1996 (the whole-cell vaccine period), the relative incidence for the risk period in the first 3 days after vaccination versus the control period (days 9–18) was 1.08 (95% confidence interval (CI): 1.02, 1.15) (Table 1). During the period from 1998 to 2000 (the acellular vaccine period), the relative incidence for comparison between the risk and control periods was 0.60 (95% CI: 0.55, 0.65) for the primary combined endpoint (ER visits and admissions). The RIR for comparison between the two periods was 1.82 (95% CI: 1.64, 2.01) for the whole-cell period versus the acellular period, suggesting that the relative incidence of admissions and ER visits was cut nearly in half after the introduction of the acellular pertussis vaccine (Table 1). This translates to 253 avoided ER visits and 41 avoided hospital admissions for every 100,000 vaccinations (Table 2). At the 4-month vaccination, the RIR was 1.91 (95% CI: 1.71, 2.13) for the whole-cell period versus the acellular period (Table 1). This translates to 248 avoided ER visits and 33 avoided hospital admissions per 100,000 vaccinations (Table 2). Smaller but still statistically significant RIRs were also observed for the 6-month vaccination (RIR = 1.54, 95% CI: 1.38, 1.72) and the 18-month booster vaccination (RIR = 1.51, 95% CI: 1.34, 1.69) for the whole-cell period versus the acellular period (Tables 1 and 2).

**Reasons for hospital admission following vaccination**

The most frequent International Classification of Diseases, Ninth Revision, codes for the diagnoses most responsible for hospital admission following the 2-month vaccination are listed in Table 3. Convulsions were prominent in the top 10 reported conditions for nearly all risk and control periods of interest at all time points. The RIR for convulsions in the whole-cell period versus the acellular period was 8.80 (95% CI: 0.99, 78.11) at 2 months, 6.88 (95% CI: 1.35, 35.06) at 4 months, 1.10 (95% CI: 0.27, 4.55) at 6 months, and 4.13 (95% CI: 0.98, 17.46) at 18 months (Figure 2). This translates to the avoidance of approximately 23 convulsions for every 100,000 children vaccinated with the acellular vaccine at 2, 4, 6, and 18 months combined.

**Sensitivity analysis of the 12-month vaccination in the same time periods**

For the combination of ER visits and hospital admissions, the relative incidence was 1.36 (95% CI: 1.31, 1.43) in the whole-cell period and 1.35 (95% CI: 1.29, 1.42) in the acellular period. The RIR was 1.01 (95% CI: 0.95, 1.07). Similarly, the RIR was 1.01 for ER visits alone and 1.08 for hospital admissions alone, both not differing significantly from 1.

**DISCUSSION**

The introduction of the acellular pertussis vaccine was intended to improve the safety profile in comparison with the previous whole-cell vaccine. To the best of our knowledge, this study was the first to examine the impact of this transition on overall utilization of acute-care and ER services following immunization. By doing so, we have demonstrated that the magnitude of the safety benefit resulting from the change in vaccine is considerably larger than would have been estimated by examining only the impact on specific adverse events.

The overall relative incidence reduction was 44% at the 2-month vaccination, 47% at the 4-month vaccination, 35% at the 6-month vaccination, and 33% at the 18-month booster vaccination. Most of the benefit was seen in a reduction in ER visits. We estimate that for every 100,000 children who received the complete course of 2-, 4-, 6-, and 18-month acellular vaccine, 879 ER visits and 92 hospital admissions were prevented in comparison with the whole-cell form of the vaccine. Given that there were approximately 130,000 births per year in Ontario during the study period (22) and assuming that about 95% of those children would be vaccinated according to the schedule, this translates into approximately 90 ER visits and 9 admissions avoided per month.

Table 1. Relative Incidence of Adverse Events (Emergency Room Visits and Hospital Admissions) Following Receipt of the Whole-Cell Pertussis Vaccine or the Acellular Pertussis Vaccine, Ontario, Canada, 1994–2000a

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Risk Events</td>
<td>No. of Control Events</td>
<td>RI</td>
<td>95% CI</td>
<td>No. of Risk Events</td>
</tr>
<tr>
<td>2-month vaccination</td>
<td>232,574</td>
<td>214,669</td>
<td>1.323</td>
<td>3,663</td>
<td>1.08</td>
</tr>
<tr>
<td>ER visits and admissions</td>
<td>1,246</td>
<td>3,271</td>
<td>1.14</td>
<td>1.07, 1.22</td>
<td>654</td>
</tr>
<tr>
<td>ER visits</td>
<td>190</td>
<td>868</td>
<td>0.66</td>
<td>0.56, 0.77</td>
<td>89</td>
</tr>
<tr>
<td>Admissions</td>
<td>223,879</td>
<td>207,667</td>
<td>1.172</td>
<td>3,577</td>
<td>0.98</td>
</tr>
<tr>
<td>4-month vaccination</td>
<td>213,087</td>
<td>199,015</td>
<td>1.029</td>
<td>4,297</td>
<td>0.72</td>
</tr>
<tr>
<td>ER visits and admissions</td>
<td>1,009</td>
<td>4,073</td>
<td>0.74</td>
<td>0.69, 0.80</td>
<td>563</td>
</tr>
<tr>
<td>ER visits</td>
<td>85</td>
<td>566</td>
<td>0.45</td>
<td>0.36, 0.57</td>
<td>59</td>
</tr>
<tr>
<td>Admissions</td>
<td>153,814</td>
<td>142,615</td>
<td>0.377</td>
<td>3,238</td>
<td>0.93</td>
</tr>
<tr>
<td>18-month booster</td>
<td>937</td>
<td>2,802</td>
<td>1.01</td>
<td>0.94, 1.09</td>
<td>590</td>
</tr>
<tr>
<td>ER visits and admissions</td>
<td>919</td>
<td>2,717</td>
<td>0.90</td>
<td>0.70, 1.16</td>
<td>30</td>
</tr>
<tr>
<td>ER visits</td>
<td>77</td>
<td>257</td>
<td>0.90</td>
<td>0.70, 1.16</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ER, emergency room; RI, relative incidence; RIR, relative incidence ratio.

a Overall, 297,043 children were eligible for inclusion in the whole-cell period, and 270,335 children were eligible for inclusion in the acellular period. Multiple events for an individual child were counted only once in any risk or control period (e.g., an ER visit leading to admission was counted as only 1 event); thus, numbers of ER visits and admissions may not sum to the totals.

b P value from a likelihood ratio test of the RIR interaction term in the self-controlled case series model.
In a recent United Kingdom study that similarly evaluated adverse events after a whole-cell vaccine versus an acellular vaccine, Andrews et al. (18) found diminishing relative incidence of fever and crying between the first and third doses of the vaccine, which is consistent with our finding of diminishing relative incidence of ER visits and admissions over the course of the 2-, 4-, 6-, and 18-month vaccinations. In a recent Cochrane review, Zhang et al. (15) reported a combined risk ratio of 0.48 (95% CI: 0.31, 0.73) for primary vaccination with acellular vaccine versus whole-cell vaccine in 15 studies with a total of 124,387 participants (or a risk ratio of approximately 2 for whole-cell vaccine versus acellular vaccine). Our findings are consistent with these past reports. An IMPACT study in Canada that compared hospitalizations for febrile and afebrile convulsions in the whole-cell and acellular periods found a 79% decrease in febrile convulsions and a 41% decrease in afebrile convulsions (17). This corresponds closely to the 40% overall reduction in relative incidence of ER visits and admissions over the course of the 2-, 4-, 6-, and 18-month vaccinations.

Across the 4 vaccinations, we observed a reduction of 23 convulsions per 100,000 children vaccinated as compared with a reduction of 879 ER visits. While the relative reductions in convulsions and ER visits were similar, the absolute reduction in ER visits was 38 times greater than the absolute reduction in the specific endpoint of convulsions. The primary explanation for this finding is that the whole-cell pertussis vaccine, in the process of creating immunity, produces a spectrum of physiologic responses. Milder responses commonly include local redness and swelling, as well as pain, fever, drowsiness, fussiness/persistent crying, vomiting, and anorexia (10, 13, 14, 23). Febrile and afebrile convulsions probably represent a more severe form of a spectrum of responses that are a consequence of this inflammation and which may affect specific vulnerable children. Our identification of increases in ER visits and admissions beyond what would be expected from convulsions probably demonstrates the impact of less severe adverse events resulting from the physiologic reaction to the vaccine.

Our study had several strengths and weaknesses. The major strengths included the large sample size and the use of the self-controlled case series design. The self-controlled case series design effectively eliminates the likelihood of selection bias and unequal distribution of confounding variables between exposed and unexposed by using only cases who serve as their own controls.

### Table 2. Numbers of Adverse Events (Emergency Room Visits and Hospital Admissions) Avoided by the Introduction of Acellular Pertussis Vaccine, Ontario, Canada, 1998–2000

<table>
<thead>
<tr>
<th>Vaccination Period</th>
<th>No. of Events Avoided per 100,000 Vaccinations</th>
<th>No. of Vaccinations per Additional Event Avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-month vaccination</td>
<td>ER visits 253</td>
<td>395</td>
</tr>
<tr>
<td>4-month vaccination</td>
<td>ER visits 248</td>
<td>403</td>
</tr>
<tr>
<td>6-month vaccination</td>
<td>ER visits 173</td>
<td>578</td>
</tr>
<tr>
<td>18-month booster</td>
<td>ER visits 205</td>
<td>489</td>
</tr>
</tbody>
</table>

Abbreviations: ER, emergency room; NS, not significant.

In a recent United Kingdom study that similarly evaluated adverse events after a whole-cell vaccine versus an acellular vaccine, Andrews et al. (18) found diminishing relative incidence of fever and crying between the first and third doses of the vaccine, which is consistent with our finding of diminishing relative incidence of ER visits and admissions over the first 3 doses. In a recent Cochrane review, Zhang et al. (15) reported a combined risk ratio of 0.48 (95% CI: 0.31, 0.73) for primary vaccination with acellular vaccine versus whole-cell vaccine in 15 studies with a total of 124,387 participants (or a risk ratio of approximately 2 for whole-cell vaccine versus acellular vaccine). Our findings are consistent with these past reports. An IMPACT study in Canada that compared hospitalizations for febrile and afebrile convulsions in the whole-cell and acellular periods found a 79% decrease in febrile convulsions and a 41% decrease in afebrile convulsions (17). This corresponds closely to the 40% overall reduction in relative incidence of ER visits and admissions over the course of the 2-, 4-, 6-, and 18-month vaccinations.

Across the 4 vaccinations, we observed a reduction of 23 convulsions per 100,000 children vaccinated as compared with a reduction of 879 ER visits. While the relative reductions in convulsions and ER visits were similar, the absolute reduction in ER visits was 38 times greater than the absolute reduction in the specific endpoint of convulsions. The primary explanation for this finding is that the whole-cell pertussis vaccine, in the process of creating immunity, produces a spectrum of physiologic responses. Milder responses commonly include local redness and swelling, as well as pain, fever, drowsiness, fussiness/persistent crying, vomiting, and anorexia (10, 13, 14, 23). Febrile and afebrile convulsions probably represent a more severe form of a spectrum of responses that are a consequence of this inflammation and which may affect specific vulnerable children. Our identification of increases in ER visits and admissions beyond what would be expected from convulsions probably demonstrates the impact of less severe adverse events resulting from the physiologic reaction to the vaccine.

Our study had several strengths and weaknesses. The major strengths included the large sample size and the use of the self-controlled case series design. The self-controlled case series design effectively eliminates the likelihood of selection bias and unequal distribution of confounding variables between exposed and unexposed by using only cases who serve as their own controls.

### Table 3. Top 5 International Classification of Diseases, Ninth Revision, Codes for the Diagnosis Most Responsible for Hospital Admission During 2 Periods of Administration of Pertussis Vaccine, Ontario, Canada, 1994–2000

<table>
<thead>
<tr>
<th>Risk Period and ICD-9 Code</th>
<th>Diagnosis</th>
<th>No. of Children</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994–1996 (whole-cell vaccine)</td>
<td>786.0</td>
<td>Dyspnea and respiratory abnormalities</td>
<td>15</td>
</tr>
<tr>
<td>466.0</td>
<td>Acute bronchiolitis</td>
<td>12</td>
<td>6.1</td>
</tr>
<tr>
<td>999.0</td>
<td>Other and unspecified complications of medical care</td>
<td>12</td>
<td>6.1</td>
</tr>
<tr>
<td>780.6</td>
<td>Fever, unspecified</td>
<td>11</td>
<td>5.6</td>
</tr>
<tr>
<td>780.3</td>
<td>Convulsions</td>
<td>10</td>
<td>5.1</td>
</tr>
<tr>
<td>1998–2000 (acellular vaccine)</td>
<td>466.1</td>
<td>Acute bronchiolitis</td>
<td>15</td>
</tr>
<tr>
<td>530.1</td>
<td>Esophagitis</td>
<td>6</td>
<td>6.6</td>
</tr>
<tr>
<td>465.9</td>
<td>Acute upper respiratory infection of unspecified site</td>
<td>≤5</td>
<td></td>
</tr>
<tr>
<td>780.6</td>
<td>Fever, unspecified</td>
<td>≤5</td>
<td></td>
</tr>
<tr>
<td>008.8</td>
<td>Intestinal infection due to other organism not elsewhere classified</td>
<td>≤5</td>
<td></td>
</tr>
</tbody>
</table>

Our findings suggest that in any evaluation of a change between vaccine products, investigators should examine the impact of the change on both specific endpoints and general health services utilization. Failing to do the latter may result in underestimation of the benefits of the purportedly safer form of the vaccine, as we demonstrated in this study. This has important implications for both clinical care and health economic assessments of vaccine programs. This observation may be relevant to assessment of the safety of other pharmaceutical products beyond vaccines and would have similar implications. We also identified the importance of using RIRs to determine the magnitude of an effect when examining vaccine safety. Failure to do so will produce an underestimate of risk through the failure to adjust for the healthy vaccinee effect.

**Figure 2.** Relative incidence of convulsions after receipt of pertussis vaccine for the whole-cell vaccine period (1994–1996) and the acellular vaccine period (1998–2000) at the 2-, 4-, 6-, and 18-month vaccinations, Ontario, Canada. Circles represent relative incidence for the whole-cell period (dashed lines, 95% confidence interval); squares represent relative incidence for the acellular period (solid lines, 95% confidence interval). Relative incidence ratios (RIRs) from a likelihood ratio test for the RIR interaction term in the self-controlled case series model, for the whole-cell vaccine period versus the acellular vaccine period, were as follows: RIR = 8.80 (95% confidence interval (CI): 0.99, 78.11) for the 2-month vaccination ($P = 0.0509$); RIR = 6.88 (95% CI: 1.35, 35.06) for the 4-month vaccination ($P = 0.0204$); RIR = 1.10 (95% CI: 0.27, 4.55) for the 6-month vaccination ($P = 0.8955$); and RIR = 4.13 (95% CI: 0.98, 17.46) for the 18-month vaccination ($P = 0.0536$).

A strength and weakness of this study was the presence of the healthy vaccinee effect, which is the observation that children tend not to receive vaccine if they have recently been ill. We previously documented this effect in an analysis of 2-, 4-, and 6-month vaccination (24), and the same effect was evident in this analysis. The healthy vaccinee effect will result in underestimation of the adverse event rate in the immediate postimmunization period. However, our use of RIRs to compare incidence ratios across time periods effectively overcame the healthy vaccinee effect, since the effect was presumed to be similar in both historical cohorts. Had we not calculated the RIRs, we might have incorrectly concluded that the rates of adverse events following the whole-cell pertussis vaccine were comparatively small because of attenuation by the health vaccinee effect. Only by comparing rates between the two vaccines does the actual magnitude of adverse events following whole-cell pertussis vaccine become evident.

A weakness of our study was the fact that vaccine-specific codes were not available for the time periods evaluated, and therefore we had to rely on general vaccination codes. However, through observation of the distribution of the timing and frequency of vaccination events through OHIP billing data and through our knowledge of the pediatric vaccination schedule in Ontario, we were confident that we were correctly identifying each specific vaccination in the children under study.

**ACKNOWLEDGMENTS**

Author affiliations: ICES@uOttawa, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada (Steven Hawken, Douglas G. Manuel, Kumanan Wilson); Department of Clinical Epidemiology, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada (Steven Hawken, Douglas G. Manuel, Kumanan Wilson); Department of Family Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada (Douglas G. Manuel); Public Health Ontario, Toronto, Ontario, Canada (Shelley L. Deeks, Jeffrey C. Kwong, Natasha S. Crowcroft); Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Shelley L. Deeks, Jeffrey C. Kwong, Natasha S. Crowcroft); Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (Jeffrey C. Kwong); Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada (Jeffrey C. Kwong); Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (Natasha S. Crowcroft); and Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada (Kumanan Wilson).

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

Conflict of interest: none declared.

**REFERENCES**


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**Appendix Figure 1.** The self-controlled case series study design.