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

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ABSTRACT. Objective. Acellular pertussis vaccines were introduced with the promise of an improved safety profile compared with whole-cell vaccines. In 1997–1998, Canada adopted 1 combination acellular pertussis vaccine, having previously used 1 particular combination whole-cell pertussis vaccine. We hypothesized that the change would result in a decrease in hospitalization rates for seizures and reports of hypotonic-hyporesponsive episodes (HHEs) temporally related to pertussis vaccination.

Methods. Active surveillance was performed between 1995 and 2001 by the Immunization Monitoring Program–Active monitors at 12 hospitals using standard case definitions. Seizures had to occur within 72 hours after immunization with a pertussis-containing vaccine or 5 to 30 days after immunization with measles-mumps-rubella vaccine. HHE episodes had to occur within 48 hours of receipt of a pertussis-containing vaccine. Poison regression models were used to compare the average number of monthly admissions for seizures and HHEs before and after introduction of the acellular pertussis vaccine.

Results. We found a 79% decrease in febrile seizures associated with receipt of pertussis vaccine but no significant decrease in febrile seizures temporally related to measles-mumps-rubella between 1995–1996 and 1998–2001. There was a 60% to 67% reduction in HHEs associated with pertussis-containing vaccines between the same time periods, depending on case definition.

Conclusions. The risks of febrile seizures and HHEs after pertussis-containing vaccine declined significantly with the introduction of acellular pertussis vaccine in Canada. Active surveillance systems are important for detecting trends in uncommon adverse events after routine immunizations.

ABBREVIATIONS. HHE, hypotonic-hyporesponsive episode; MMR, measles-mumps-rubella; VAERS, Vaccine Adverse Events Reporting System; IMPACT, Immunization Monitoring Program–Active.

Pertussis immunization has been controversial because of concerns about neurologic complications, including seizures and hypotonic-hyporesponsive episodes (HHEs).1–8 Although studies have noted a low risk of afebrile seizures after pertussis immunization,9,10 a small but increased risk of febrile seizures has been observed. Relative risk has been estimated to be between 1.5 and 5 compared with unvaccinated children.9–16 The relative risk of febrile seizures in children 6 to 14 days after the receipt of measles-mumps-rubella (MMR) vaccine has been estimated at 2 to 3 compared with nonimmunized children.10,14,16,17

Collapse or “shock-like” states known as HHEs have also been recognized as a rare but important adverse event usually occurring within 24 hours of receipt of whole-cell pertussis vaccine. An excellent review of the topic was recently published.18 The reported risk of HHEs after whole-cell pertussis vaccine has been estimated at 1 per 1000 to 1 per 6000 doses.11 The Vaccine Adverse Events Reporting System (VAERS) in the United States has documented a decrease in reports of HHEs since the introduction of acellular pertussis vaccines.19

Concerns about the safety of whole-cell pertussis vaccine prompted the development of acellular vaccines. Risk estimates of adverse effects from prelicensure trials of acellular vaccines were encouraging but derived from studies of carefully selected healthy infants. Two prelicensure trials with between 2000 and 4000 children per arm that compared whole-cell and acellular vaccines did not demonstrate significant differences in the rates of seizures or HHEs.20,21 The largest study, with 13 000 doses per arm, showed a significant decrease in the incidence of HHEs after acellular compared with whole-cell vaccine but no significant difference in the rate of seizures.22 One postlicensure safety study in the United States determined that fever and febrile seizures were less frequent after acellular vaccine compared with whole-cell vaccine given for the fourth and fifth
doses. Another study showed a low rate of febrile seizures after acellular vaccine when compared with rates previously reported for whole-cell vaccine. In addition, risk estimates may vary according to the type of acellular vaccine. Additional data on comparative risks in large, nonselected populations under routine conditions of vaccine administration for all 5 recommended doses are needed.

The Immunization Monitoring Program–Active (IMPACT) is a Canadian surveillance program that actively documents severe vaccine-associated adverse events in children who are admitted to pediatric tertiary care hospitals. In 1995, participating hospitals represented nearly 90% of the nation’s pediatric tertiary care beds. Targets of surveillance include postimmunization seizures and HHEs. From 1995 to 1996, all Canadian provinces used the same whole-cell pertussis-based combination vaccine (Penta, Aventis Pasteur, Toronto, Ontario, Canada). During 1997, all switched to the same acellular pertussis-based combination vaccine (Pentacel, Aventis Pasteur). In addition to the pertussis component, both vaccines contain diphtheria and tetanus toxoids and inactivated poliomyelitis vaccine and are reconstituted with *Haemophilus influenzae* type b conjugate vaccine before administration as a single dose. All children are routinely vaccinated at 2, 4, and 6 months with a booster dose at 18 months. Once whole-cell vaccine production was discontinued by the manufacturer in Canada, it could no longer be obtained by the provinces, accounting for complete switchover to acellular pertussis component during 1997, except for 1 small province doing so by April 1, 1998. Since then, only 1 acellular-type vaccine has been used nationwide. MMR is given after the first birthday with a second dose at 18 months or between 4 and 6 years. Between 1995 and 2001, no other vaccines were given routinely as part of an early infant immunization schedule in Canada. Conjugated pneumococcal vaccine was not available in Canada at that time, and hepatitis B is not routinely given as an infant immunization. This provided a unique opportunity to determine whether the acellular vaccine was associated with fewer hospital admissions for seizures and reports of HHEs in a nonselected population of children undergoing routine immunization. We hypothesized that the number of admissions for seizures and reports of HHEs (admitted and emergency department visits) after pertussis vaccine would decrease whereas admissions for febrile seizures after MMR vaccine would remain unchanged during this period.

**METHODS**

Children who were hospitalized with seizures or HHEs or seen in the emergency department for HHEs were identified by the IMPACT group of Canadian pediatric hospitals. Eleven hospitals contributed data from 1995 and a 12th from 1999. Ethics approval for surveillance was obtained at each site for each year of the study. The period between January 1, 1995, and December 31, 2001, was chosen to highlight the transition from whole-cell to acellular pertussis vaccine. Nurse monitors at each center actively searched for children who were admitted with seizures or HHEs or shock (International Classification of Diseases, Ninth Revision code 785.5) by reviewing daily admission lists and visiting the inpatient units. To ascertain the outpatient presentations of HHEs, the nurse monitors scanned emergency department discharge lists for the diagnosis of “shock,” “collapse episode,” or HHE and reviewed the health record in more detail to determine whether the case definition was met. Uniform case definitions and case-report forms devised by the investigators were used. When a clinical event met the case definition, the immunization history was verified by consulting the chart, the admitting physician, or the primary care physician. The nurse monitors were not blinded as to type of vaccine administered or time period.

A case was accepted as a seizure when there was a compatible history or the event was witnessed by a health professional and characterized by generalized or focal stiffening of limbs with or without rhythmic shaking or loss of consciousness. Seizures caused by trauma, poisoning, bacterial meningitis, or other obvious causes were excluded. Seizures were classified as febrile when a temperature equivalent to >38.5°C rectal was measured within 1 hour of the event; otherwise, they were classed as afebrile. Only seizures that occurred within 72 hours after immunization with a pertussis-containing vaccine or within 5 to 30 days after MMR vaccine were analyzed.

The case definition for HHE required 1) a sudden onset of decreased muscle tone, 2) skin pallor or cyanosis, and 3) decreased level of responsiveness or consciousness, lasting minutes to hours and occurring within 48 hours of receipt of a pertussis-containing vaccine. Cases that met all 3 criteria were rated as definite, whereas those that lacked a criterion (absent or overlooked) were rated as possible cases. The cases of HHE did not require hospital admission.

Data collected included age and sex, presence or absence of preexisting neurologic disorders, nonneurologic symptoms, interval between vaccination and onset of symptoms, type of vaccine received, investigations in hospital, and outcome at hospital discharge. Reports with unique identifiers were forwarded to a data center for scrutiny and data entry.

**Data Analysis**

Poisson models were used to compare the average number of seizures and HHEs per month during 1995–1996 and 1998–2001. Because 1997 was a transition year, it was excluded from the comparisons. We analyzed events on a monthly basis to have sufficient temporal resolution to detect changes. The Poisson model does not take into account other factors that may influence the incidence and reporting of events such as asymmetry in number of reports within time periods. A common reason for poorly fitting Poisson models is overdispersion of counts, which can result in overstating the statistical significance of differences between time periods. To protect against this, significance levels were computed using quasilikelihood estimation of the Poisson model including a dispersion parameter. To assess the adequacy of our models, we computed goodness-of-fit statistics based on the residual deviance.

**RESULTS**

There were 218 reports of seizures that met the case definitions for inclusion in this report. Characteristics of the children are summarized in Table 1. No other vaccine had been given concomitantly or was temporarily related to the neurologic event being reported. Children who had been given other vaccines concurrently, such as influenza vaccine, were removed from the data analysis to maintain homogeneity.

**Febrile Seizures After Receipt of Pertussis Vaccine**

There were 50 reports of hospitalization for febrile seizures after a pertussis-containing vaccine. Of these, 27 (54%) children were <12 months, 21 (42%) were 12 to 24 months, and 2 (4%) were 4 to 6 years of age. Forty-three (86%) children had onset of seizure within 24 hours, 3 (6%) between 24 and 48 hours, and 4 (8%) between 48 and 72 hours after immunization. Within this group, 4 children had concurrently received pertussis and MMR vaccine, but because seizures occurred within 72 hours, they are included in...
this analysis. Echovirus 7 meningitis was documented in 1 case, and 1 child had influenza A.

The average number of reports per month of febrile seizures after a pertussis-containing vaccine decreased from 1.21 for 1995–1996 to 0.25 for 1998–2001 (P = 0.000084), a 79% decrease between periods (Fig 1). The Poisson model did not show significant evidence of lack of fit (P = 0.80). The results did not change with removal of the case in which infection with echovirus 7 was documented.

Febrile Seizures After Receipt of MMR Vaccine

Of 107 children with febrile seizures temporally associated with MMR, 105 (98%) were between 12 and 24 months, 1 (1%) was 4 to 6 years, and 1 (1%) was 2.6 years. Fifty-five (51%) children had onset of seizures between 5 and 10 days, 26 (24%) between 11 and 20 days, and the remaining 26 (24%) between 21 and 30 days. Thirteen children had concurrently received a pertussis-containing vaccine and MMR, but because onset of seizures occurred >5 days after vaccination, they were included in the MMR analysis. Ten children had documented coexistent respiratory or gastrointestinal viral infections (5 in 1995–1996 and 5 in 1998–1999).

The number of reports per month of febrile seizures associated with MMR vaccine did not change significantly over time. There was an average of 1.54 reports per month during 1995–1996 and 1.19 per month between 1998 and 2001 (P = 0.19), a 23% decrease between periods (Fig 1). The Poisson model did not show significant evidence of lack of fit (P = 0.29).

Afebrile Seizures After Receipt of Pertussis Vaccine

Of 28 children with afebrile seizures associated with pertussis vaccine (Table 1), 24 (86%) were <12 months and 4 (14%) were between 12 and 24 months. The number of reports of afebrile seizures per month temporally associated with pertussis-containing vac-

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**TABLE 1.** Characteristics of Children Admitted to Hospital With Seizures Temporally Related to Administration of Pertussis or MMR Vaccine 1995–2001 (1997 Cases Included)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Febrile Seizures</th>
<th>Afebrile Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pertussis-Containing Vaccine (N = 50)</td>
<td>MMR (N = 107)</td>
</tr>
<tr>
<td>Age (y; median [range])</td>
<td>0.83 (0.16–5.07)</td>
<td>1.13 (1.02–5.03)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>19 (38)</td>
<td>59 (55.1)</td>
</tr>
<tr>
<td>Previously neurologic abnormality (%)</td>
<td>12 (24)</td>
<td>40 (37.4)</td>
</tr>
<tr>
<td>Nonneurologic symptoms at presentation (%)</td>
<td>39 (78)</td>
<td>89 (83.2)</td>
</tr>
<tr>
<td>Admitted to intensive care units (%)</td>
<td>8 (16)</td>
<td>26 (24.3)</td>
</tr>
<tr>
<td>Median number of days in hospital (range)</td>
<td>2.5 (1–12)</td>
<td>3 (1–9)</td>
</tr>
<tr>
<td>Type of Seizure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New-onset seizures (%)</td>
<td>40 (80)</td>
<td>78 (72.9)</td>
</tr>
<tr>
<td>Febrile seizures previously (%)</td>
<td>6 (12)</td>
<td>25 (23.4)</td>
</tr>
<tr>
<td>Other seizures previously (%)</td>
<td>4 (8)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Seizure History: Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical seizure type (%)</td>
<td>42 (84)</td>
<td>90 (84.1)</td>
</tr>
<tr>
<td>Atypical seizure type (%)</td>
<td>8 (16)</td>
<td>17 (15.9)</td>
</tr>
<tr>
<td>Partial seizure type (%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Generalized seizure type (%)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Event with other features such as respiratory symptoms or gastrointestinal symptoms, etc.

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Fig 1. A, Number of reports of hospitalizations for febrile seizures occurring within 72 hours of receipt of pertussis (P)-containing vaccine per month. B, Number of reports of hospitalizations for febrile seizures occurring between 5 and 30 days of receipt of an MMR vaccine. The horizontal lines indicate the mean number of reports in each time period 1995–1996 and 1998–2001. Note that in 1997, the number of reports per month is indicated by Xs; in all other years, the number of reports per month is indicated by circles.
cine decreased slightly from an average of 0.46 for 1995–1996 to an average of 0.19 for 1998–2001 (P = .053). The Poisson model did not show significant evidence of lack of fit (P = .89). None had documented viral infections. Two cases in the latter time period had other potential contributing factors (1 child had hypocalcemia and the other hypoxia). When these 2 cases are removed, the difference between the 2 time periods becomes slightly more marked with P = .026 with no evidence of lack of fit (P = .94).

Afebrile Seizures After Receipt of MMR Vaccine
There were 33 reports of hospitalization for afebrile seizures occurring 5 to 30 days after receipt of MMR vaccine. Of these, 24 (73%) children were between 12 and 24 months, 7 (21%) were between 4 and 6 years, 1 (3%) was 3.2 years, and 1 (3%) was 6.2 years.

The number of reports of afebrile seizures per month temporally associated with MMR vaccine decreased slightly from an average of 0.5 for 1995–1996 to an average of 0.35 for 1998–2001 (P = .39). The Poisson model did not show significant evidence of lack of fit (P = .39). Three children had coexistent viral infections.

HHEs After Receipt of Pertussis Vaccine
There were 68 reports of HHEs after pertussis vaccine. The median age of affected children was 0.2 years (range: 0–6.25 years). Thirty-five (51%) were female; 65 (95.6%) were previously healthy. Three had previous neurologic abnormalities consisting of hypotonia and developmental delay in 1 instance and a history of seizures in 2 others. Of 68 children with clinical HHEs, 40 (59%) were hospitalized. The interval to onset after vaccination was <2 hours in 13 (19.1%) reports, 2 to 12 hours in 43 (63.2%), 13 to 24 hours in 5 (7.4%), and 25 to 48 hours in 7 (10.3%). All recovered from the episode without apparent neurologic sequelae.

The average number of reports of HHEs per month decreased from 1.29 for 1995–1996 to 0.42 for 1998–2001 (P = .0012), a 67% decrease between periods (Fig 2). The Poisson model, however, showed evidence of lack of fit (P = .043), suggesting an unexplained heterogeneity among cases.

A possible explanation of the observed heterogeneity was the broad case definition. Of the 68 cases, 38 (55.9%) met all 3 clinical criteria (limpness or hypotonia, reduced responsiveness, and pallor or cyanosis) for definite HHE as outlined in a subsequent case definition.28 Restricting analysis to these cases, the Poisson model no longer showed significant evidence of lack of fit (P = .6). The average number of reports of definite HHE per month decreased from 0.67 for 1995–1996 to 0.27 for 1998–2001 (P = .018), a 60% decrease (Fig 2).

DISCUSSION
Using an established active surveillance system in Canada, we have documented a marked decline in hospitalizations for postimmunization febrile seizures and reports of HHEs after the abrupt switchover from one particular whole-cell pertussis-based to another particular acellular pertussis-based vaccine in 1997. The validity of the observation depends to a large extent on the consistency of surveillance and admission practices for such conditions. The IMPACT surveillance project meets such a requirement.25,26 At each center, a well-trained nurse monitor actively searched for HHE cases and reviewed every nonelective admission for seizures for recent immunization. Although the nurse monitors were not blinded as to the vaccine or time period, all hospitalized cases of seizures and potential HHEs were investigated to determine any receipt of vaccine. Consistent case-finding methods and case definitions were used throughout the study. The addition of a new site in 1999 added only 1 case of febrile seizure after MMR vaccine.

We included only children who were hospitalized
for their seizure. We did not capture the children who had seizures that were brief and single; however, this would have applied equally to both periods. Admission criteria for children younger than 2 years have not changed appreciably from 1995 to 2001. Hospital admissions for febrile and afebrile seizures since the early 1990s were based on whether the seizure was prolonged (>30 minutes), frequent, or recurrent. Younger children (<12 months) were usually admitted for any seizure because the peak age for febrile seizures is 14 to 18 months of age. Children 12 to 24 months of age were admitted depending on clinical judgment and the concern of parents. Admissions for seizures over the time period have changed most appreciably for children older than 2 years in whom investigations are increasingly performed as outpatients. Only a minority (13) of our patients were older than 2 years. In 1996, second doses of MMR vaccine were instituted for children aged 4 to 6 years in 8 provinces and children older than 18 months in 2, but there was no change in MMR vaccination policy for younger infants. These factors permitted us to use admissions for seizures associated with MMR as a comparison group.

As to whether more aggressive fever management practices could have accounted for the decrease in the second time period, we do not believe that this had a significant impact. The immunization guidelines in Canada published in 1993 recommended prophylactic acetaminophen for children receiving pertussis vaccine. This recommendation, however, was dropped in the 1998 version except for children who were at high risk for seizures. As a result, we suspect that fewer children were given acetaminophen in the latter time period compared with the former.

Admissions for afebrile seizures within 72 hours of immunization with pertussis vaccine declined slightly ($P = .05$), whereas afebrile seizures temporarily associated with MMR vaccine did not decline between study periods. It is possible that the risk for afebrile seizures actually is lower after acellular vaccine compared with whole-cell pertussis. Even a small decrease in risk could become manifest in a large population under postmarketing surveillance conditions. As well, in the afebrile group, there may have been children with transient or minor increases in temperature of $<38.5°C$ that were not recognized. A higher proportion of children with afebrile seizures had had previous afebrile seizures (29%–36%) compared with children in the febrile seizure group (4%–8%). This suggests that children with underlying neurologic or seizure disorders likely had decreased seizure thresholds, resulting in seizures without reaching a temperature of $>38.5°C$. Thus, acellular vaccine that produces less fever would potentially also cause fewer afebrile seizures in the population of predisposed individuals. It is also possible that improved seizure prevention in children who had underlying neurologic disorders could have contributed to the small decrease. Hospitalization rates for afebrile seizures, however, could not be calculated because hospital databases at most centers were not adequate for this purpose.

This surveillance data represents approximately 25% of the Canadian population of children between the ages of 0 and 12 years (D. Scheifele, personal communication). On the basis of the referral population data available for the 12 IMPACT centers in 2001, an estimated 2.2 million doses of acellular pertussis vaccine were given to children younger than 6 years during the 4 years studied. During this time, only 12 febrile seizure admissions followed its administration, giving an estimated rate of hospitalization for febrile seizure within 72 hours of acellular pertussis vaccine of 0.5 per 100 000 doses. Although all instances of febrile seizure were not accounted for, the low ratio between admitted cases and doses administered speaks to the infrequency of the adverse event. A recent postmarketing study estimated the rate of hospitalization for febrile seizures after another acellular pertussis vaccine to be 1 per 19 496 (5.1 per 100 000) children younger than 2 years. A postmarketing survey based on the VAERS in the United States also documented a decrease in the reporting rate of seizures from 1.7 per 100 000 doses of diphtheria-tetanus-pertussis to 0.5 per 100 000 doses of diphtheria-tetanus-acellular pertussis in children aged 15 months to 7 years who had received the acellular vaccine as their fourth and fifth doses. This suggested a 71% decrease in reports of seizures associated with the use of diphtheria-tetanus-acellular pertussis compared with whole-cell vaccine in an older group of children, a decline consistent with the present study.

Although the case definition stipulated that cases with an “obvious alternate cause” were noneligible, we included children who had concurrent identification of common viral infections, which may have contributed to the seizure. The rigor with which these viral infections are sought differs by center; however, this imprecision applied to both phases of the study.

This study also demonstrated a significant decrease (60%–67%) in HHEs after the switch to acellular pertussis-based vaccine. Vigilance in the outpatient areas may have been less rigorous particularly in the later years when fewer cases were noted. This may have introduced some bias in the later time period for nonhospitalized cases only. The decrease in reports that we noted is consistent with previously reported decreases in reports from the VAERS in the United States since 1998 related to the switch from whole-cell to acellular pertussis vaccines. Diagnosis of such episodes is difficult because most episodes are brief and observed only by parents, whose ability to appreciate and describe multiple symptoms varies considerably. Similar “spells” can result from fainting, seizures, breath-holding, aspiration, anaphylaxis, and variations on sleep. Each of the 3 cardinal signs (limpness, unresponsiveness, and pallor) involves subjective judgments, often made in suboptimal conditions of lighting, undress, and parental state of mind. No efficient illness classification code is available for HHE, so ascertainment of admitted and nonadmitted cases may have been incomplete despite the best efforts of monitors. We chose to accept reports of possible as well as definite cases,
based on the clinical criteria, and analyzed all cases as well as only the definite ones. A total of 68 reports were available, but only 38 met the case definition in full.28 The observed decline was similar in both instances (67% and 60%, respectively), but the findings are likely more robust with “true” cases.

Our results are specific for the combination pertussis-containing vaccine used in Canada and may not necessarily apply to all combination pertussis vaccines. These findings, however, illustrate the value of active surveillance programs in monitoring trends in rare vaccine-associated adverse events. The results should encourage health care workers to continue to advocate immunization against vaccine-preventable diseases and provide reassurance to parents that acellular pertussis vaccines represent a substantial improvement in vaccine safety.

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