ORIGINAL ARTICLE

Burden of Children Hospitalized With Pertussis in Canada in the Acellular Pertussis Vaccine Era, 1999–2015

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Background. Recent increases in pertussis morbidity and mortality rates among young infants have led to a recommendation in some countries for vaccination against pertussis during pregnancy. Having data on the burden of pediatric pertussis in a large population over time is important for establishing the true burden of disease in the acellular pertussis (aP) vaccine era. Here, we describe age-specific epidemiology and morbidity and mortality rates in children hospitalized with pertussis over 17 years across Canada in the aP vaccine era.

Methods. Patients aged ≤16 years who were admitted to 1 of 12 pediatric tertiary-care hospitals across Canada between 1999 and 2015 with confirmed (laboratory-confirmed or epidemiologically linked) or probable (clinically diagnosed) pertussis were included.

Results. Overall, 1402 patients with pertussis were included. Infants aged <2 months had the highest mean annual incidences of pertussis hospitalization and intensive care unit (ICU) admission (116.40 [95% confidence interval (CI), 85.32–147.49] and 33.48 [95% CI, 26.35–40.62] per 100 000 population, respectively). The overall proportion of children who required ICU admission was 25.46%, and the proportion was highest in infants aged <2 months (37.90%). Over the span of this study, 21 deaths occurred. Age of <16 weeks, prematurity, encephalopathy, and a confirmed pertussis diagnosis were independent risk factors for ICU admission. Age of <4 weeks, prematurity, and female sex were independent risk factors for death.

Conclusions. In the aP vaccine era, endemic pertussis still contributes considerably to childhood morbidity and death, particularly in infants aged <2 months. Vaccination against pertussis during pregnancy has the potential to reduce this disease burden.

Keywords. *Bordetella pertussis*; infant pertussis; whooping cough; vaccination in pregnancy.

Pertussis remains a major global public health concern, with a global estimate of 24.1 million cases of and 160 700 deaths caused by pertussis in children aged <5 years in 2014 [1]. Most industrialized countries use diphtheria-tetanus-acellular pertussis vaccines for primary and/or booster immunization against pertussis [2, 3]. Despite the high rate of vaccination coverage with acellular pertussis (aP) vaccine, pertussis outbreaks that result in substantial morbidity and death continue to occur [4, 5].

Previous reports on the burden of pertussis disease in the aP vaccine era described incidence rates and clinical outcomes in small populations, a single center, a single region, a specific epidemic period, or another limited time period or years during which both whole-cell pertussis (wP) and aP vaccines were used [4, 6–11]. Moreover, estimates of the burden of severe pertussis disease that requires intensive care unit (ICU) admission were made from studies that spanned over a limited time period [10, 12]. Having data on the burden of pediatric pertussis from a large population over time is important for establishing the true burden of disease in the aP vaccine era, not only in an epidemic or outbreak setting but also to inform cost-effectiveness analyses of different immunization strategies. This data is especially important, because several countries have recommended universal vaccination against pertussis during pregnancy in response to a recent rise in pertussis morbidity and mortality rates among young infants [13–15].

Between 1997 and 1998, all Canadian provinces and territories changed from wP to the aP vaccine, given at 2, 4, 6, and 18 months and 4 to 6 years of age [16]. The burden of pertussis disease among children in Canada during the wP and wP–aP vaccine transition periods has been described [16, 17]. In this study, we report the age-specific epidemiology and morbidity

and mortality rates in children hospitalized with pertussis disease in Canada in the aP vaccine era. We also identify risk factors associated with poor outcomes (morbidity and death) among pediatric patients hospitalized with pertussis.

METHODS

Study Locations
Patients with pertussis who were admitted to a hospital that is part of the Immunization Monitoring Program, Active (IMPACT) were included. IMPACT is an active surveillance network that has collected data from 12 pediatric tertiary-care hospitals across Canada since 1991 and accounts for approximately 90% of the pediatric tertiary-care beds in the country [16].

Study Subjects
Patients aged ≤16 years with pertussis who were admitted to an IMPACT hospital between January 1, 1999, and December 31, 2015 were included. A clinical case of pertussis was defined as a cough illness that lasted for ≥2 weeks with paroxysmal coughing. Posttussive vomiting, whoop, cyanosis during coughing, or apnea episodes were supportive evidence of a pertussis case. Consistent with the Canadian national pertussis case definitions [18], confirmed cases were laboratory confirmed (at least 1 positive microbiological test result for *Bordetella pertussis* [from culture, polymerase chain reaction, direct fluorescent assay, or serology]) or epidemiologically linked (ie, the patient met our clinical case definition and had contact with another patient with laboratory-confirmed pertussis). A probable case was defined as illness that met the clinical case definition but none of the confirmed-case criteria. Compatible illnesses shown to be attributable to another cause were excluded, but coinfections with *B pertussis* or another *Bordetella* species were included. Cases confirmed to be caused only by *Bordetella* species other than *B pertussis* were not included.

Data Collection and Management
Standardized case-report forms were used at all IMPACT hospitals. Pertussis cases were identified via microbiology laboratories, ward and ICU admission lists, infection-control practitioners, and/or a search of hospital records for International Classification of Diseases, Ninth or Tenth Revision, discharge codes that included terms for pertussis. Clinical data were collected from patient health records. Prematurity was defined as birth before 37 weeks' gestation. Encephalopathy was defined as a decreased level of consciousness not associated with the postictal period. For each patient admitted with pertussis, vaccination records in the hospital record were reviewed. Data in the hospital records were confirmed from the relevant vaccine provider (public health or family physician), which varied according to region. When a discrepancy was found, the vaccine provider's record was considered accurate. All data were reviewed at the IMPACT data center in Vancouver before being entered into an electronic database by using a dual-entry system with preprogrammed consistency checks.

Pertussis Vaccination Status
A valid vaccine dose was considered any dose administered ≥28 days before hospital admission with pertussis, and this information was used to classify children aged ≥3 months with laboratory-confirmed pertussis disease (see Supplementary Table 1).

Statistical Analysis
We used Pearson's χ^2 test to compare categorical variables, the Student t test for normally distributed continuous variables, and the Mann Whitney U test for nonnormally distributed continuous variables.

Annual age-specific pertussis hospitalization incidences were calculated using population estimates of each study hospital's catchment area obtained from the 2006 Canadian census [19]. Each IMPACT hospital defined its estimated local population catchment area. Pertussis cases from the IMPACT hospital were matched to this catchment area using the first 3 characters of the postal code. The first 3 characters of the postal code form the forward sortation area, which represents a specific area within a major geographic region or province. Cases from outside the hospital catchment areas and 1 hospital with a large referral population and an undefined catchment area (The Hospital for Sick Children, Toronto) were not included in these hospitalization incidence calculations (Supplementary Table 2). Annual age-specific pertussis ICU admission incidences were calculated using relevant provincial population estimates obtained from the 2006 Canadian census [19]. Outside the province of Ontario, IMPACT hospitals are the only pediatric centers that admit to an ICU. Age-specific population estimates of the study population areas included the respective province. Patients with pertussis admitted to an IMPACT hospital ICU were matched to their respective province. Case-patients who were admitted to an IMPACT hospital ICU but resided in the Canadian territories were excluded from the ICU incidence analysis. Ontario also was excluded from the ICU incidence analysis, because patients also might have been admitted to another ICU not included in the IMPACT network (Supplementary Table 2). The overall mean annual pertussis hospitalization and ICU admission incidence rates and their 95% confidence intervals (CIs) were calculated for the 17-year period using the annual hospitalization and ICU admission incidence rates, respectively.

The variability of the median hospital lengths of stay (LOS), the proportion of children who required ICU admission during the study period, and the proportions of children who required ICU admission according to their gestational age at birth were analyzed using the Kruskal-Wallis test and the χ^2 test for trend for continuous and categorical variables, respectively.

Univariate logistic regression analysis was used to identify risk factors for ICU admission and death. To identify the most

Table 1. Characteristics of Patients with Pertussis Admitted to IMPACT Hospitals in Canada, 1999–2015

Characteristic	Pertussis Cases			
	All (n = 1402)[a]	Confirmed (n = 1157)[b]	Probable (n = 245)[c]	P[d]
Demographics				
Sex, male (n [% of total])	655 (46.71)	525 (45.37)	130 (53.06)	.0340
Age (median [overall range (IQR)]) (wk)	10 (1–886 [6–17])	9 (1–884 [6–16])	11 (1–886 [7–22])	.0027
Age group (n [% of total])				
<1 year	1265 (90.23)	1056 (91.27)	209 (85.30)	
0–1 mo	612 (43.65)	523 (45.20)	89 (36.32)	
2–3 mo	460 (32.81)	381 (32.92)	79 (32.24)	
4–5 mo	119 (8.48)	91 (7.86)	28 (11.42)	
6–11 mo	74 (5.27)	61 (5.27)	13 (5.30)	
1–4 years	72 (5.14)	53 (4.58)	19 (7.75)	
5–9 years	24 (1.71)	15 (1.29)	9 (3.67)	
10–16 years	41 (2.92)	33 (2.85)	8 (3.26)	
Clinical features				
Comorbidity (n [% of total])[e]				
Underlying condition(s)	178 (12.69)	152 (13.13)	26 (10.61)	.5002
Prematurity[f]	50 (3.56)	44 (3.80)	6 (2.44)	
Pulmonary	31 (2.21)	23 (1.98)	8 (3.26)	
Neurologic	27 (1.92)	24 (2.07)	3 (1.22)	
Congenital cardiac	23 (1.64)	20 (1.72)	3 (1.22)	
Gastrointestinal	20 (1.42)	16 (1.38)	4 (1.63)	
Genetic-metabolic	13 (0.92)	10 (0.86)	3 (1.22)	
Failure to thrive	12 (0.85)	11 (0.95)	1 (0.40)	
Immunocompromised	10 (0.71)	10 (0.86)	0 (0.00)	
Other	34 (2.42)	30 (2.59)	4 (1.63)	
Seizures (n [% of total])				.1204
New seizures	30 (2.13)	28 (2.42)	2 (0.81)	
Exacerbation of an existing seizure disorder	8 (0.57)	8 (0.69)	0 (0.00)	
Encephalopathy (n [% of total])	8[g] (0.57)	8 (0.69)	0 (0.00)	.3443
Outcome				
Hospitalization				
Median (overall range [IQR]) (days)	7 (1–185 [3–13])	8 (1–185 [4–14])	4 (1–45 [2–7])	<.0001
Age-specific median LOS (overall range [IQR]) (days)				
<1 year	8 (1–185 [3–14])	9 (1–185 [4–15])	4 (1–45 [2–8])	<.0001
0–1 mo	10 (1–87 [5–16])	11 (1–87 [6–17])	5 (1–45 [2–9])	<.0001
2–3 mo	6 (1–185 [3–12])	7 (1–185 [3–12])	4 (1–37 [2–9])	.0003
4–5 mo	4 (1–59 [2–8])	5 (1–59 [3–9.50])	3 (1–15 [2–4])	.0002
6–11 mo	4 (1–38 [2–9.75])	4 (1–38 [2–10])	3 (1–8 [2–5])	.0507
1–4 years	3 (1–60 [1–5])	3 (1–60 [2–5])	2 (1–13 [1–4.50])	.2307
5–9 years	2 (1–8 [1–5])	2 (1–68 [1–4.5])	3 (1–5 [2–5])	.5019
10–16 years	3 (1–14 [1–5])	1 (1–14 [2–5])	1 (1–5 [1–5])	.1244
ICU admission (n [% of total])	357 (25.46)	316 (27.31)	41 (16.73)	.0007
Median ICU LOS (overall range [IQR]) (days)	4 (1–79 [2–9])	5 (1–79 [2–10])	3 (1–23 [2–7])	.0268
Age-specific median ICU LOS (overall range [IQR]) (days)				
<1 year	5 (1–79 [2-10])	5 (1–79 [2.5-10])	3 (1–23 [2–7])	.0333
0–1 mo	5 (1–79 [3–9])	5 (1–79 [3-9.75])	3 (1–23 [2–6])	.0314
2–3 mo	4 (1–62 [2–10])	4 (1–62 [2-9])	3 (1–13 [3–11])	.8883
4–5 mo	7 (1–42 [2–12])	7 (1–42 [2.50-12.25])	7 (1–8 [4–7.50])	.5595
6–11 mo	2.5 (1–16 [1.75–9])	5 (1–16 [2.25–13])	1.5 (1–2 [1.25–1.75])	.2377
1–4 years	2 (1–29 [1–4])	2.5 (1–29 [1.75–5.25])	1 (1–1 [1–1])	.3226
Death (n [% of total])	21 (1.49)	21 (1.81)	0 (0.00)	.0664

Abbreviations: IMPACT, Canadian Immunization Monitoring Program, Active; IQR, interquartile range; LOS, length of stay.
[a]Includes confirmed and probable pertussis cases.
[b]Laboratory-confirmed (n = 1145) or epidemiologically linked (n = 12) pertussis cases.
[c]Clinical pertussis cases.
[d]For the comparison of confirmed versus probable pertussis cases.
[e]As clinically denoted in the records; patients could have >1 comorbidity.
[f]Prematurity was defined as birth at <37 weeks' gestation.
[g]Five case-patients had both new seizures and encephalopathy.
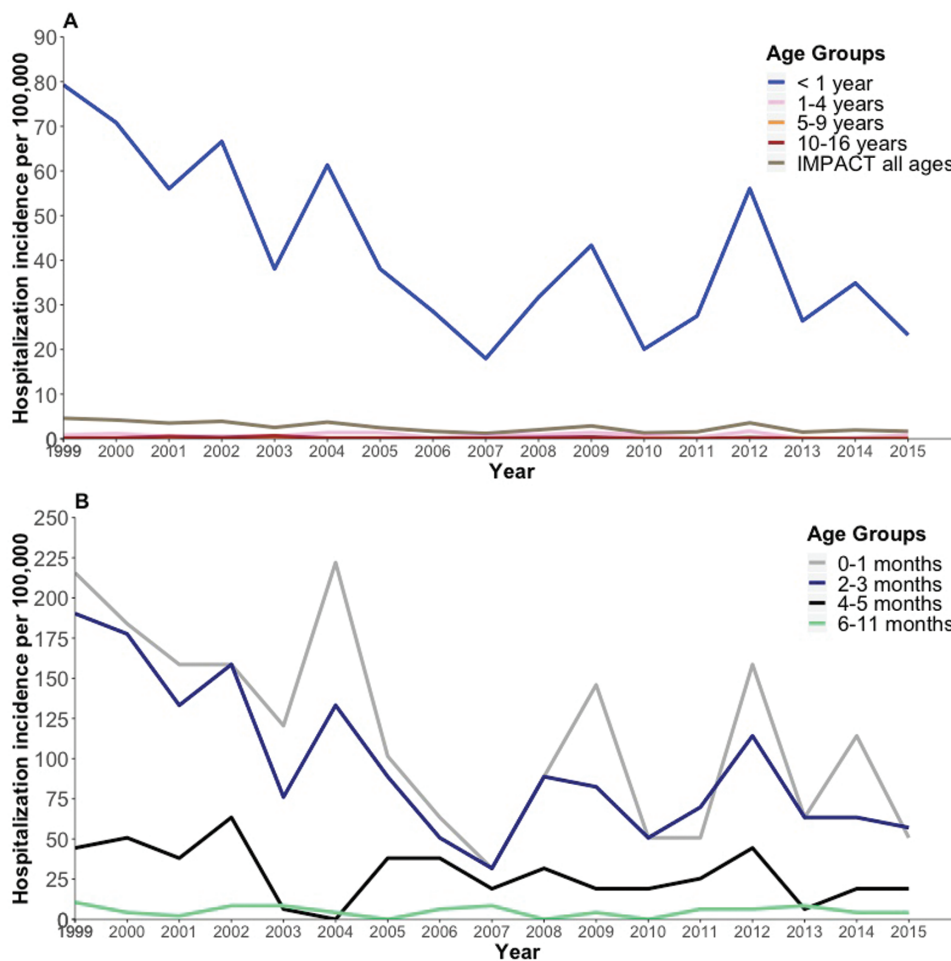
Figure 1. Hospitalization incidences among case-patients with pertussis at Canadian Immunization Monitoring Program, Active (IMPACT) hospitals, 1999–2015. Shown are age-specific population-based pertussis hospitalization incidences in children aged ≤16 years (A) and children aged <1 year (B).

appropriate age cutoff as a risk factor for ICU admission and death, we generated regression models using all ages between 0 and 16 years in 1-week intervals. The model with the lowest Akaike information criterion (AIC) was used as the final model. Forward stepwise multivariable logistic regression models were developed to identify independent risk factors for ICU admission and death. These models included all variables identified in the univariate regression model with a *P* value of ≤.25 and the age cutoff with the lowest AIC. Variables with a *P* value of <.05 were retained in the final model. All *P* values of <.05 were considered statistically significant for all tests. R 3.4.0 (R Project, Vienna, Austria) was used for all analyses.

RESULTS

Study Population

Overall, we included 1402 children, 1157 (82.52%) of whom had a confirmed case of pertussis (1145 [81.67%] laboratory confirmed, 12 [0.85%] epidemiologically linked) and 245 (17.48%) of whom had a probable case. The majority (810 [70.74%] of

1145) of laboratory-confirmed cases were diagnosed by polymerase chain reaction alone (Supplementary Figure 1). Patients with a confirmed case of pertussis were significantly

Table 2. Mean Annual Pertussis Hospitalization and Intensive-Care Unit Admission Incidence at IMPACT According to Age Groups, 1999-2015

Age	Hospitalization Incidence (per 100 000 population [(95% CI)][a]	ICU Admission Incidence (per 100 000 population [(95% CI)][b]
<1 year	42.34 (32.53–52.15)	8.64 (6.96–10.31)
<2 mo	116.40 (85.32–147.49)	33.48 (26.35–40.62)
2–3 mo	95.88 (71.56–120.20)	14.58 (10.55–18.61)
4–5 mo	28.35 (19.49–37.22)	2.52 (1.13–3.90)
6–11 mo	5.09 (3.42–6.77)	0.42 (0.15–0.68)
1–4 years	0.81 (0.56–1.05)	0.06 (0.02–0.09)
5–9 years	0.16 (0.10–0.22)	0.005 (0–0.017)
10–16 years	0.19 (0.09–0.29)	0.004 (0–0.012)
All age groups	2.61 (2.03–3.18)	0.50 (0.40–0.60)

Abbreviations: CI, confidence interval; IMPACT, Canadian Immunization Monitoring Program, Active.
[a]The analysis included 11 of 12 IMPACT hospitals (excluding The Hospital for Sick Children, Toronto)
[b]The analysis included 10 of 12 IMPACT hospitals and their 7 respective provinces, excluding 2 hospitals from the province of Ontario (The Hospital for Sick Children and Children's Hospital of Eastern Ontario [Ottawa]).

younger, had longer hospital and ICU LOS, and were more likely to be admitted to the ICU than those who had a probable case (Table 1). The median hospital LOS among infants aged <6 months was 8 days (Table 1). We found significant year-to-year variation in the median hospital LOS (range, 4–10 days) over the study period (*P* = .0016).

Incidence of Pertussis Hospitalization

In total, 747 (58.81%) of 1270 pertussis cases occurred in the defined catchment areas for the study hospitals and were included in the hospitalization incidence calculations (Figure 1). The case-patients used for the hospitalization incidence analysis had similar baseline characteristics (age, sex, and comorbidities) as those not included in this analysis (data not shown). The overall mean annual pertussis hospitalization incidence was highest among infants aged <2 months (Table 2). Pertussis hospitalization incidence rates in young infants fluctuated over time, and peaks occurred every 2 to 5 years (Figure 1B).

ICU Admission

In total, 357 (25.46%) of the 1402 children were admitted to an ICU. We found significant year-to-year variation between years in the proportions of children admitted to an ICU over the 17 years (from 14.03% to 41.66%; *P* < .0001). Of the case-patients admitted to the ICU, 316 (88.51%) of 357 had a confirmed pertussis case. Case-patients who required admission to the ICU were younger, had a higher rate of neurological complications, had longer hospital LOS, and were more likely to have a comorbidity than those who were not admitted to an ICU (Table 3). The proportion of case-patients admitted to an ICU was 37.90% (232 of 612) for infants aged <2 months, 19.78% (91 of 460) for those aged 2 to 3 months, 12.60% (15 of 119) for those aged 4 to 5 months, 10.81% (8 of 74) for those aged 6 to 11 months, and 27.35% (346 of 1265) for those aged <1 year. The proportion of case-patients admitted to an ICU decreased as gestational age at birth increased (*P* < .0001) (Supplementary Figure 2). With the exception of 2007, the proportion of children admitted to an ICU was higher for infants aged <2 months than for those aged 2 to 3 months (Figure 2A).

In total, 298 (83.47%) of 357 case-patients with pertussis who were admitted to the ICU were from provinces in which almost all ICU admissions are captured by IMPACT hospitals (excluding Ontario and the Canadian territories) and were included in the ICU incidence calculations. The overall mean annual incidence of ICU admission over the 17-year period was highest among infants <2 months of age (Table 2). With the exception of 2006, the incidence of ICU admission was higher for case-patients aged <2 months than for those aged 2 to 3 months; a peak occurred in 2004, 2009, and 2012 (Figure 2B).

Death

Twenty-one children (aged 2 to 14 weeks at admission) died during the study period (Table 4). None of the infants who

Table 3. Characteristics of Patients with Pertussis Admitted to IMPACT Hospitals ICU in Canada, 1999–2015

Characteristic	Admitted to the ICU (n = 357)	Not Admitted to the ICU (n = 1045)	*P*[a]
Demographics			
Sex, male (n [% of total])	171 (47.89)	484 (46.31)	.6482
Age (median [overall range (IQR)]) (wk)	7 (2–872 [4–10])	11 (1–886 [7–19])	<.0001
Age groups (n [% of total])			
<1 year	346 (96.91)	919 (87.94)	
0–1 mo	232 (64.98)	380 (36.36)	
2–3 mo	91 (25.49)	369 (35.31)	
4–5 mo	15 (4.20)	104 (9.95)	
6–11 mo	8 (2.24)	66 (6.31)	
1–4 years	9 (2.52)	63 (6.02)	
5–9 years	1 (0.28)	23 (2.20)	
10–16 years	1 (0.28)	40 (3.82)	
Clinical features			
Comorbidity (n [% of total])[b]			
Underlying conditions (n [% of total])	61 (17.08)	117 (11.19)	.0133
Prematurity[c]	30 (8.40)[d]	20 (1.91)[e]	<.0001
Congenital cardiac	8 (2.24)	10 (0.95)	
Pulmonary	3 (0.84)	24 (2.29)	
Genetic-metabolic	3 (0.84)	5 (0.47)	
Gastrointestinal	3 (0.84)	8 (0.76)	
Failure to thrive	2 (0.56)	5 (0.47)	
Neurologic	1 (0.28)	14 (1.33)	
Immunocompromised	0 (0.00)	9 (0.86)	
Other	11 (3.08)	22 (2.10)	
Evidence of diagnosis (n [% of total])			.0007
Confirmed[f]	316 (88.51)	841 (80.47)	
Probable[g]	41 (11.48)	204 (19.52)	
Seizures (n [% of total])			<.0001
New seizures	17 (4.76)	13 (1.24)	
Exacerbation of an existing seizure disorder	4 (1.12)	4 (0.38)	
Encephalopathy (n [% of total])	6 (1.68)	2 (0.19)	.0046
Outcome			
Hospitalization			
Median LOS (overall range [IQR]) (days)	13 (1–185 [7–22])	5 (1–60 [3–10])	<.0001
Death (n [% of total])	21 (5.88)	0 (0.00)	<.0001

Abbreviations: ICU, intensive care unit; IQR, interquartile range; IMPACT, Canadian Immunization Monitoring Program, Active; LOS, length of stay.

[a]For the comparison of case-patients admitted to an ICU versus those not admitted to an ICU.

[b]As clinically denoted in the records; patients could have >1 comorbidity.

[c]Prematurity was defined as birth at <37 weeks' gestation.

[d]Data on gestational age at birth were available for 28 of 30 prematurely born case-patients admitted to the ICU; 5 were born at 24 to 26 weeks' gestation, 7 were born at 27 to 31 weeks' gestation, and 16 were born at 32 to 36 weeks' gestation.

[e]Data on gestational age at birth were available for 19 of 20 prematurely born case-patients not admitted to the ICU; 1 was born at 25 weeks' gestation, 4 were born at 27 to 31 weeks' gestation, and 14 were born at 32 to 36 weeks' gestation.

[f]Laboratory-confirmed or epidemiology linked pertussis cases.

[g]Clinical pertussis cases.

died had received a valid dose of vaccine, although 17 of these infants were aged <3 months and therefore were too young to have received a valid pertussis vaccine dose. Death occurred 1 to 47 days after admission; 61.90% (13 of 21) of these children died within the first 3 days after admission (Supplementary Figure 3). The overall case-fatality rate (CFR) was 1.49% (21 of 1402). The CFRs for infants aged <2 months, those aged 2 to
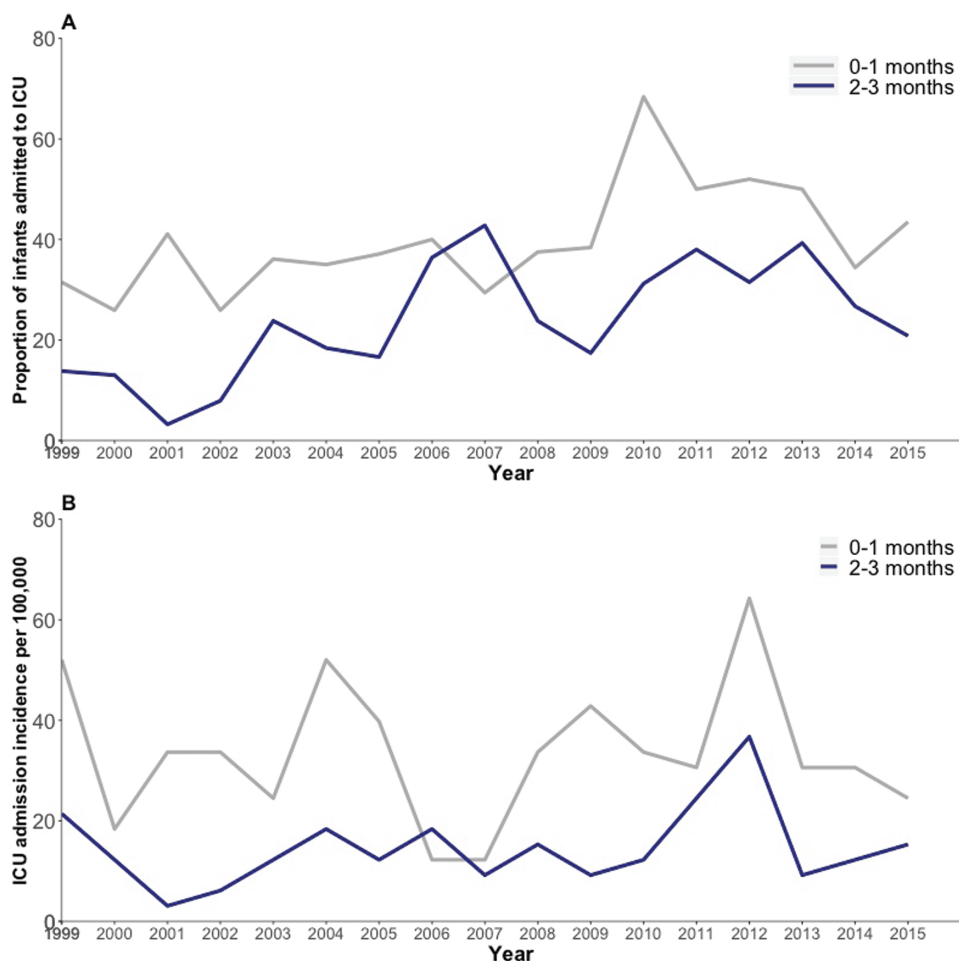
Figure 2. Intensive care unit (ICU) admission rates and admission incidences at Canadian Immunization Monitoring Program, Active (IMPACT) hospitals, 1999–2015. Shown are age-specific (<4 months) population-based ICU admission incidences (per 100 000 population) (A) and ICU admission rates (percentages) (B) among infants hospitalized with pertussis in IMPACT hospitals, 1999–2015. The small numbers of patients older than 4 months who were admitted to an ICU precluded description of the incidence rates here.

3 months, and those aged <1 year were 2.28% (14 of 612), 1.52% (7 of 460), and 1.66% (21 of 1265), respectively.

Risk Factors for Admission to ICU and Death

Independent risk factors for ICU admission were age of <16 weeks, prematurity, encephalopathy, confirmed pertussis diagnosis, and a more recent year of admission (Table 5). Independent risk factors for death were age of <4 weeks, prematurity, female sex, and a more recent year of admission (Table 5).

Vaccination Status of Case-Patients With Laboratory-Confirmed Pertussis

Among hospitalized patients aged 3 months to 16 years with laboratory-confirmed pertussis (n = 355), 31.83% (113 of 355) had received an age-appropriate number of pertussis vaccine doses, and 51.54% (183 of 355) were unvaccinated (Supplementary Figure 4 and Supplementary Results).

DISCUSSION

In this study, infants aged <2 months had the highest hospitalization incidence rate and were the major contributor to the burden of children hospitalized with pertussis disease. Almost 25% of all case-patients were admitted to an ICU, and the majority of these admissions were of infants aged <2 months. Age of <16 weeks was independently associated with a 5-fold increase in the risk for ICU admission over that in older children. Encephalopathy, prematurity, and confirmed pertussis diagnosis were independently associated with 21-fold, 6-fold, and 1.5-fold increased risk for ICU admission, respectively. Age of <4 weeks was the most significant independent risk factor for death; this age was associated with a 7-fold increased risk for death over that of older children. Prematurity and female sex were significantly associated with increased risk for death (5-fold and 3.5-fold increase, respectively). Our data have important implications in establishing the true burden

Table 4. Characteristics of Patients with Fatalities From Pertussis at IMPACT Hospitals, 1999–2015

Characteristic	Deaths (n = 21)	No Deaths (n = 1381)	P
Sex, male (n [% of total])	4 (19.04)	651 (47.13)	.0192
Age			
Median (overall range [IQR]) (wk)	5 (2–14 [3–9])	10 (1–886 [6 minus]17])	<.0001
Age groups (n [% of total])			
<1 year	21 (100)	1244 (90.07)	
0–1 mo	14 (66.66)	598 (43.30)	
2–3 mo	7 (33.33)	453 (32.80)	
4–5 mo	0 (0.00)	119 (8.61)	
6–11 mo	0 (0.00)	74 (5.35)	
1–4 years	0 (0.00)	72 (5.21)	
5–9 years	0 (0.00)	24 (1.73)	
10–16 years	0 (0.00)	41 (2.96)	
Evidence of diagnosis			.0569
Confirmed	21 (100)	1124 (81.39)	
Probable	0 (0.00)	257 (18.60)	
Morbidity			
Seizures (n [% of total])			.665
No seizures	20 (95.23)	1344 (97.32)	
New seizures	1 (4.76)	29 (2.09)	
Exacerbation of an existing seizure disorder	0 (0.00)	8 (0.57)	
Encephalopathy (n [% of total])[a]			<.0001
Not present	19 (90.47)	1373 (99.42)	
Present	0 (0.00)	8 (0.57)	
Hospitalization			
Median LOS (overall range [IQR]) (days)	3 (1–79 [2–14])	7 (1 185 [2–14])	.0501
Comorbidity (n [% of total])[b]			
Underlying conditions	5 (23.80)	173 (12.52)	.3031
Prematurity[c]	4 (19.04)	46 (3.33)	.0011

Abbreviations: IMPACT, Canadian Immunization Monitoring Program, Active; IQR, interquartile range; LOS, length of stay.

[a]Two cases of fatality with no data on encephalopathy.

[b]As clinically denoted in the records; patients could have >1 comorbidity.

[c]Prematurity was defined as birth at <37 weeks' gestation. One case-patient was born at 29 weeks' gestation, 2 were born at 34 weeks' gestation, and 1 was born at 35 weeks' gestation.

of endemic pertussis disease and thus can assist public health policy makers in reaching evidence-based conclusions regarding the optimal cost-effective preventive approach. The identification of risk factors for poor outcome aids appropriate prioritization in management of young infants with pertussis and counseling for families during hospitalization.

In our study, the majority of children hospitalized with pertussis were <4 months old, which is consistent with previous data from Canada, the United States, and Australia in the aP vaccine era [4, 5, 7, 16]. Although almost 21% of global pertussis cases occur in infants aged <1 year [1], 90% of hospitalized patients with pertussis in the aP era and 92% of hospitalized patients with pertussis in the wP vaccine era in Canada were in this age group [17]. In addition, 85% of hospitalized patients with pertussis in this study and 79.1% of hospitalized patients with pertussis in the wP vaccine era in Canada were infants aged <6 months, which emphasizes the point that young infants are at a disproportionately high risk for severe pertussis. The

incidence of hospitalization for pertussis among infants aged <2 months (116.40 of 100 000) was lower than that reported in the wP vaccine era in England from 1995 to 1997 (164 of 100 000 among infants aged <3 months) [20] and in Australia 4 years after the introduction of aP vaccine (~200 of 100 000 among infants aged <2 months) [7]. Thus, although the incidence of pertussis that requires hospitalization among infants aged <2 months in the aP era is lower than that in the wP era, this age group accounts for a high proportion of pertussis-related hospital admissions. In addition, the incidence of hospitalization for pertussis among infants <1 year of age (42.3 of 100 000) is lower than that reported in the wP vaccine era in Canada (136 of 100 000) [16].

Children with pertussis had a median LOS of 7 days, which is notably higher than the median LOS of 4 days among patients hospitalized with pertussis (median age, 2.6 months) reported during the 2010 California pertussis epidemic [5]. This difference might stem from the fact that IMPACT hospitals are pediatric tertiary-care centers that admit children with more severe cases of pertussis. Moreover, the median LOS of 8 days among infants aged <6 months in this study is comparable to the median LOS of 9.3 days among infants aged <6 months with pertussis who were admitted to an IMPACT center during the wP era, and both studies used the same clinical case definition of pertussis [17]. In this study, 77.2% of patients aged 7 to 18 months had received fewer than 3 vaccine doses, whereas 44.9% of the patients aged 6 to 24 months who were admitted to an IMPACT center with pertussis during the wP era received fewer than 3 vaccine doses. This result emphasizes the fact that in the aP era, undervaccination is an important contributor to hospitalization for pertussis. Neurological manifestations (new-onset seizures and/or encephalopathy) were observed in 2.6% of patients admitted with pertussis, consistent with data from IMPACT centers in the wP era (2.4% among patients aged <2 years). Moreover, the CFR for all age groups in this study was 1.5% (2.3% for infants aged <2 months), which is higher than the CFR reported in Canada in the wP era (0.9% among patients aged <2 years). In our study, two-thirds of deaths were among infants aged <2 months, which is comparable with the data from IMPACT centers during the wP era, in which 80% of deaths that resulted from pertussis were among infants aged <2 months.

In our study, patients hospitalized with pertussis had frequent ICU admissions, and the highest proportion was among infants aged <2 months. The proportion of ICU admissions among infants aged <1 year was comparable to that reported for an epidemic in California (33% among hospitalized infants aged <1 year) [6] and higher than the rate reported during the wP era in Canada (16% among children aged <2 years and 19.2% among infants aged <6 months) [17]. In addition, the median ICU LOS found in our study (4 days) was comparable to that in reports from Australia and New Zealand (3.6 and 3.9 days, respectively) [21, 22].

Table 5. Risk Factors for Admission to ICU and Death in Patients With Pertussis (n = 1392)

Variable (N)	Univariate Analysis		Multivariable Analysis[a]	
	P	OR (95% CI)	*P*	aOR (95% CI)
Risk factors for admission to intensive care unit				
Age				
≥16 wk (380)	<.0001	Reference	<.0001	Reference
<16 wk (1012)		4.47 (3.12–6.59)		4.83 (3.30–7.27)
Sex				
Male (648)	.569	Reference		Not included
Female (744)		0.93 (0.3–1.18)		
Seizures				
No new seizures (1363)	.0004	Reference		Not included
New seizures (29)		3.77 (1.80–8.06)		
Encephalopathy				
No (1385)	.0074	Reference	.0073	Reference
Yes (7)		18.08 (3.07–342.22)		21.13 (3.18–425.21)
Prematurity[b]				
No (1343)	<.0001	Reference	<.0001	Reference
Yes (49)		4.59 (2.58–8.35)		5.81 (3.04–11.37)
Comorbidity (other than prematurity)				
No (1252)	.58	Reference		Not included
Yes (140)		1.11 (0.75–1.64)		
Evidence for diagnosis				
Probable (245)	.0008	Reference	.0405	Reference
Confirmed (1147)		1.84 (1.29–2.67)		1.51 (1.03-2.27)
Admission date (year)	<.0001	1.05 (1.03-1.08)	.0005	1.05 (1.02–1.07)
Vaccination status (3–4 mo) (n = 184)[c]				
Unvaccinated (102)	.665	Reference		Not included
Age-appropriately vaccinated (n = 82)		0.83 (0.35-1.89)		
Risk factors for death				
Age				
≥4 wk (1280)	<.0001	Reference	.0002	Reference
<4 wk (112)		7.04 (2.57–17.89)		6.73 (2.39-17.88)
Sex				
Male (648)	.0341	Reference	.0318	Reference
Female (744)		3.31 (1.19-11.66)		3.46 (1.21-12.47)
Prematurity[b]				
No (1343)	.0090	Reference	.0147	Reference
Yes (49)		5.40 (1.23–16.95)		5.36 (1.15–18.61)
Comorbidity other than prematurity				
No (1252)	.493	Reference		Not included
Yes (140)		0.49 (0.03–2.41)		
Admission date (year)	.0217	1.11 (1.01–1.22)	.0143	1.13 (1.03–1.25)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

[a]The multivariable ICU analysis was adjusted for patient age, occurrence of encephalopathy, existence of prematurity, admission year, Canadian Immunization Monitoring Program, Active (IMPACT) hospital, and evidence for diagnosis. The multivariable death analysis was adjusted for patient age, admission year, IMPACT hospital, and sex.

[b]Prematurity was defined as birth at <37 weeks' gestation.

[c]The subanalysis included case-patients aged 3 to 4 months with laboratory-confirmed pertussis who received >1 vaccine dose or were unvaccinated.

To our knowledge, no data on risk factors for admission to the ICU exist, and data on the risk factors for death attributable to pertussis are scarce. Identifying infants at higher risk can help physicians in their clinical management decisions; thus, close monitoring and early consideration of the need for ICU admission are required for infants who have these risk factors. Infants with confirmed pertussis had longer hospital and ICU LOS than those with probable pertussis, which indicates that

the clinical severity of confirmed pertussis disease is higher than that of clinically diagnosed pertussis disease, which might be because some case-patients with probable pertussis disease did not have it. A case-control study performed during a period in which both wP and aP vaccine were used in Canada found that the white blood cell (WBC) count was a risk factor for death caused by pertussis [23], which is consistent with recent data from California showing that patients with pertussis

who had died had higher WBC counts than did those who did not die [24]. Lower birth weight, higher peak WBC count, pulmonary hypertension, seizures [25], and female sex [26] were independent risk factors for death among infants with pertussis. In the United States in the aP vaccine era, prematurity was a risk factor for death caused by pertussis in univariate analyses only [25, 26]. Premature infants were overrepresented (12 of 20) in a cohort of US patients with fatal pertussis in the wP vaccine era [27]. Our study found prematurity to be an independent risk factor for death caused by pertussis in the aP era.

Our study has a number of strengths. This report provides a detailed characterization of hospitalized pediatric patients with pertussis in the aP vaccine era. The study is unique for its inclusion of a national population, long duration, and extensive active case finding. IMPACT reporting is active, prospective, standardized, and performed by trained nurse monitors, and as such, the accuracy and completeness of the data are high. The 17-year time period enabled an evaluation of the burden and characteristics of pertussis disease that spanned over a prolonged period. IMPACT hospitals constitute 90% of Canada's pediatric tertiary-care beds and thus provide good estimates of severe pediatric pertussis cases that necessitate hospitalization in a tertiary-care center. Moreover, the IMPACT hospitals' catchment area covers 57% of the Canadian population aged <16 years.

Our study also has some limitations. Patients with less severe pertussis would have been admitted to a smaller hospital that is not part of the IMPACT network or diagnosed and treated in the community. This limitation is less significant in an assessment of severe pertussis that necessitated ICU admission, because IMPACT centers comprise most of the pediatric tertiary-care beds in Canada. Misclassification of probable cases is possible, although probable cases were minority of cases. Our data did not capture readmissions. However, readmissions are expected to be uncommon, because pertussis is a monophasic disease. A possibility exists that some of the patients included in this study were primed with wP vaccine; however, the proportion of such patients is expected to be low, because 90% of the patients were <1 year of age and admitted after 1999 (aP was introduced in Canada in 1997–1998). Our data did not capture the onset of cough, an important variable in defining a vaccine dose as valid. However, the 4-week interval between recent vaccine dose and admission, used in this study, minimizes this misclassification.

Vaccination against pertussis in pregnancy has proven effective in preventing pertussis disease among infants aged <3 months [13, 28, 29] and to decrease the risk of hospitalization, risk of ICU admission, and hospital LOS [30]. Given the significant morbidity from endemic pertussis disease among infants during the first months of life, as shown in this study, vaccination against pertussis in pregnancy has the potential to control the burden of pertussis among young infants in countries with long-standing use of aP vaccine. Vaccination against pertussis in pregnancy has proved to be highly (nearly 90%) effective in preventing pertussis disease

and hospitalization among infants aged <3 months in the United Kingdom and United States [13, 29]. Assuming that vaccination against pertussis in pregnancy is 90% effective in the prevention of pertussis hospitalization among infants aged <3 months, approximately 825 cases of pertussis that necessitated hospitalization could have been prevented via maternal immunization in the study hospitals during this 17-year period.

Universal vaccination against pertussis in pregnancy is now recommended in an increasing number of countries and most recently in Canada [15]. Although the optimal timing of vaccination against pertussis in pregnancy is being researched, our finding that prematurity is an independent risk factor for ICU admission and death caused by pertussis might support vaccination earlier in pregnancy.

Supplementary Data

Notes

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