September 6, 2018 • Volume 44-9

CCDR

CANADA COMMUNICABLE DISEASE REPORT

RESPIRATORY INFECTIONS

Public Health Agency of Canada
Agence de la santé publique du Canada

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The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice.

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This Shutterstock photo shows a mother taking the temperature of a sick infant to highlight that infants under six months of age are at greatest risk of severe disease from a pertussis infection (https://www.shutterstock.com/image-photo/mother-checking-thermometer-holding-her-ill-684469132?src=UdElmKIDtQJABo_ZW_-7IA-1-24).

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RESPIRATORY INFECTIONS

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COHORT STUDY

Clinical characteristics of pediatric pertussis cases, Quebec 2015–2017

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Abstract

Background: The introduction of the acellular pertussis vaccine may have changed the epidemiological and clinical features of pertussis in Canadian children.

Objective: To describe the demographics, clinical presentation and outcomes of children and adolescents with pertussis presenting to a tertiary care hospital.

Methods: Retrospective cohort of consecutive patients evaluated at the Centre Hospitalier Universitaire Sainte-Justine (CHUSJ) and tested with a bacterial multiplex real-time polymerase chain reaction (PCR) for *Bordetella pertussis* or *B. parapertussis* between June 2015 and March 2017. Demographics, clinical presentations and outcomes were described for positive test results. The Modified Preziosi Scale was used to assess disease severity; severe disease was defined as a score ≥7.

Results: The age distribution of the 144 positive patients with a clinical encounter at CHUSJ was as follows: less than three months (n=25/144, 17.4%), four months to nine years (n=63/144, 43.8%) and 10 to 18 years (n=56/144, 38.9%). The most common symptoms at presentation were paroxysmal cough (70.1%), post-tussive emesis (47.2%) and coryza (33.3%). Over 84.0% of cases in infants less than three months of age had severe pertussis (92.0% required hospitalization and 28.0 % intensive care admission). In children four months to nine years of age, 22.2% had severe pertussis and 11.1% required hospitalization. Only two (3.6%) children greater than 10 years had severe disease.

Conclusion: Pertussis still affects children of all ages in Quebec. In older children, it tends to be a milder disease. When it affects infants, who do not yet have full protection from pertussis vaccination, it often causes severe disease, especially in those less than three months of age. This evidence further supports the implementation of a pertussis vaccination program in pregnant women.

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Suggested citation: Desjardins M, Iachimov D, Mousseau S, Doyon-Plourde P, Brousseau N, Rallu F, Quach C. Clinical characteristics of pediatric pertussis cases, Quebec 2015–2017. Can Commun Dis Rep 2018;44(9):190-5. https://doi.org/10.14745/ccdr.v44i09a01

Keywords: pertussis, pediatric, symptoms, outcomes, Quebec

Introduction

Pertussis, or whooping cough, is a respiratory tract infection caused by *Bordetella pertussis* and *B. parapertussis*. Infected patients may display a wide range of symptoms depending on age, immunization status and coinfections, often making pertussis difficult to diagnose (1,2).

Pertussis is a vaccine-preventable disease. Vaccination against pertussis with a whole cell vaccine, which was introduced in Canada in 1943, led to a significant decrease in the disease incidence (3). The whole cell vaccine was replaced with the acellular pertussis vaccine in the late 1990s to decrease the incidence of adverse events following immunization.

The pertussis-containing vaccine is currently administered at two, four, six and 18 months of age with a booster between four and six years of age. In Quebec, the universal acellular vaccination program was introduced in 1998 with a marked impact on pertussis incidence (4-6). In 2016, despite vaccination coverage of 97.3% in children at one year of age (7), the incidence of pertussis in those less than 18 years of age was still 60 cases per 100,000 children (8).

It has been shown that immunity and protection provided by the acellular vaccine wanes rapidly (9), and this may have changed the clinical presentation of pertussis in children. Young infants are particularly vulnerable to pertussis, possibly because those less than three months of age have only received

one dose of pertussis vaccine, which provides only partial protection (6,10,11). To address this, the National Advisory Committee on Immunization (NACI) evaluated the evidence on vaccination of pregnant women and found this to be highly effective in preventing pertussis in infants (12-14). In 2018, NACI recommended the immunization of pregnant women against pertussis (15), noting it could lead to a 90% reduction of the incidence of pertussis in infants born to vaccinated mothers (16).

The last hospital-based studies describing the epidemiological and clinical features of pertussis in Canadian children were conducted from 1991 to 2004 (17,18); thus, the current burden of illness in children in Canada is currently unknown.

The objective of this study was to describe the clinical presentation and outcomes of children with pertussis who were evaluated between June 2015 and March 2017 at the Centre Hospitalier Universitaire Sainte-Justine (CHUSJ). This hospital is in Montréal (Quebec) and is the only free-standing children's hospital in the province of Quebec, with 80,000 emergency care visits annually (19).

Methods

Study design

This was a retrospective, observational cohort study of consecutive patients evaluated at CHUSJ for suspected pertussis. Children presenting for suspected pertussis were primarily from the hospital's catchment area and were assessed in the emergency department. Occasionally, children were tested for pertussis as inpatients. All children were tested with a bacterial multiplex polymerase chain reaction (PCR) (*B. pertussis*, *B. parapertussis*, *B. holmesii*, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*). Since 2015, all suspected pertussis cases seen at CHUSJ are tested using this multiplex PCR.

Cases positive for *B. pertussis* or *B. parapertussis* between June 2015 and March 2017 were identified through the laboratory information system and clinical data were extracted using manual chart review. The study protocol was approved by the CHUSJ ethics committee.

Study population

The study included consecutive patients aged zero to 17 years, who had a positive multiplex PCR (cycle threshold [Ct] value less than 36) for *B. pertussis* or *B. parapertussis*, and whose clinical and laboratory data were available in the CHUSJ microbiology laboratory information system between June 2015 and March 2017. Since *B. parapertussis* may cause a disease similar to pertussis and the current vaccine against *B. pertussis* may offer cross-protection to *B. parapertussis* (20), patients with *B. parapertussis*-positive PCR were included in the study. Patients with equivocal PCR results (Ct values 36–39.9) were also included, as they are currently considered as pertussis cases by public health authorities in Quebec, if they present symptoms compatible with pertussis (6). Patients who tested positive for *B. holmesii* were not included, since this *Bordetella* species may cause a significant different disease (1). Patients 18 years and older, as well as patients without a clinical encounter at CHUSJ (e.g., samples received from other hospitals), were excluded.

Data collection and analysis

In addition to reviewing the laboratory data, manual chart reviews of electronic medical records were performed (using Chartmaxx; Quest Diagnostics, Secaucus, New Jersey, United States [US]), using standardized case report forms to collect information on 1) clinical presentation (using triage nurses' evaluation and physicians' clinical notes on the day the PCR was ordered), 2) investigation results and 3) outcomes (hospitalization, length of stay, macrolide treatment, intensive care admission or death). Data collection was performed by two members of the research team (MD, DI) and 10% of the charts were reviewed by both researchers to evaluate inter-rater agreement (tested using kappa statistics). Patients were divided in three age groups, as suggested at the Global Pertussis Initiative roundtable meeting held in February 2011 (21): less than or equal to three months; four months to nine years; and 10 to 18 years of age. Absolute numbers and proportions were used to analyze demographics, clinical presentations and outcomes. Interquartile range (IQR) was used to evaluate the statistical dispersion of continuous variables. The Modified Preziosi Scale (MPS) (22) was used to assess disease severity. Severe pertussis was defined by MPS score greater or equal to seven (23,24). Microsoft Excel 2016 (Redmond, Washington, US) was used to generate proportions and IQR. Statistical analyses were descriptive.

Results

Of the 1,526 multiplex PCR tests performed between June 11, 2015 and March 31, 2017, 173 patients were positive or equivocal for *B. pertussis* or *B. parapertussis* (11.3% positivity). Twenty-nine patients were excluded: two were 18 years or older and 27 did not have a clinical encounter at CHUSJ.

Demographics

A total of 144 patients were analyzed: 133 *B. pertussis* cases (109 positive, 24 equivocal); and 11 *B. parapertussis* cases (seven positive, four equivocal) (**Table 1**). Patients were pooled together for analysis because of the small number of patients who tested

Table 1: Characteristics of children with PCR-confirmed pertussis

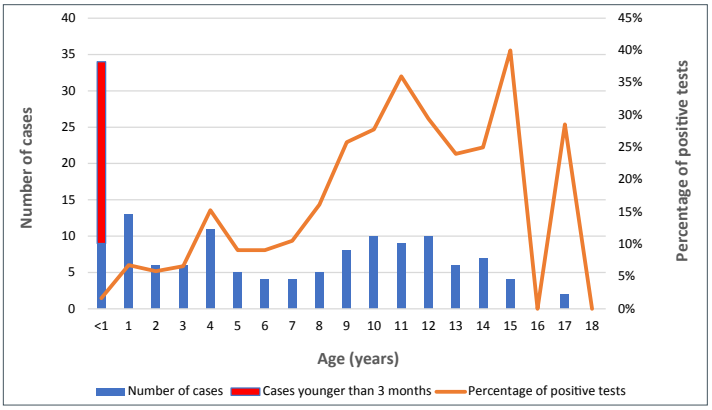
Characteristics	Age groups, n (%)			
	0–3 mos	4 mos – 9 yrs	10–18 yrs	Total
Laboratory result	25 (17.4)	63 (43.8)	56 (38.9)	144 (100.0)
B. pertussis positive	19 (76.0)	45 (71.4)	45 (80.4)	109 (75.7)
B. parapertussis positive	1 (4.0)	5 (7.9)	1 (1.8)	7 (4.9)
B. pertussis equivocal	5 (20.0)	9 (14.3)	10 (17.9)	24 (16.7)
B. parapertussis equivocal	0 (0.0)	4 (6.3)	0 (0.0)	4 (2.0)
Female	14 (56.0)	33 (52.4)	35 (62.5)	82 (56.9)
Past medical history				
Asthma	0 (0.0)	11 (17.5)	11 (19.6)	22 (15.3)
Immunization status up to date	22 (88.0)	42 (66.7)	48 (85.7)	112 (77.8)
Prematurity	4 (16.0)	4 (6.3)	1 (1.8)	9 (6.3)

Abbreviations: *B.*, *Bordetella*; mos, months; n, number; PCR, polymerase chain reaction; yrs, years

positive for *B. parapertussis* and because both bacteria cause similar respiratory syndromes.

Among the 144 children, 25 (17.4%) were less than three months old, 63 (43.8%) were between four months and nine years and 56 (38.9%) were between 10 and 18 years. The proportion of positive tests increased with age, reaching a peak of 35–45% in adolescents 10 to 15 years old (**Figure 1**).

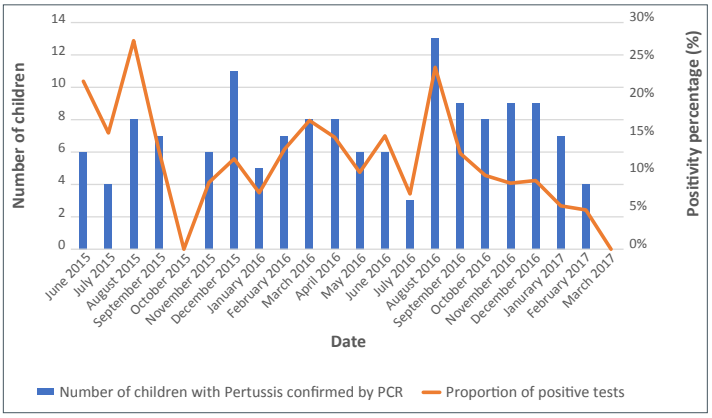
Figure 1: Distribution of patients with positive pertussis PCR per age (n=144)



Abbreviations: n, number; PCR, polymerase chain reaction

Pertussis was reported all year round (**Figure 2**).

Figure 2: Distribution of patients with positive pertussis PCR during the study period (n=144)



Abbreviations: n, number; PCR, polymerase chain reaction

Clinical presentation

The most common symptoms at presentation were paroxysmal cough (70.1%), post-tussive emesis (47.2%) and coryza (33.3%) (**Table 2**). From the 100 chest X-rays performed (69.4% of all cases), only eight (8.0%) were consistent with pneumonia.
The 25 children under the age of three months were the most severely affected by pertussis, with a median MPS score of 12 (interquartile range [IQR]: 9-15). The disease was considered severe in 84.0% of children less than three months of age. All 10 reported cases of apnea, 75.0% (n=15/20) of cases with cyanosis, 76.9% (n=10/13) of cases with chest retractions and 45% (n=9/20) of cases with inspiratory whoop were in this age group.

Table 2: Clinical presentation and paraclinical tests of children with PCR-confirmed pertussis

Characteristics	Age groups, n (%)[a]			
	0–3 mos n=25	4 mos – 9 yrs n=63	10–18 yrs n=56	Total n=144
Clinical presentation				
Paroxysmal cough	20 (80.0)	47 (74.6)	34 (60.7)	101 (70.1)
Inspiratory whoop	9 (36.0)	7 (11.1)	4 (7.1)	20 (13.9)
Post-tussive emesis	10 (40.0)	32 (50.8)	26 (46.4)	68 (47.2)
Cyanosis	15 (60.0)	4 (6.3)	1 (1.8)	20 (13.9)
Chest retractions	10 (40.0)	3 (4.8)	0 (0.0)	13 (9.0)
Fever	2 (8.0)	10 (15.9)	4 (7.1)	16 (11.1)
Coryza	14 (56.0)	20 (31.8)	14 (25.0)	48 (33.3)
Pulmonary signs on exam	8 (32.0)	8 (12.7)	2 (3.6)	18 (12.5)
Apnea	10 (40.0)	0 (0.0)	0 (0.0)	10 (6.9)
Otitis	2 (8.0)	6 (9.5)	2 (3.6)	10 (6.9)
Pharyngitis	2 (8.0)	2 (3.2)	7 (12.5)	11 (7.6)
Sub-conjunctival hemorrhage	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.7)
Seizures	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MPS				
Average	11.8	4.7	3.3	5.4
Median	12	5	3	5
– IQR 25–75	9–15	3–6	2–5	IQR 3–7
Severe cases (MPS ≥7)	21 (84.0)	12 (22.2)	2 (3.6)	37 (25.7)
Paraclinical tests				
Viral multiplex done	13 (52.0)	6 (9.5)	5 (8.9)	24 (16.7)
– Respiratory virus found[b]	5 (38.5)	2 (33.3)	1 (20.0)	8 (33.3)
Complete blood count done	21 (84.0)	10 (15.9)	3 (5.4)	34 (23.6)
– Lymphocytosis[b]	10 (47.7)	3 (30.0)	0 (0.0)	13 (38.2)
Chest x-ray done	20 (80.0)	43 (68.3)	37 (66.1)	100 (69.4)
– Pneumonia identified[b]	0 (0.0)	6 (14.0)	2 (5.4)	8 (8.0)

Abbreviations: IQR, interquartile range; mos, months; MPS, Modified Preziosi Scale; n, number; yrs, years
[a] All results reported as n (%) with the exception of MPS average, MPS median (and IQR)
[b] These percentages were calculated according to the number of respective tests done

Children four months to nine years of age were also significantly affected: 22.2% had severe pertussis. In comparison, only two (3.6%) children older than 10 years of age had severe pertussis. Inter-rater agreement using kappa statistics was 0.86, showing good validity of data collection.

Outcomes

Overall, 20.8% of patients were hospitalized (**Table 3**).
Infants less than three months of age had the highest risk of hospitalization (92%) with a significant proportion (28%) requiring

intensive care admission. In comparison, 11% of children four months to nine years of age and none of older children were hospitalized. The majority of patients (75.2%) were treated with macrolides. There were no deaths.

Table 3: Outcomes of children with PCR-confirmed pertussis

Outcomes	Age groups, n (%)[a]			
	0–3 mos n=25	4 mos – 9 yrs n=63	10–18 yrs n=56	Total n=144
Hospitalization	23 (92.0)	7 (11.1)	0 (0.0)	30 (20.8)
Length of stay				
Average, days	11.0	3.0	0.0	9.1
Median	8	3	0	5
– IQR 25–75	3–14	2–4	0	3–12
Intensive care	7 (28.0)	0 (0.0)	0 (0.0)	7 (4.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Received macrolide	18 (72.0)	46 (73.0)	45 (80.4)	109 (75.7)

Abbreviations: IQR, interquartile range; mos, months; n, number; yrs, years
[a] All results reported as n (%) with the exception of Length of stay which is average (in days) and Median with IQR

Discussion

This study draws a brief portrait of the clinical presentation and outcomes of patients with pertussis presenting to a tertiary care pediatric hospital. Despite the introduction of a universal acellular pertussis immunization program in Quebec, infants less than three months of age are still affected by pertussis. Most suffered a severe disease (84%) and required hospitalization (92%), including in the intensive care unit (28%), for a median length of stay of eight days, similar to previous studies (10,18,21,25–31). Disease was milder in older children, as shown by lower MPS scores and hospitalization rates. Only a minority of children had severe pertussis, with no hospitalization in those 10 years or older, suggesting that older children, like adults, were less severely affected by this infection (25,32).

Overall, symptoms suggestive of pertussis, such as paroxysmal cough, inspiratory whoop and post-tussive emesis, were found in a large proportion of children of all ages, but less frequently than what was previously reported (25,29,31). For example, in previous studies children age nine years or younger, paroxysmal cough, inspiratory whoop and post-tussive emesis were previously reported in 89–93% (cough), 69–92% (whoop) and 48–60% (emesis) of children. In contrast, in our study these symptoms were present in 76% (cough), 25% (whoop) and 48% (emesis) of children of similar age. These differences could be due in part to an attenuation of disease following immunization, but could also be the result of the increased sensitivity of PCR compared with culture, which allows for detection of less symptomatic cases (33). It was previously shown that immunity and protection provided by the acellular vaccine wanes rapidly, (9), which may explain the high proportion of positive tests in children 10-15 years of age (25–40%).

This study offers a description of pediatric cases of pertussis in Quebec. There are several limitations to consider. First, this study was from a single centre; nevertheless, the 144 cases analyzed in this study represented approximately 12.4% of all pertussis cases <18 years of age diagnosed in the province of Quebec during the study period (8). Second, there was the risk of information bias, including potential misclassification of the vaccination status, an intrinsic risk associated with chart review. We tried to minimize the risk by documenting a high inter-rater agreement. Third, we analyzed only patients who sought medical attention in a hospital setting, which may overestimate the severity of disease. However, this bias is probably not significant in infants less than three months of age, as reported cases of pertussis in this age group usually seek emergency care and are hospitalized (34). Finally, the study period included the peak of a four-year epidemic cycle (2016), which could have led to a slight overestimation of the incidence of pertussis.

In terms of next steps and future research, this study could provide a baseline for a future evaluation of the impact of the vaccination of pregnant women on the pertussis disease burden in young children.

Conclusion

Pertussis still affects children of all ages in Quebec. In older children it tends to be a milder disease. When it affects infants, who do not yet have full protection from pertussis vaccination, it often causes severe disease, especially in those less than three months of age. This evidence further supports the implementation of a pertussis vaccination program in pregnant women and provides a baseline to assess the impact of this program.

Authors' statement

MD[†] – conceptualization, methodology, validation, investigation, data curation, writing of original draft, review and editing of final version
DI[†] – conceptualization, methodology, validation, formal analysis, investigation, data curation, writing of original draft, review and editing of final version
SM – methodology, review and editing of final version
PDP – formal analysis, review and editing of final version
NB – methodology, review and editing of final version
FR – Investigation, resources, review and editing of final version
CQ – conceptualization, methodology, review and editing of final version, supervision, funding acquisition

[†] Both MD and DI contributed equally to the work.

Conflict of interest

None.

Funding

Dr. Quach is supported through an external salary award (FRQ-S merit, grant # 252775). This research was supported by the CHU Sainte-Justine Research Institute (C. Quach's start-up funds).

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Canada Communicable Disease Report
CCDR
INFOGRAPHIC

PERTUSSIS (WHOOPING COUGH) STILL A DANGER TO INFANTS

Pertussis vaccine immunity wanes over time

Pertussis, or whooping cough, is a respiratory tract infection that can be prevented with vaccination.

PROTECTION

However, protection takes several shots to establish and then protection wanes over time.

Young infants are most at risk

Infants less than three months of age have only received one dose of the vaccine.

Infants get the most sick
A recent study found most infants less than three months with pertussis had severe disease and of those[1]:

- 92% required hospitalization
- 28% intensive care admission

How to prevent infection

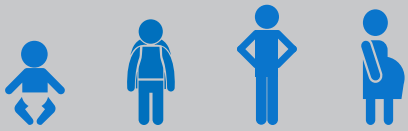
Make sure you and your family are up to date with your vaccines[2]:

1. ROUTINE CHILDHOOD IMMUNIZATION SCHEDULE
- 2, 4, 6, 12-23 months and 4-6 years

2. ADOLESCENT BOOSTER
- at 14-16 years

3. ADULT BOOSTER

4. WITH EVERY PREGNANCY
- Protective antibodies are transferred to the baby
- Best between 27-32 weeks



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Suggested citation: Pertussis (whooping cough) still a danger to infants. Can Commun Dis Rep 2018;44(9):195.

COHORT STUDY

Should equivocal *Bordetella pertussis* PCR results in children be reported to public health?

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Abstract

Introduction: Real-time polymerase chain reaction (PCR) is the preferred method for the diagnosis of pertussis. In Quebec, positive and equivocal results are reportable to public health; in contrast, in Ontario equivocal results are not reportable.

Objective: To determine the clinical significance of equivocal, compared with positive results, in children with suspected pertussis.

Methods: Retrospective cohort of consecutive patients seen at the Centre Hospitalier Universitaire Sainte-Justine in Montréal, Quebec, with suspected pertussis and tested with a bacterial multiplex PCR (including *Bordetella pertussis*) between 2015 and 2017. Medical records were reviewed using a standardized form. Univariate analyses (Student's t-test and chi-square test) and multivariable logistic regression were used to compare cases of positive and equivocal results.

Results: Of the 1,526 multiplex PCR performed, 109 were positive and 24 equivocal. Both groups were similar in terms of demographics and disease severity assessments, but patients in the equivocal group had less paroxysmal cough (33.3% vs 79.8%, adjusted odds ratio [aOR] 0.11, 95% confidence interval [CI] 0.04-0.29) and whoop (0% vs 18.3%, $p<0.001$), lower lymphocyte counts (6.6 vs 11.9 x10^9/L, $p=0.008$), were more likely to be diagnosed with a viral co-infection (16.7% vs 3.7%, aOR 5.62, 95% CI 1.17–27.54) and were less likely to receive a macrolide (25% vs 89%, aOR 0.04, 95% CI 0.01–0.11). When admitted, patients with equivocal results had a shorter average length of stay (3.3 vs 12.2 days, $p=0.001$).

Conclusion: Although there were similarities in disease severity, children with suspected pertussis who had equivocal PCR results had significantly different clinical presentations compared with those with positive results. In the context of limited public health resources, these results may inform the decision whether or not equivocal results need to be reported to public health by laboratories.

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Suggested citation: Desjardin M, Mousseau S, Doyon-Plourde P, Brousseau N, Iachimov D, Rallu F, Quach C. Should equivocal *Bordetella pertussis* PCR results in children be reported to public health? Can Commun Dis Rep 2018;44(9):196-200. https://doi.org/10.14745/ccdr.v44i09a02

Keywords: pertussis, pediatrics, testing, equivocal results

Introduction

Pertussis is a highly contagious disease caused by *Bordetella pertussis*. Despite universal vaccination, pertussis still represents a major public health burden in Canada, particularly in children under the age of 15 years (1). Certain groups, such as infants, have an increased risk of severe disease. Pertussis cases are therefore reported to public health authorities within 48 hours of diagnosis, for epidemiological surveillance and contact management (2).

The clinical diagnosis of pertussis is challenging considering the wide spectrum of symptoms at presentation (3). Both nasopharyngeal culture and polymerase chain reaction (PCR) are accepted laboratory confirmation methods (4); however, given its increased sensitivity, PCR has become the preferred diagnostic method for pertussis in most provinces and territories (2,5).

The Centre Hospitalier Universitaire Sainte-Justine (CHUSJ), a pediatric tertiary care hospital in Montreal, uses an *IS481*-based real-time PCR for identification of *B. pertussis*. PCR is considered positive when cycle threshold (Ct) is less than 36 and equivocal when Ct is 36–39.9. Currently, in Quebec, laboratories report equivocal results to public health authorities. These cases are investigated, including contact tracing, and interpreted according to clinical features (symptoms compatible with pertussis) and epidemiological information (history of contact) (2). In contrast, due to questions about the significance of equivocal results (5), Public Health Ontario determined that such results were not to be reported (6). Our study objective was to determine the clinical significance of an equivocal PCR result, when compared with positive PCR results, in children evaluated for suspected pertussis.

Methods

Study design

This was a retrospective, observational cohort study of consecutive patients who were seen at CHUSJ for suspected pertussis and were tested with a bacterial multiplex PCR (*B. pertussis*, *B. parapertussis*, *B. holmesii*, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*) between June 2015 and March 2017. The study protocol was approved by the CHUSJ's ethics committee.

Study participants

The overall cohort consisted of participants less than or equal to 17 years of age, with a bacterial multiplex PCR result available in the microbiology laboratory information system. Patients with a positive or equivocal PCR result for *B. pertussis* were included in our case series, regardless of where the test was ordered (emergency, ward, clinic, pediatric intensive care unit or neonatal intensive care unit). Patients not evaluated by a CHUSJ's physician on the day the test was performed were excluded, as data on their clinical presentation (symptoms and signs) were not available.

Data collection

Manual chart review of electronic medical records using Chartmaxx (Quest Diagnostics, Secaucus, New Jersey, United States [US]) was performed for all patients included in the cohort by two members of the research team (MD, DI). Data were extracted using a standardized case report form. Ten percent of charts were reviewed by both researchers to evaluate inter-rater agreement using kappa statistics. Collected data included demographic characteristics, past medical history and vaccination status, clinical presentation, disease severity and outcomes. When not recorded in the chart, specific signs and symptoms, as well as past medical history were considered absent. Disease severity was determined using two different severity scores: the Modified Preziosi Scale (MPS) and the Respiratory Severity Score (RSS). The MPS was used to measure pertussis severity in pediatrics. Severe disease is defined as a MPS greater than six (7). The RSS evaluates the severity of respiratory tract infections in pediatric patients. It was used to distinguish upper from lower respiratory infections and is correlated with the need for hospitalization (8). Because these two scores measure different constructs of respiratory infections, we compared both patients groups using the two scores.

Data analysis

Univariate analyses, using chi-square and Student's t-test as appropriate, were first performed to compare characteristics of patients with an equivocal (vs positive) result. Variables that were statistically significant upon univariate analysis, that were considered to be potential confounders based on the literature review, or had an impact on the model fit Akaike information criterion (AIC) were included in the multivariable logistic regression model (odds ratios – OR – and 95% confidence intervals). All *p* values were two-sided and considered significant at less than 0.05 (SPSS software, version 24, IBM Analytics, Armonk, New York US and R, version 3.4.3).

Results

A total of 1,526 consecutive bacterial multiplex PCR with available results, performed at CHUSJ between June 11, 2015 and March 31, 2017, were extracted from the laboratory information system. Of these, 109 patients tested positive for *B. pertussis* and 24 had equivocal results. The two groups were similar in terms of demographics (age, sex) and past medical history (history of asthma, prematurity), with the exception of a lower vaccination rate in those with a positive PCR (**Table 1**). The proportion of patients with a history of contact with a pertussis case was also similar.

Table 1: Patient demographic characteristics and past medical history

Characteristics	PCR positive n=109 (%)[a]	PCR equivocal n=24 (%)[a]	*p*-value	OR (95% CI)
Age, mean (SD)	6.65 (5.35)	6.26 (5.23)	0.75	NA
Male sex	45 (41.3)	11 (45.8)	0.68	1.20 (0.49–2.93)
Immunization up-to-date	79 (72.5)	22 (91.7)	0.046	4.18 (1.13–27)[b]
Asthma	16 (14.7)	7 (29.2)	0.09	2.39 (0.82–6.56)
Prematurity	5 (4.6)	3 (12.5)	0.14	2.97 (0.57–13.08)
Immunosuppression	0 (0.0)	0 (0.0)	NA	NA
Contact with pertussis case	18 (16.5)	3 (12.5)	0.63	0.72 (0.16–2.39)
Patient location				
Emergency	89 (81.7)	16 (66.7)	0.10[c]	0.44 (0.17–1.23)[c]
Ward	14 (12.8)	7 (29.2)	-	-
Clinic	5 (4.6)	1 (4.2)	-	-
NICU	0 (0.0)	0 (0.0)	-	-
PICU	1 (0.9)	0 (0.0)	-	-
Ordering physician specialty				
Pediatric Emergency	55 (50.5)	8 (33.3)	0.13[d]	0.49 (0.19–1.21)[d]
Pediatrics	43 (39.4)	12 (50)	-	-
Infectious Disease	5 (4.6)	3 (12.5)	-	-
Family medicine	6 (5.5)	0 (0.0)	-	-
Other specialty	0 (0.0)	1 (4.2)	-	-

Abbreviations: CI, confidence interval; n, number; NA, not applicable; NICU, neonatal intensive care unit; OR, odds ratio; PCR, polymerase chain reaction; PICU, pediatric intensive care unit; SD, standard deviation; "-", part of the above calculation
[a] With the exception of age which is reported as a mean and standard deviation
[b] Statistically significant results ($p<0.05$)
[c] Emergency vs other locations
[d] Pediatric Emergency vs other specialties

Signs and symptoms at laboratory and radiological investigations (paraclinical) performed are shown in **Table 2**. When comparing the two groups, there was no difference in terms of fever, rhinorrhea, cough, post-tussive vomiting, abnormal auscultation, wheezing, acute otitis media or pharyngitis. MPS scores were also similar in both groups. However, patients in the positive PCR group had significantly more paroxysmal cough, whoop, and lymphocytosis and less rhinorrhea and retractions than patients in the equivocal PCR group. In addition, there was no apnea reported in the latter group. Finally, patients with equivocal PCR tended to be more frequently tested for viral pathogens using a multiplex PCR (adjusted OR [aOR] 3.03 (0.82–11.35), with a greater proportion having a confirmed viral infection (16.7% vs 3.7%, aOR: 5.62, 95% CI: 1.17 to 27.54).

Table 2: Clinical presentation and investigations

Presentation	PCR positive n=109 (%)[a]	PCR equivocal n=24 (%)[a]	*p*-value	Crude OR (95% CI)	Adjusted OR (95% CI)
Clinical presentation					
Fever	10 (9.2)	5 (20.8)	0.10	2.61 (0.74–8.25)	2.30 (0.62–7.57)[d]
Rhinorrhea	31 (28.4)	12 (50.0)	0.04[a]	2.52 (1.02–6.26)[a]	2.53 (1.01–6.42)[b,e]
Proven apnea	10 (9.2)	0 (0.0)	0.12	NA	NA
Length of cough, days (SD)[c]	15.5 (14.2)	16.3 (67.9)	0.82	NA	NA
Post-tussive vomiting	55 (50.5)	8 (33.3)	0.13	0.49 (0.19–1.21)	0.49 (0.19–1.21)[e]
Paroxysmal cough	87 (79.8)	8 (33.3)	< 0.001[a]	0.13 (0.05–0.32)[b]	0.11 (0.04–0.29)[b,e]
Whooping cough	20 (18.3)	0 (0.0	< 0.001[a]	NA	NA
Abnormal auscultation	12 (11.0)	5 (20.8)	0.19	2.13 (0.62–6.49)	2.18 (0.60–7.19)[e]
Wheezing	2 (1.8)	2 (8.3)	0.09	4.86 (0.56–42.34)	3.38 (0.36–31.52)[f]
Retractions (any type)	6 (5.5)	6 (25.0)	0.003[a]	5.72 (1.62–20.29)[b]	5.61 (1.55–20.76)[b,g]
Acute otitis media	5 (4.6)	3 (12.5)	0.14	2.97 (0.57–13.08)	1.72 (0.26–8.92)[h]
Pharyngitis	9 (8.3)	1 (4.2)	0.49	0.48 (0.02–2.76)	0.50 (0.03–2.91)[e]
Cyanosis	15 (13.8)	4 (16.7)	0.71	1.25 (0.33–3.90)	0.69 (0.13–3.16)[f]
Severity score					
MPS, mean	5.7	4.8	0.31	NA	NA
MPS, severe disease	30 (27.5)	6 (25.0)	0.80	0.88 (0.30–2.32)	0.40 (0.06–1.86)[i]
RSS, mean	0.5	1.3	0.07	NA	NA
Investigations					
Viral PCR	14 (12.8)	8 (33.3)	0.01	3.39 (1.19–9.33)	3.03 (0.82–11.35)[f]
Another virus found	4 (3.7)	4 (16.7)	0.02	5.25 (1.16–23.92)[b]	5.62 (1.17–27.54)[b,e]
Lymphocytes ($x10^9$/L), mean (SD)	11.9 (10.9)	6.6 (2.8)	0.008[b]	NA	NA
Pneumonia on X-Ray	5 (4.6)	2 (8.3)	0.46	1.89 (0.26–9.41)	3.34 (0.41–22.40)[j]

Abbreviations: CI, confidence interval; n, number; NA, not applicable; MPS, Modified Preziosi Scale; OR, odds ratio; PCR, polymerase chain reaction; RSS, Respiratory Severity Score; SD, standard deviation
[a] All results reported as n (%) with the exception of length of cough (days) and lymphocytes, which are reported as a mean with standard deviation, and MPS and RSS severity score, which are reported as a mean
[b] Statistically significant results ($p<0.05$)
[c] Three missing data in each group
[d] Adjusted for sex group and another virus found
[e] Adjusted for age
[f] Adjusted for age and patient location
[g] Adjusted for immunization up-to-date
[h] Adjusted for age and another virus found
[i] Adjusted for age, other virus found and patient location
[j] Adjusted for age and immunization up-to-date

Patients' outcomes are presented in **Table 3**. Notably, patients in the equivocal PCR group were less likely to have a macrolide prescribed (aOR 0.04; 95% CI: 0.01 to 0.11), adjusting for age and presence of pneumonia on X-ray. In fact, only 25% of equivocal cases were treated for pertussis, despite having similar symptoms duration compared with patients in the positive PCR group. Moreover, despite a similar proportion of hospitalization in the two groups, patients with equivocal PCR had a shorter average length of stay, when admitted (3.3 vs 12.2 days, $p=0.001$) and did not require intensive care admission.

Table 3: Patients' outcomes

Outcomes	PCR positive n=109 (%)[a]	PCR equivocal n=24 (%)[a]	*p*-value	Crude OR (95% CI)	Adjusted OR (95% CI)
Received amoxicillin	0 (0.0)	4 (16.7)	< 0.001[b]	NA	NA
Received macrolide	97 (90.0)	6 (25.0)	< 0.001[b]	0.04 (0.01–0.12)[a]	0.04 (0.01–0.11)[c]
Hospitalization	20 (18.3)	7 (29.2)	0.24	1.81 (0.63–4.83)	4.63 (0.75–47.96)[d]
Length of stay, mean (SD)	12.2 (10.2)	3.3 (1.0)	0.001[b]	NA	NA
ICU stay	7 (6.4)	0 (0.0)	0.20	NA	NA
Death	0 (0.0)	0 (0.0)	NA	NA	NA
Return visits	21 (19.3)	4 (16.7)	0.73	0.82 (0.22–2.45)	0.81 (0.22–2.45)[c]

Abbreviations: CI, confidence interval; ICU, Intensive Care Unit; n, number; NA, not applicable; OR, odds ratio; SD, standard deviation
[a] With the exception of length of stay, which is reported as a mean and standard deviation
[b] Statistically significant results ($p<0.05$)
[c] Adjusted for age and pneumonia on X-ray
[d] Adjusted for age

Discussion

At CHUSJ, between June 2015 and March 2017, MPS and the RSS scores indicated that children with positive and equivocal *B. pertussis* PCR results showed certain similarities with respect to disease severity. However, there were many significant differences in terms of clinical presentations, paraclinical results and outcomes between the two groups. In fact, patients in the positive PCR group presented typical symptoms of pertussis, such as apnea, paroxysmal cough, post-tussive vomiting and whooping cough. The vast majority of positive cases were treated with a macrolide. In comparison, patients in the equivocal group presented more frequently with nonspecific upper respiratory tract infection symptoms such as rhinorrhea, fever, retractions and wheezing. In addition, the majority of patients with equivocal results were not treated with a macrolide, which suggests that the treating physician did not feel that treatment for pertussis was indicated.

Previously, using Ontario's reportable disease database, Bolotin et al. (5) also compared patients with positive and equivocal PCR results. They reported that patients with equivocal PCR results were less likely to be hospitalized than patients with positive PCR results, even if both groups were similar in terms of their clinical presentation. In our study, the two groups were significantly different with regards to their clinical presentations and outcomes, possibly because our population consisted of children, who are usually more severely affected by pertussis than adults. DeVincenzo et al. (9) also evaluated the relationship between PCR Ct value and pertussis severity. They showed that

Ct values significantly correlated with length of hospitalization and lymphocytosis (9). Our results follow the same trend.

From an analytical point of view, many factors may explain differences found between patients with an equivocal and positive result. *B. pertussis* PCR target, *IS481*, is present in 50 to 200 copies/bacterial cell. It was previously shown that a PCR result with a Ct greater than 35 may represent the detection of less than one bacterium per sample (10). The significance of a late-cycle positive result remains thus uncertain. On the one hand, equivocal result may represent a true pertussis infection with a small bacterial load, as could be seen in the context of a disease lasting for more than three weeks, previous vaccination, partial immunity, or recent antibiotic use (2). In our study, the duration of symptoms was similar in the two groups, which makes the hypothesis of a longer lasting disease unlikely. Low-quality sampling could also result in equivocal results. On the other hand, equivocal results may be due to transient colonization in which *B. pertussis* is unrelated to the clinical syndrome. Waters et al. described an outbreak of atypical pertussis that occurred in Toronto in 2005–2006. Among 189 cases of pertussis, defined as PCR Ct value less than 40, only 42% met the clinical definition of pertussis and up to one third were positive for another respiratory pathogen. The mean Ct value for these cases was 38.41, from which arose the idea that some of these cases might represent transient colonization (11). Consequently, Papenburg and Fontela postulated an association between high Ct values and the presence of coinfection with respiratory pathogens (12). In our study, despite the fact that viral multiplex PCR was performed in a relatively low number of patients in the two groups, viral co-infections were four times more likely in patients with equivocal PCR results.

This large retrospective study evaluated consecutive children who were tested with a multiplex bacterial PCR for respiratory symptoms during a 22-month period in a tertiary care pediatric hospital in Montreal. One limitation of our study is the use of manual chart review for data collection, with hand-written notes that could have been interpreted differently by investigators. However, 10% of the charts were reviewed by two members of the team and inter-rater agreement was strong (kappa coefficient = 0.86) (13). Another limitation is that this study was a single centre study; patients who were investigated at the CHUSJ could have consulted elsewhere for treatment in the days following their visit—these data would be impossible to capture. However, our case series describes 12.5% of all pertussis cases reported in the province of Quebec during the study period (14).

Conclusion

Although there were some similarities in terms of disease severity, children with suspected pertussis, who had equivocal PCR results, had significantly different clinical presentations compared with those with positive results. In the context of limited public health resources, these results may inform the decision whether or not equivocal results need to be reported to public health by laboratories.

Authors' statement

MD – conceptualization, methodology, validation, investigation, data curation, writing of original draft, review and editing of final version
SM – conceptualization, methodology, validation, investigation, review and editing of final version
PDP – formal analysis, review and editing of final version
NB – methodology, review and editing of final version
DI – investigation, data curation, review and editing of final version
FR – investigation, resources, review and editing of final version
CQ – conceptualization, methodology, review and editing of final version, supervision, funding acquisition

Conflict of interest

None.

Funding

Dr. Quach is supported through an external salary award (FRQ-S merit, grant # 252775).

This research was supported by the CHU Sainte-Justine Research Institute (C. Quach's start-up funds).

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Influenza outbreaks in Ontario hospitals, 2012–2016

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Abstract

Background: Influenza outbreaks in hospital settings affect vulnerable patient populations and pose considerable risk of morbidity and mortality; however, key information regarding these outbreaks is limited.

Objective: To describe surveillance data on influenza outbreaks in Ontario hospitals between 2012–13 and 2015–16 and compare H3N2- and H1N1-dominant influenza seasons.

Methods: Hospital laboratory-confirmed influenza outbreaks occurring between September 1, 2012 and August 31, 2016 were analysed for indicators of outbreak duration and severity (case attack rate, pneumonia rate and fatality rate). Frequency, duration and severity of influenza A outbreaks were compared between H3N2- (2012–13, 2014–15) and H1N1-dominant seasons (2013–14, 2015–16).

Results: Over the four years, there were 256 hospital outbreaks involving 1,586 patients that included 91 cases of pneumonia and 40 deaths. The total number of outbreaks was lowest in the 2015–16 (n=36) and highest in the 2014–15 (n=117) influenza seasons. The 2014-15 season also had the highest number of influenza cases (n=753), pneumonia cases (n=46), fatalities (n=18) and hospital sites reporting ≥1 outbreak (n=72). Median outbreak duration ranged from 4.5 days in 2013–14 to 6.0 days in 2015–16. Comparisons of H3N2 and H1N1 seasons did not identify statistically significant differences in outbreak duration or severity; however, significantly more influenza A outbreaks than influenza B outbreaks were reported in H3N2 seasons compared with H1N1 seasons ($p<0.05$).

Conclusion: While H3N2-dominant years contribute to influenza morbidity and mortality through an increased number of hospital outbreaks, the duration and severity of influenza A outbreaks are not significantly different in H3N2 and H1N1 seasons.

Suggested citation: Murti M, Whelan M, Friedman L, Savic J, Johnstone J, Sider D, Warshawsky B. Influenza outbreaks in Ontario hospitals, 2012–2016. Can Commun Dis Rep 2018;44(9):201-5. https://doi.org/10.14745/ccdr.v44i09a03

Keywords: influenza, outbreak, acute care, hospital, morbidity, mortality

Introduction

Influenza is a significant cause of morbidity and mortality in Canada where there are approximately 3,500 deaths and 12,200 hospitalizations attributable to seasonal influenza annually (1). As of March 31, 2018, the Public Health Agency of Canada's FluWatch national influenza surveillance reported 1,663 influenza outbreaks in hospitals, long-term care facilities (LTCFs) and other settings during the 2017–18 influenza season (2). While LTCFs account for the majority of nationally reported influenza outbreaks, 10.5% (n=175/1,663) of outbreaks occurred in hospitals (2). Influenza introduced by patients, staff and visitors, poses a concern since many hospital patients are vulnerable to influenza and its complications due to their age, baseline health status and admission illness. For example, a 2002 review of 12 nosocomial influenza outbreak reports in acute care hospital settings in the United States found patient attack rates as high as 50% (range: 3–50%), with notably high mortality rates (range: 33–60%) (3).

Beyond outbreak totals reported in FluWatch, there is very limited information available on the characteristics of influenza outbreaks, such as duration and severity, in Canadian hospitals (4). Jurisdictions that have summarized characteristics of influenza outbreaks typically combine hospitals with other institutions, such as LTCFs, even though these settings differ in terms of patient populations, infection prevention and control standards, respiratory virus testing, and infrastructure differences, which can impact the detection, control and outcomes of outbreaks (5). Compared with LTCFs, where the vast majority of residents are older adults, hospital outbreaks may involve patients of varying ages, including younger adults who tend to be more vulnerable to H1N1 strains (6). Older adults typically experience higher morbidity and mortality in H3N2-dominant years (7-10). Therefore, influenza outbreaks in acute care settings warrant separate consideration and examination.

Further, characteristics of outbreaks may differ based on influenza subtype. In Ontario, H3N2-dominant

seasons are typically associated with greater numbers of laboratory-confirmed influenza A outbreaks in institutions compared with H1N1 dominant seasons; FluWatch reports indicate similar trends nationally (4,11). While there are more total numbers of outbreaks in H3N2 seasons, it is unknown whether hospital outbreaks in these seasons are more severe in terms of duration and complications compared to the hospital outbreaks that occur during H1N1 seasons (3,12). The aim of this report is to describe influenza outbreaks in Ontario hospitals for the four influenza seasons between 2012–13 and 2015–16, including their frequency, duration and severity, and to assess differences by H3N2- and H1N1-dominant seasons.

Methods

Data source

In Ontario, LTCFs, retirement homes, hospitals and other institutional settings must report all influenza outbreaks within their institution to their local public health unit (13). The provincial case definition for an influenza outbreak in a hospital is two or more cases of nosocomially-acquired acute respiratory infection (infection that is acquired during the delivery of health care that was not present or incubating at the time of admission) occurring within 48 hours on a specific hospital unit, with at least one of the cases being laboratory-confirmed influenza (13,14). The area (e.g., unit(s) or ward(s)) declared under outbreak within the hospital is referred to as the "at-risk area", and includes all patients in those areas.

Outbreak information (e.g., onset date, number of patient cases) is entered into Ontario's integrated Public Health Information System (iPHIS) (13). Reporting in iPHIS includes the number of outbreak cases, cases with pneumonia (confirmed by chest x-ray), deaths among cases where the fatality is related to the outbreak and the total number of patients in the at-risk area (13). Influenza typing (influenza A and/or B) is available, but influenza A subtyping (H3N2 versus H1N1) is not routinely reported in iPHIS.

On March 20, 2018, we extracted the following from iPHIS: data for reported and closed outbreaks with 'hospital' exposure setting or hospital indicated in the outbreak name that occurred between September 1, 2012 and August 31, 2016 that met the provincial case definition for an influenza outbreak. Influenza seasons were defined as the period between September 1 and August 31 of each year. We excluded outbreaks with missing case count data as well as outbreaks with hospital names that could not be matched to a list of 230 Ontario hospital sites from the Ministry of Health and Long-Term Care (15). We included outbreaks with fewer than two patient cases in the analyses if staff cases were also part of the outbreak (thereby fulfilling the Ontario case definition).

Data analysis

For each of the four seasons, we calculated the total number of outbreak cases and medians and ranges for the following outcomes: hospital sites reporting one or more outbreaks; outbreaks per hospital reporting an outbreak; duration of outbreaks; number of cases per outbreak; case attack rate (cases per patients in at-risk area); number of pneumonia cases; and number of case fatalities. Specific analyses for case attack rate and duration per year excluded individual outbreaks with missing data or that have an attack rate greater than 100%.

Outbreak duration was defined as the difference in number of days between the onset date of the index case and the onset date of the last case associated with the outbreak, as entered in iPHIS. This definition ensures consistent measurement of duration across outbreaks as there is hospital outbreak management team discretion on when an outbreak is declared over after illness onset in the last case.

Based on testing performed by Public Health Ontario Laboratory, the Ontario Respiratory Pathogen Bulletin's annual summary includes the dominant influenza A strain and proportion of all subtyped influenza A specimens (from community, hospital and outbreak) with that subtype: 2012–13 was H3N2-dominant (90.6%), 2013–14 was H1N1-dominant (85.7%), 2014–15 was H3N2-dominant (99.0%) and 2015-16 was H1N1-dominant (89.4%)(11). We aggregated data on influenza A outbreaks occurring in H3N2- and H1N1-dominant years. We compared the number of outbreaks and the proportions of cases with pneumonia and case fatalities between H3N2 and H1N1 seasons using chi-square tests. We compared the median duration of outbreaks, median number of outbreak cases and median attack rate between H3N2- and H1N1-dominant seasons using a Mann-Whitney-Wilcoxon non-parametric test for comparison of medians (16-19). Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, North Carolina, United States). As these analyses were consistent with routine surveillance, it was determined that they were exempt from Public Health Ontario Research Ethics Board review.

Results

Between 2012–13 and 2015–16, 101 hospitals in Ontario reported one or more influenza outbreaks, for a total of 256 outbreaks. **Table 1** summarizes the outbreak characteristics for each season. Of the 256 outbreaks, 19 had missing or nonsensical duration or case attack rate data and were only excluded from the applicable year-specific summaries. One outbreak included in the count of influenza A outbreaks had both influenza A and B detected.

Table 1: Comparison of hospital influenza outbreak characteristics across the 2012–13 to 2015–16 seasons in Ontario

Outcomes	Influenza season			
	2012–13	2013–14	2014–15	2015–16
Total number of outbreaks	65	38	117	36
– Influenza A: n (%)	63 (96.9%)	16 (42.1%)	112 (95.7%)	27 (75.0%)
– Influenza B: n (%)	2 (3.1%)	22 (57.9%)	5 (4.3%)	9 (25.0%)
Number of hospital sites reporting ≥1 outbreaks (% of total sites)	45 (19.6%)	30 (13.0%)	72 (31.3%)	29 (12.6%)
Median number of outbreaks per hospital site with an outbreak	1.0	1.0	1.0	1.0
– Range	1-6	1-2	1-7	1-4
Median duration of outbreaks, in days (range)	5.0	4.5	5.0	6.0
– Range	0–29	1–20	0–32	0–16
Total number of outbreak cases per season	465	179	753	189

Table 1: (*continued*) **Comparison of hospital influenza outbreak characteristics across the 2012–13 to 2015–16 seasons in Ontario**

Outcomes	Influenza season			
	2012–13	2013–14	2014–15	2015–16
Median number of cases per outbreak	5.0	3.0	5.0	5.0
– Range	1–45	2–11	2–60	1–14
Median percent case attack rate by at-risk area	16.1%	18.5%	15.9%	18.0%
– Range	4.1–70.8%	4.4–75.0%	4.1–66.7%	4.5–36.8%
Number of pneumonia cases (% of cases)[a]	25 (5.4%)	15 (8.4%)	46 (6.1%)	5 (2.6%)
Number of fatal cases (% of cases)[a]	12 (2.6%)	3 (1.7%)	18 (2.4%)	7 (3.7%)

Abbreviations: n, number
[a]Based on the total number of cases (n=1,586)

The median number of outbreaks per site remained constant at one per season across all four years, though some sites had as many as six (in 2012–13) or seven (in 2014–15) outbreaks. The median duration of an outbreak ranged from 4.5 to 6.0 days. There were a total of 1,586 cases of influenza associated with outbreaks over the four seasons, with 91 cases of pneumonia (5.7%) and 40 deaths (2.5%). The percentages of cases with pneumonia and death both show fluctuations and no consistent trend across seasons. The 2014–15 season had the highest number of outbreaks (n=117), the highest proportion of sites with one or more outbreak(s) (31.3%), the greatest number of cumulative outbreak cases (n=753), the site with the most number of outbreaks in a single season (n=7) and the outbreaks with the most number of cases (n=60) and longest duration (32 days) of the four seasons.

Table 2 summarizes the 218 influenza A outbreaks in H3N2- (n=175) vs H1N1- (n=43) dominant seasons. There were 17 outbreaks that due to missing or nonsensical data, were excluded from either or both duration and case attack rate summaries. There was significantly more influenza A than influenza B outbreaks in H3N2-dominant vs H1N1-dominant influenza seasons ($p<0.05$). The outbreak duration, number of cases per outbreak, case attack rate, percentage of cases with pneumonia and percentage of fatal case did not differ significantly with the dominant circulating strain.

Table 2: Comparison of hospital influenza A outbreaks in H3N2- versus H1N1-dominant seasons between 2012–13 and 2015–16 in Ontario

Outcomes	H3N2 seasons (2012–13, 2014–15)	H1N1 seasons (2013–14, 2015–16)	*p*-value
Number of influenza A outbreaks (% of influenza A out of influenza A and B outbreaks)	175 (96.2%)	43 (58.1%)	< 0.0001[a]
Median duration of outbreaks, in days	5.0	4.0	0.56[b]
– Range	0–32	0–16	0
Median number of cases per outbreak	5.0	5.0	0.49[b]
– Range	1–60	1–14	0

Table 2: (*continued*) **Comparison of hospital influenza A outbreaks in H3N2- versus H1N1-dominant seasons between 2012–13 and 2015–16 in Ontario**

Outcomes	H3N2 seasons (2012–13, 2014–15)	H1N1 seasons (2013–14, 2015–16)	*p*-value
Median percent attack rate by at-risk area per outbreak	16.0%	18.8%	0.66[b]
– Range	4.1–70.8%	4.5–58.3%	0
Number of pneumonia cases (% of cases)	69 (5.9%)	14 (6.2%)	0.85[a]
Number of fatal cases (% of cases)	30 (2.5%)	9 (4.0%)	0.23[a]

[a] Chi-square
[b] Mann-Whitney-Wilcoxon

Discussion

This study identified that hospital outbreaks occur on a regular basis in Ontario and contribute to overall influenza-associated morbidity and mortality. The majority of hospitals did not report any outbreaks during the four influenza seasons studied. Hospitals with outbreaks reported a median of one per season, lasting five days with five cases. A minority experienced a high burden of illness, with as many as seven outbreaks in one season, lasting up to 32 days, and as many as 60 cases in an outbreak; all of these occurred in the 2014–15 season, consistent with other evidence that 2014–15 was particularly severe due to the circulating strain and the low vaccine effectiveness that was documented that year (20). Our comparison of influenza A outbreaks in H3N2- and H1N1-dominant seasons found no significant differences in the median duration, median number of cases, case attack rates, cases with pneumonia or fatal cases.

This is the first surveillance report describing characteristics of hospital outbreaks in Ontario over multiple seasons. We did not identify any published reports comparing the characteristics of influenza A outbreaks in hospitals in H3N2 and H1N1 seasons. The limited comparable published data from other jurisdictions suggests public health surveillance reporting, beyond total numbers of outbreaks, should be leveraged to understand and reduce outbreak-associated morbidity and mortality.

Other published studies using the same definition of outbreak duration as applied in these analyses (i.e., time from the first case to last case), found longer median outbreak durations than observed here. In a 2002 review of acute hospital influenza outbreaks, Salgado et al. (3) reported a median outbreak duration of seven days; however, this was based on 12 outbreak reports from a range of hospital setting types compared with hospital outbreak surveillance in our study. Additionally, in a review of outbreaks of influenza-like illnesses in LTCFs in Winnipeg, Mahmud et al. (9) reported a median outbreak duration of 16 days. The longer duration seen in the present study may be due to the different exposure setting (LTCF vs hospital) and the inclusion of cases of influenza-like illnesses vs only laboratory-confirmed influenza. Notably, we included outbreaks where all of the cases occurred on the same day (i.e., duration of 0 days) in our analyses. It is unclear whether these entries represent the rapid implementation of outbreak control measures such that cases did not occur past the first day, or inaccuracies of data reporting.

The case attack rates in our analyses are consistent with the wide ranges reported in the hospital outbreak literature (3,21). The overall case fatality rate in this study (2.5%; n=40 deaths/1,586 cases) is lower than the 16% median mortality rate in acute and geriatric hospitals reported in the review by Salgado et al. (3), which was based on three outbreak reports from 1960 to 1982. The increased frequency of influenza A outbreaks in H3N2-dominant years is consistent with studies showing that H3N2 infection is more common than H1N1 in hospitalized seniors (12,22).

The primary strength of our work is that we analysed a large number of outbreaks over four influenza seasons and across seasons with both varying levels of community influenza activity and reported vaccine effectiveness (16–19, 23). Limitations of our findings arise from the use of routinely collected surveillance data. Outbreak data in iPHIS does not routinely include influenza A subtyping results, preventing comparisons by actual subtype. It is possible that some influenza A outbreaks in H1N1 years were due to H3N2, which could explain similarities in outbreak characteristics in H1N1- and H3N2-dominant seasons. Other data elements reported in iPHIS had a high frequency of missing data and/or data quality issues that restricted comparing other aspects of hospital outbreaks. Aggregate statistics on staff illness and patient and staff influenza immunization coverage within at-risk areas of the outbreak were subject to varying levels of completeness and accuracy, and were therefore too unreliable to include in these analyses.

The use of provincially reported aggregate outbreak data in iPHIS is also limited as data elements that could illuminate reasons for differences in outbreak characteristics are not captured in iPHIS. Individual case information (e.g., patient age, underlying health status, symptoms, laboratory testing or use of antivirals) is not available to assess its impact on the severity of an outbreak. In addition, information regarding the risk of transmission within the outbreak area (e.g., acuity/type of hospital ward, age of hospital, room/ward layout, level of infection prevention and control resources in the hospital) is not reported.

There are several uncertainties associated with these data; for example, the observation of hospital sites without outbreaks or those with a high number of outbreaks may indicate variation in infection control practices or outbreak reporting. Acute wards, with higher turnover of patients, may be more likely to 'miss' an outbreak if patients are discharged prior to their identification as a nosocomial case, while complex chronic care hospitals have longer patient stays, increasing both the risk of influenza transmission and the probability of influenza detection. Interpretation of how to report outbreak-related information may differ across hospitals and public health units, contributing to variability in reported values; for example, some outbreaks reported the same number of patients in the at-risk area as for the total number of patients in the hospital. It is unclear whether these outbreaks involved the entire hospital or instead represent reporting inaccuracies. Interpretation differences in the patient denominator for the at-risk area (available beds vs total number of patients present at any time during the outbreak) could also impact case attack rates.

These analyses are specific to Ontario and outbreak characteristics are influenced by the provincial guidance on management of influenza outbreaks in hospitals as well as reporting practices (24). Studies of hospital influenza outbreaks from other jurisdictions are needed to compare with our Ontario findings and establish targets for public health action to reduce the morbidity and mortality associated with hospital influenza outbreaks. Based on the very low vaccine effectiveness reported for the 2014–15 season (23) and other year-over-year differences in influenza seasons, future studies should include multiple seasons to further characterize the range of hospital outbreak activity.

Conclusion

Hospital outbreaks occur on a regular basis and contribute to influenza morbidity and mortality. Overall, we found a number of hospital influenza outbreak characteristics, including median duration, median number of cases per outbreak and patient attack rate, remained fairly consistent across the four influenza seasons studied. This consistency was regardless of the dominant influenza A subtype, although more hospital influenza A outbreaks were reported in H3N2-dominant seasons than in H1N1-dominant seasons. Improvements in completeness, accuracy and consistency of outbreak summary statistics from public health surveillance reporting would strengthen future analyses. Further consideration is also needed to determine the necessary minimum data set of case, outbreak and hospital level information for aggregate reporting to be able to address public health questions with respect to the monitoring, management and evaluation of hospital influenza outbreaks.

Authors' statement

MM – Conceptualization, writing-original draft, writing-review and editing, visualization
MW – Formal analyses, writing-original draft sections, writing-review and editing, visualization
LF – Writing-original draft sections, writing-review and editing
JS – Formal analyses, writing-review and editing
JJ – Writing-review and editing
DS – Writing-review and editing
BW – Writing-review and editing

Conflict of interest

None.

Acknowledgements

The authors would like to acknowledge the hospital and public health unit staff involved in managing and reporting these outbreaks. The authors would like to acknowledge Shelly Bolotin and Karin Hohenadal for their support in reviewing this work.

Funding

This work was supported by Public Health Ontario.

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Vaccine safety surveillance in Canada: Reports to CAEFISS, 2013–2016

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Abstract

Background: Canada has one of the strongest vaccine safety surveillance systems in the world. This system includes both passive surveillance of all vaccines administered and active surveillance of all childhood vaccines.

Objectives: To provide 1) a descriptive analysis of the adverse events following immunization (AEFI) reports for vaccines administered in Canada, 2) an analysis of serious adverse events (SAEs) and 3) a list of the top ten groups of vaccines with the highest reporting rates.

Methods: Descriptive analyses were conducted of AEFI reports received by the Public Health Agency of Canada (PHAC) by August 14, 2017, for vaccines marketed in Canada and administered from January 1, 2013 to December 31, 2016. Data elements in this analysis include: type of surveillance program, AEFIs, demographics, health care utilization, outcome, seriousness of adverse events and type of vaccine.

Results: Over the four year period, 11,079 AEFI reports were received from across Canada. The average annual AEFI reporting rate was 13.4/100,000 doses distributed in Canada for vaccines administered during 2013–2016 and was found to be inversely proportional to age. The majority of reports (92%) were non-serious events, involving vaccination site reactions rash, and allergic events. Overall, there were 892 SAE reports, for a reporting rate of 1.1/100,000 doses distributed during 2013–2016. Of the SAE reports, the most common primary AEFIs were anaphylaxis followed by seizure. Meningococcal serogroup C conjugate vaccines (given concomitantly) were responsible for the highest rates of AEFIs, at 91.6 per 100,000 doses distributed. There were no unexpected vaccine safety issues identified or increases in frequency or severity of expected adverse events.

Conclusion: Canada's continuous monitoring of the safety of marketed vaccines during 2013–2016 did not identify any increase in the frequency or severity of AEFIs, previously unknown AEFIs, or areas that required further investigation or research. Vaccines marketed in Canada continue to have an excellent safety profile.

Suggested citation: Ahmadipour N, Watkins K, Fréchette M, Coulby C, Anyoti H, Johnson K. Vaccine safety surveillance in Canada: Reports to CAEFISS, 2013–2016. Can Commun Dis Rep 2018;44(9):206-14. https://doi.org/10.14745/ccdr.v44i09a04

Keywords: vaccine safety, adverse events, immunization, surveillance

Introduction

Vaccines are the most cost-effective public health measure known. Despite this, Canada has one of the lowest immunization rates among developed countries. According to a 2013 UNICEF study, Canada was 28 out of 29 high income countries in terms of immunization rates (1). One reason for these low rates may be due to vaccine hesitancy. Fortunately, according to the 2015 Childhood National Immunization Coverage Survey this hesitancy is decreasing, with 97% of parents agreeing that childhood vaccines are safe and effective. Concern about potential side-effects was still common at 66% but this had decreased from 74% in 2011 (2).

Canada's vaccine safety surveillance system is considered one of the best in the world (3). The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is a federal, provincial, territorial (FPT) public health post-market vaccine safety surveillance system. CAEFISS is unique in that it includes both passive and active surveillance. Its primary objectives are to 1) continuously monitor the safety of marketed vaccines in Canada, 2) identify increases in the frequency or severity of previously identified vaccine-related reactions, 3) identify previously unknown adverse events following immunization (AEFIs) that could possibly be related to a vaccine, 4) identify areas that require further investigation and/or research

and 5) provide timely information on AEFI reporting profiles for vaccines marketed in Canada, which could help inform immunization programs and guidelines (4).

In Canada, health care providers, manufacturers and the public each have a role to play in vaccine pharmacovigilance (5). FPT public health officials maintain a close watch on vaccine safety through the Vaccine Vigilance Working Group (VVWG) of the Canadian Immunization Committee. The VVWG includes representatives from all FPT immunization programs as well as Health Canada regulators and the Immunization Monitoring Program ACTive (IMPACT) active surveillance program. The AEFI data from passive surveillance are subject to continuous analysis by the VVWG to detect potential vaccine safety concerns, which facilitates rapid identification and communication of emerging safety issues to enable an effective public health response. This report was developed with input and support from the VVWG membership.

A more comprehensive description of the roles and responsibilities for post-market pharmacovigilance can be found in the Canadian Immunization Guide and the CAEFISS webpage (4,5). Details on provincial and territorial (PT) vaccination schedules can be found on the PHAC website (6).

National reports on vaccine safety surveillance data are published periodically (7–17). The objective of this report is to provide a) a descriptive analysis of the adverse events following immunization reports for vaccines administered in Canada from 2013–2016, b) an analysis of serious adverse events (SAEs) and c) a list of the top ten groups of vaccines with the highest reporting rates.

Methods

Definitions

An AEFI is defined as any untoward medical occurrence that follows immunization but does not necessarily have a causal relationship with the administration of the vaccine. The adverse event may be a sign, symptom or defined illness (18).

A SAE is defined as any AEFI that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or results in a congenital anomaly/birth defect (19). This represents a temporal association and does not necessarily have a causal relationship with the vaccine.

Data sources

The CAEFISS is an FPT collaborative process that includes submission of AEFI reports from both passive and active surveillance.

Passive surveillance is initiated at the local public health level and relies on reporting of AEFIs by health care providers, vaccine recipients or their caregivers. Completed reports are sent to PT health authorities, where population level public health actions, as well as ongoing evaluation of immunization programs take place. AEFI reporting to the regional public health authority is mandatory in eight PT's and voluntary in the remaining six PT's. These reports are then submitted on a voluntary basis to PHAC for inclusion into CAEFISS (20). The PT health authorities also receive reports from federal authorities that provide immunization within their jurisdiction (including First Nations and Inuit Health Branch, Correctional Services Canada and Royal Canadian Mounted Police). Any AEFIs received by National Defence and the Canadian Armed Forces are reported directly to PHAC. On rare occasions, AEFI reports are submitted to PHAC directly from physicians, pharmacists, travel clinics and the public. These reports are entered into CAEFISS and a copy and/or reporter information is sent to the health authorities of the PT of origin.

As of January 2011, a change in reporting regulations required Market Authorization Holders (MAHs) to report AEFIs to Health Canada hence, MAHs gradually stopped reporting AEFI to PHAC. All MAH reports were therefore excluded from this report (accounting for 0.6% of all AEFI reports received by PHAC).

Active surveillance has been conducted by IMPACT since 1991. IMPACT is a pediatric, hospital-based network funded by PHAC and administered by the Canadian Paediatric Society (21). This network currently includes 12 pediatric centres across Canada where nurses, under the supervision of pediatric and/or infectious disease medical specialists, screen hospital admissions for target AEFIs, including neurologic events (e.g., seizures and Guillain-Barré syndrome), thrombocytopenia, vaccination site abscess/cellulitis, intussusception and other complications that may have followed vaccination and that led to a hospital admission (22,23).

During report processing, personal identifiers are removed from the AEFI reports prior to submission (via either hard or soft copies) to PHAC, where data are entered into CAEFISS (24). During entry, quality assurance is performed to resolve data discrepancies and identify and reconcile duplicate reports. Serious AEFIs are identified based on the case definition, and reported AEFIs and medical history information are coded using the International Medical Dictionary for Regulatory Activities (MedDRA, version 17) (25). Medical interventions, including concomitant medications are coded using the International Anatomical Therapeutic Chemical classification system. This coding is followed by a systematic medical case review by trained health professionals to assign a primary reason for reporting. For purposes of the medical case review, national case definitions for AEFI classification from the CAEFISS user guide were used (24).

Data elements in the analysis include the number and rate of AEFIs per year, primary reason for reporting, age and sex distribution, outcomes, an analysis of all SAEs, and a list of the top ten groups of vaccines with the highest reporting rates. Results in this report are presented by year of vaccine administration (2013–2016).

Data analysis

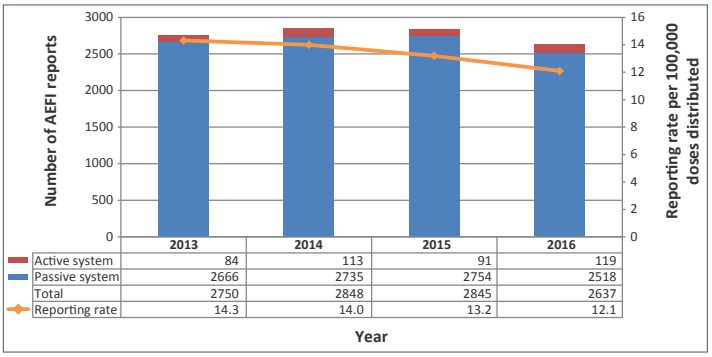
All AEFI reports submitted to CAEFISS by August 14, 2017 with a vaccination date from January 1, 2013 through December 31, 2016 were included in this report. Data from one jurisdiction was not included in this analysis due to technical issues with transmitting and receiving data to CAEFISS. Since this data was not included in the numerator, the population of this jurisdiction was not included in the denominator when calculating the national rate per 100,000 population.

Descriptive analyses were conducted using SAS enterprise guide software, version 5.1 (26). Where possible, reporting rates were calculated using vaccine doses distributed data provided by Market Authorization Holders under an agreement with PHAC. The number of doses distributed was used as a proxy measure of persons vaccinated in rate calculations for both overall rates and vaccine-specific rates. Statistics Canada annual population estimates were used as a denominator in rate calculations when a doses distributed-based rate could not be calculated (27).

Results

A total of 11,080 AEFI reports (2,750 AEFI reports in 2013, 2,848 in 2014, 2,845 in 2015 and 2,637 in 2016) from 12 PTs were received by CAEFISS during 2013–2016. Over 80 million vaccine doses were distributed, representing reporting rates of 12.1–14.3 per 100,000 doses distributed (**Figure 1**).

Figure 1: Total number of adverse events following immunization reports and reporting rate by year, 2013–2016

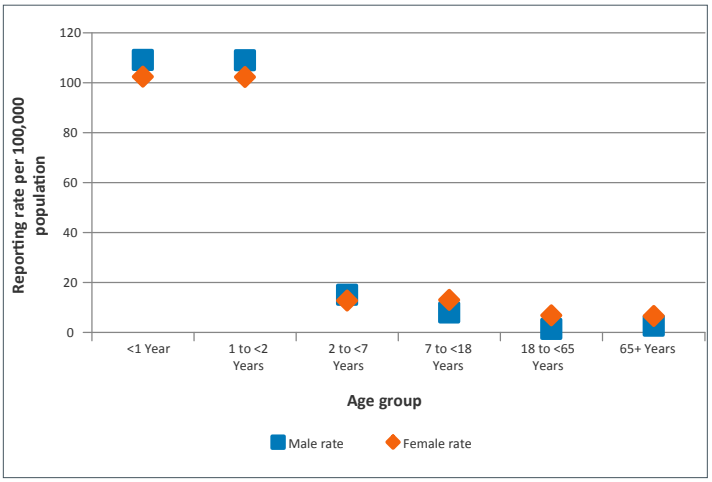


Abbreviation: AEFI, adverse events following immunization

Age and sex distribution

The reporting rates per 100,000 population, by age group and sex, are presented in **Figure 2**. The median age of all reports during the reporting period was 12 years (range: <1 month to 104 years). The majority (56%) of AEFI reports were for children and adolescents under 18 years of age. The highest reporting rates were in infants under one year of age (121.8/100,000 population), followed by children aged one to two years (with a rate of 121.3/100,000 population). Of the 11,080 reports, 63% were in females. Male predominance was observed for children under seven years of age and female predominance was observed among those seven years of age and older.

Figure 2: Proportion of adverse events following immunization reports by age group and sex, 2013–2016[a]



[a] Excluded: 56 reports with missing age, 136 reports with missing sex and three reports indicating sex as "other"

Table 1 provides the number of reports and reporting rates per 100,000 population by age group and year of vaccination. For all years, the highest reporting rates were observed in the less than one year and the one to less than two year age groups. Rates fluctuate slightly over the years in the two to less than seven year age group and for those seven years of age and older rates were relatively stable over the four years.

Table 1: Number of adverse events following immunization reports and reporting rate by age group, 2013–2016[a]

Subpopulation by age group	Count of AEFI reports (reporting rate per 100,000 population)				
	2013	2014	2015	2016	All years
<1 year	396 (117.8)	442 (131.2)	386 (114.0)	425 (124.9)	1,649 (121.8)
1 to <2 years	379 (112.6)	399 (117.9)	422 (124.7)	444 (130.6)	1,644 (121.3)
2 to <7 years	313 (18.3)	331 (19.3)	242 (14.1)	213 (12.5)	1,099 (16.0)
7 to <18 years	425 (11.5)	436 (11.8)	453 (12.2)	458 (12.2)	1,772 (11.9)
18 to <65 years	944 (4.8)	1,006 (5.0)	1,028 (5.1)	802 (4.0)	3,780 (4.7)
65+ years	279 (6.0)	225 (4.7)	306 (6.2)	270 (5.3)	1,080 (5.5)
All ages[a]	2,736 (9.0)	2,839 (9.2)	2,837 (9.1)	2,612 (8.3)	11,024 (8.9)

Abbreviation: AEFI, adverse events following immunization
[a] Excluded: 56 reports with missing age

Primary reason for reporting

During the medical case review, a primary AEFI category was assigned as the main reason for reporting and was further classified to a sub-category. **Table 2** lists the primary AEFIs and their sub-categories, by total reports. The most common primary

reasons for reporting were vaccination site reactions followed by rash alone which accounted for 54% of all reports submitted (8% of all SAE reports) in 2013–2016.

Table 2: Frequency of events and percent of serious events for each primary adverse event following immunization sub-category, 2013–2016

Primary AEFI	Primary AEFI sub-category	Number of Reports (N=11,080)	Serious %
Allergic or allergic-like events	Anaphylaxis	111	100
	Other allergic events[a]	1,526	1
	Oculo-respiratory syndrome	158	1
Infection/ syndrome/ systemic symptoms (ISS)	Fever only	52	21
	Infection	182	34
	Influenza-like illness	82	4
	Rash with fever and/or other illness	346	5
	Syndrome as indicated in AEFI reports (e.g., Kawasaki)	90	79
	Systemic (when several body systems are involved)	389	14
Neurologic events	Aseptic meningitis	16	81
	Ataxia/cerebellitis[b]	9	67
	Bell's palsy	29	0
	Encephalitis / acute disseminated encephalomyelitis (ADEM) / myelitis	25	87
	Guillain-Barré syndrome	32	88
	Other paralysis lasting more than 1 day	7	43
	Seizure	389	48
	Other neurologic event[c]	94	20
Rash alone	Generalized	1,493	0
	Localized	225	0
	Location not specified/ extent unknown	122	0
Immunization anxiety	Presyncope	31	3
	Syncope	57	2
	Other anxiety-related event[d]	33	6
Vaccination site reactions	Abscess (infected or sterile)	54	11
	Cellulitis	907	4
	Extensive limb swelling[e]	363	1
	Pain in the vaccinated limb of 7 days or more	134	1
	Other local reaction[f]	2,691	1
Vaccination error	Vaccination error	9	0
Other events[g]	Arthralgia	73	5
	Arthritis	36	28
	Gastrointestinal event	549	3
	Hypotonic-hyporesponsive episode	74	26
	Intussusception	29	83

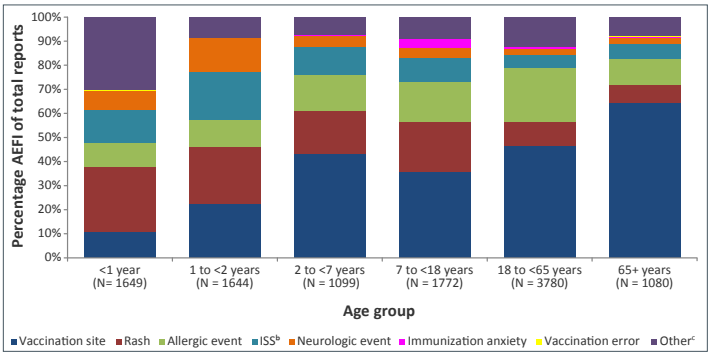
Table 2: *(continued)* **Frequency of events and percent of serious events for each primary adverse event following immunization sub-category, 2013–2016**

Primary AEFI	Primary AEFI sub-category	Number of Reports (N=11,080)	Serious %
Other events[g]	Anaesthesia/Paraesthesia	203	2
	Parotitis	9	0
	Persistent crying	72	3
	Sudden infant death syndrome	6	100
	Sudden unexpected/ unexplained death syndrome	3	100
	Thrombocytopenia	43	81
	Other events[h]	327	14

Abbreviations: AEFI, adverse events following immunization; N, number
[a] "Other" includes, but is not limited to, hypersensitivity and urticarial
[b] "Cerebellar ataxia" is defined as sudden onset of truncal ataxia and gait disturbances (22). Of note, this assumes absence of cerebellar signs appearing with other evidence of encephalitis or Acute Disseminated Encephalomyelitis (ADEM), in which case it would be classified according to the Brighton-Collaboration case definition (23)
[c] "Other" includes, but is not limited to, seizure like phenomena and migraine
[d] "Other" includes, but is not limited to, dizziness and dyspnoea
[e] Extensive limb swelling of an entire proximal and/or distal limb segment with segment defined as extending from one joint to the next (24)
[f] "Other" includes, but is not limited to, vaccination site pain and vaccination site swelling
[g] "Other" Other events in the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) form
[h] "Other" includes, but is not limited to, lymphadenopathy and arthralgia

Figure 3 presents the distribution of AEFIs by primary reason and age group for reporting as determined during the medical case review. Vaccination site reactions were the most common, followed by rash and allergic events. Vaccination site reactions represented the majority for all the age groups except for children under the age of two. For children under the age of one, the most commonly reported AEFI was other (includes sub-categories such as gastrointestinal disorder, persistent crying and hypotonic-hyporesponsive episode), followed by rash. For children between the ages of one and less than two years, the most commonly reported AEFI was rash, followed by vaccination site reactions and infection/syndrome/systemic symptoms (ISS).

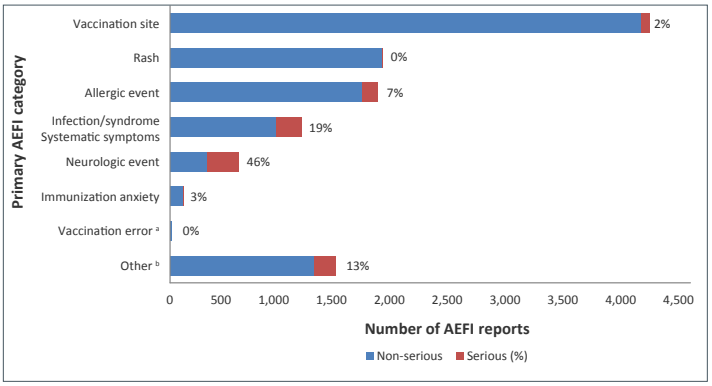
Figure 3: Percentage of adverse events following immunization reported by age group, 2013–2016[a]



Abbreviations: AEFI, adverse event following immunization; ISS, infection/syndrome/systemic symptoms; N, number
[a] Excluded: 56 reports with missing age
[b] ISS are primarily events involving many body systems often accompanied by fever. It includes sub-categories such as recognized syndromes (e.g. Kawasaki syndrome, fibromyalgia, etc.), fever alone, influenza-like illness, and systemic events (such as fatigue, malaise, and lethargy). It also includes evidence for infection of one or more body parts
[c] Other includes arthralgia, arthritis, hypotonic-hyporesponsive episode, intussusception, gastrointestinal diseases, anaesthesia/paraesthesia, parotitis, persistent crying, thrombocytopenia, sudden infant death syndrome (SIDS) and sudden unexpected/unexplained death syndrome (SUDS)

Figure 4 shows the primary AEFI categories and the proportion of each category that is considered serious. The proportion ranged from 0–46%. The proportion of serious events was highest for the neurological event category (46%), followed by ISS (19%). Of note, vaccination errors included only a small number of reports (nine AEFI reports) and no serious reports.

Figure 4: Primary adverse event following immunization category by seriousness, 2013–2016



Abbreviation: AEFI, adverse event following immunizations
[a] Vaccination errors included only a small number of reports (nine AEFI Reports) and no serious reports
[b] Other includes arthralgia, arthritis, hypotonic-hyporesponsive episode, intussusception, gastrointestinal diseases, anaesthesia/paraesthesia, parotitis, persistent crying, thrombocytopenia, sudden infant death syndrome (SIDS) and sudden unexpected/unexplained death syndrome (SUDS)

For children less than 18 years of age, 7% (n=407) of all submitted AEFI reports were through active surveillance. Even though the proportion is small, they represented 56% (n=401) of all serious AEFI reports submitted for this age group, reflecting the contribution of the hospital-based active surveillance system. (*Note: Data not shown; numbers do not completely correspond to the percentages as the percentages have been rounded to the nearest integer.*)

Health care utilization

Table 3 shows the reported highest level of care sought following an AEFI. The most frequently reported health care usage was non-urgent health care visit (37%). Most people with a reported AEFI (93%) did not require hospitalization. In almost 25% of cases, no health care was sought.

Table 3: Health care utilization sought for adverse events following immunization, 2013–2016

Highest level of care sought	N	%
Required hospitalization (>24 hrs)	764	7
Resulted in prolongation of existing hospitalization	4	<1
Emergency visit	2,126	19
Non-urgent visit	4,084	37
Telephone advice from a health professional	487	4
None	2,542	23
Unknown	323	3
Missing	750	7
Total	11,080	100

Abbreviation: N, number

Outcome

The outcome at time of reporting for all AEFI reports is shown in **Table 4**. Full recovery was reported in 76% of the reports. For those not fully recovered at the time of reporting (18%), the reports are revised when updated information is sent to CAEFISS.

Table 4: Outcome at time of reporting for all reports, 2013–2016

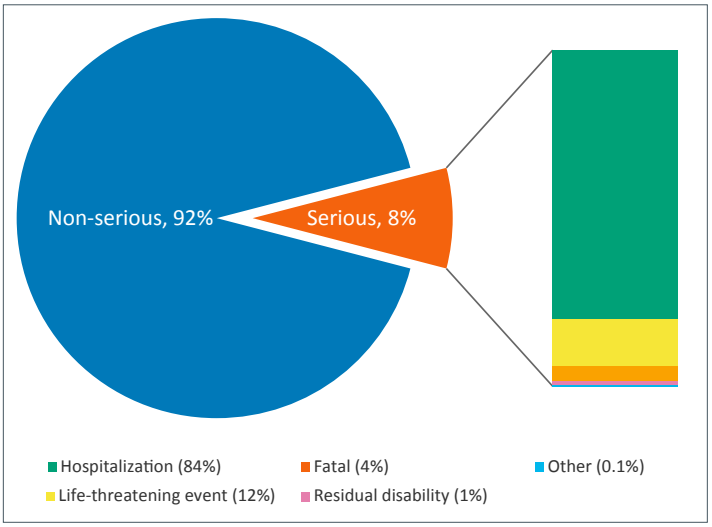
Outcome	N	%
Fully recovered	8,464	76
Not yet recovered at time of reporting	1,948	18
Permanent disability/incapacity	12	<1
Death	32	<1
Unknown	532	5
Missing	92	<1
Total	11,080	100

Abbreviation: N, number

Serious adverse events reports

Overall there were 892 SAE reports out of over 80 million vaccine doses distributed during the reporting period. This represents a rate of 1.1/100,000 doses distributed and 8% of all AEFI reports over the four year time period (range: 1.0 to 1.2 reports per 100,000 doses distributed). **Figure 5** shows the proportion of SAE reports resulting from hospitalization (n=745), life threatening events (n=103), fatal outcome (n=32), residual disability (n=11) and other reasons (n=1).

Figure 5: Classification of serious adverse events reports, 2013–2016



Note: Percentage rounding leads to slightly more than 100%

Among the SAE reports, the most frequently reported primary AEFI was seizure (20.1%), followed by anaphylaxis (12.4%). The majority of SAEs were in children and adolescents less than 18

years of age (80%). Over half of these were reported in children under two years of age; which was to be expected, due to the number of vaccines provided to this age group to protect them when they are most vulnerable to vaccine-preventable diseases.

The majority (73%) of SAE reports had fully recovered at the time of reporting. There were roughly 15% (n=137) of SAE reports where patients had not fully recovered, at the time of reporting. These reports are revised when updated information is received by CAEFISS. The remaining outcomes for SAE reports included fatal outcome (n=32, 3.6%), permanent disability/incapacity (n=10, 1.1%), outcome unknown (n=60, 6.7%) and information on outcome was missing (n=2, 0.3%).

All 32 reports of death underwent a careful review and all were found not to be attributable to the vaccines administered. Nine of these (28%) were reported in the youngest age group (less than one year of age); of which six were reported as sudden infant death syndrome (SIDS) and three as resulting from other underlying medical conditions (cerebral infarction, cardiac arrest and complications during nasogastric feeding). Seven deaths were reported in the one to less than two years old age group, of which three were reported as sudden unexplained death syndrome (SUDS), three due to infection not related to the administered vaccine(s) (pneumococcal, streptococcus pneumonia/staphylococcus, necrotizing encephalitis) and one due to a pre-existing condition (brain injury). There were two deaths due to underlying conditions (congenital disease and severe brain injury during birth) reported in the two to less than seven years old age group, and one death due to pre-existing condition (epilepsy) in the seven to less than 18 years old age group. The remaining 13 deaths were reported in adults: six in the 18 to 65 year old age group and seven in the 65+ year old age group (age range: 49–93 years), all of whom had pre-existing medical conditions. The listed causes of death included cardiovascular diseases (myocardial infarction, ischemic heart disease and atherosclerosis), lung disease (chronic obstructive pulmonary disease, asthma), central nervous system disease (dementia, H1N1 encephalitis, cerebral palsy and intracranial empyema), malignancy (lung and breast cancer), immunosuppression and diabetes mellitus.

Top 10 vaccine groups for highest reported AEFIs

During a vaccination visit, one or more vaccines may be administered. Among the 11,080 reports, a total of 18,134 vaccines were administered, an average of two vaccines per report (range 1–6). **Table 5** lists the 10 vaccine groups with the highest reporting rates, and shows 1) the number and reporting rates of AEFI reports for each of these vaccines (given alone or concomitantly with other vaccines), 2) the number and proportion of reports when the vaccine was administered alone and 3) the number and reporting rate of serious reports associated with the administration of that vaccine alone. The vaccine with the highest rate of AEFI reports submitted was Meningococcal serogroup C conjugate vaccine with a rate of 91.6 per 100,000 doses distributed (n= 1,346) with the vast majority non SAEs. Although the Meningococcal serogroup C vaccine had the highest rate, the greatest number of AEFI reports submitted was for the influenza vaccine (n=3,405; 7.1 per 100,000 doses distributed; data not shown).

Table 5: List of top ten vaccines for total adverse event reports following immunization and total number of reports and serious adverse events when vaccine administered alone, 2013–2016

Vaccine group	Vaccine trade name	Reporting rate per 100,00 doses distributed		Reports vaccine administered alone		Reports of SAEs from vaccine administered alone[a]	
		N	%	N	%	N	Rate[a]
Meningococcal serogroup C conjugate	Meningitec® Menjugate® Neis Vac-C®	1,346	91.6	33	2	4	0.3
Diphtheria, tetanus toxoid, acellular pertussis, inactivated poliomyelitis	Quadracel® Infanrix™-IPV	167	76.8	92	55	4	1.8
Diphtheria, tetanus toxoid, acellular pertussis, hepatitis B, inactivated poliomyelitis, haemophilus type b	Infanrix hexa™	462	65.9	35	8	2	0.3
Pneumococcal conjugate	Prevnar® Synflorix™ Prevnar® 13	2,098	64.4	64	3	5	0.2
Measles, mumps, rubella, varicella	Priorix-Tetra™ Proquad™	1,075	59.8	86	8	11	0.6
Meningococcal B	Bexsero®	212	57.1	160	75	17	4.6
Haemophilus influenzae type b conjugate	ACT-HIB® Hiberix® Liquid PedvaxHib®	39	45.9	4	10	0	0.0
Rabies	Imovax® Rabies RabAvert®	80	43.2	64	80	4	2.2
Pneumococcal polysaccharide	Pneumo® 23 Pneumovax® 23	915	42.9	452	50	28	1.3
Diphtheria, tetanus toxoid, acellular pertussis, inactivated poliomyelitis, Haemophilus type b	Pediacel® Infanrix™ - IPV/HIB Pentacel®	1,512	40.7	422	28	38	1.0

Abbreviations: N, number; SAE, serious adverse events
[a] Rate is per 100,000 doses distributed

Discussion

Between 2013 and 2016, the overall average annual AEFI reporting rate was 13.4/100,000 doses distributed (range: 12.1 to 14.3) or 8.9/100,000 population. This rate is lower than that reported in the 2012 CAEFISS annual report which had a rate of 10.1/100,000 population (17) and the 2015 Australian annual report, which had a rate of 12.3 per 100,000 population (28). Missing data from the one jurisdiction would have accounted for an estimated 2,000 AEFI reports over the four years, so we recalculated the rate per 100,000 and the overall rates were

still lower than the 2012 rates. The differences in Canadian reporting rates may be due to under-reporting, the use of combined vaccines in children could result in fewer reports being submitted (e.g., measles, mumps, rubella vaccine (MMR) and varicella vaccines were combined into MMRV), variations in the reporting of expected milder events, and the exclusion of Market Authorization Holders reports from this analysis. Additionally for Australia there would be differences in reporting structures. No unexpected vaccine safety issues or increases in frequency or severity of expected adverse events were identified during the reporting period.

The majority of AEFI reports involved vaccines given to infants and young children. This was as expected, given that this age group receives many vaccines—both at a single visit and spaced closer together— affording more opportunities to report to a health care provider. A greater proportion (63%) of reports involved females. This is similar to other findings where females in the adult population were found to consistently report more adverse effects (7-17,29). The reported sex differences by age can also be explained in part by higher vaccine coverage in female adults (30). Sex-specific differences were significant ($p<0.05$) in those seven years of age and older, with a higher AEFI reporting rate seen in females compared with males. This is similar to results found in other studies that have studied sex-specific differences in AEFI reporting rates (29,31,32). There were more male than female AEFI reports submitted for those under seven years of age; however, this difference was not significant.

The majority of reported adverse events from approximately 80 million doses of vaccine distributed in Canada were the expected, non-serious vaccination site reactions, such as pain and redness, rash and allergic events, such as hypersensitivity. Over the four year time period, 8% of AEFIs reported were serious adverse events. This proportion is slightly higher than that reported in the United States for the same time period (5%) and compared to previous years in Canada, but lower than that reported in Australia in 2015 (15%) (17,28,33). The majority of SAEs occurred in children and adolescents, which may in part be due to IMPACT, which contributes over half of all serious AEFI reports for those under the age of 18 years and looks for specific surveillance targets in children (20,34). At the time of reporting, the majority of the SAEs had fully recovered. Of the 32 deaths reported over the four year time period, none were found to be attributable to the vaccines administered.

Limitations

Passive surveillance for AEFIs is subject to limitations such as underreporting, lack of certainty regarding the diagnostic validity of a reported event, missing information regarding other potential causes such as underlying medical conditions or concomitant medications and the different AEFI reporting practices by jurisdictions within Canada, possibly leading to over/under-reporting of mild AEFIs from some FPTs. Despite these limitations, passive surveillance is useful for detecting potential vaccine signals, which can be further investigated and verified. Seasonality was not analyzed as a potential variable in this report.

There are also limitations associated with active surveillance. IMPACT uses predetermined AEFI targets (such as seizure), which may limit its ability to identify new adverse reactions to immunizations. In addition, IMPACT focuses on admitted pediatric cases, which means only the most serious cases are detected. Lastly, IMPACT is not comprehensive, as it covers only 90% of Canada's tertiary care pediatric beds and hospital admissions (23,34). Despite these limitations, IMPACT is able to fulfill an important role in vaccine safety surveillance by actively identifying targeted serious AEFIs in the pediatric population.

In addition, the number of doses administered in the population cannot be determined therefore either doses distributed or population statistics are used as the denominator. The use of the doses distributed can underestimate rates, as they do not take wastage into account. Furthermore, doses distributed in one year may not be administered in that same year, further limiting the accuracy of the doses distributed denominator. Despite these limitations, a doses distributed-based denominator for rate calculations was used when possible in this report as a population-based denominator assumes similar distribution of vaccine doses across population subgroups, although this may not be true in all cases.

Conclusion

Canada has a comprehensive vaccine surveillance system that revealed an average AEFI rate of 8.9/100,000 population. There were no unexpected vaccine safety issues identified or increases in frequency or severity of expected adverse events. The majority of reported AEFIs were expected and mild in nature and there were no unexpected or increases in serious adverse events. Vaccines marketed in Canada continue to have an excellent safety profile.

Authors' statement

NA – Conceptualization, methodology, validation, writing-original draft
KW – Writing-review and editing, supervision
MF – Conceptualization, methodology, validation, software, formal analysis, writing-original draft, writing-review and editing
CC – Software, formal analysis, validation, writing-original draft, writing-review and editing
HA – Validation, writing-review and editing, supervision
KJ – Writing-review and editing

Conflict of Interest

None.

Acknowledgments

This report would not be possible without the contribution of the public, public health professionals, and local/regional and

provincial/territorial public health authorities who submit reports to CAEFISS as well as the ongoing collaboration of the members of the Vaccine Vigilance Working Group. Furthermore, we would like to thank the members of this group for input and support in the development of this report. We would like to thank each individual who takes the time to submit an AEFI report for their contribution to vaccine safety in Canada.

Funding

This work was funded, in entirety, by the Public Health Agency of Canada.

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Rat bite fever on Vancouver Island: 2010–2016

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Abstract

Background: Rat bite fever (RBF) is a rare bacterial zoonotic infection caused by *Streptobacillus moniliformis* and *Spirillum minus*, which are found naturally in rodent respiratory tracts. Recently, multiple cases of RBF were observed on Vancouver Island, British Columbia.

Objective: To conduct a case series analysis of cases of RBF on Vancouver Island between 2010 and 2016 to characterize the epidemiology, presentation, microbiology and treatment of RBF.

Methods: Cases were identified through queries of discharge diagnosis and microbiology laboratory information. Clinical details were collected through review of electronic and paper chart reviews of hospital documentation from Island Health.

Results: Eleven cases of RBF on Vancouver Island were identified between 2010 and 2016. Most cases of RBF were confirmed with identification of *S. moniliformis* by culture or molecular techniques. All cases presented with fever, and a subset had one or more of the following: myalgia, rash, polyarthralgia, joint effusions, and emesis. All cases were successfully treated with penicillin, ceftriaxone or doxycycline. Seven cases required hospitalization, but there were no deaths or significant morbidity.

Conclusion: This is the largest single case series of RBF in Canada. Diagnosis requires a high index of suspicion by clinicians and early intervention is necessary to prevent morbidity and mortality.

Suggested citation: Hryciw BN, Wright CP, Tan K. Rat bite fever on Vancouver Island: 2010–2016. Can Commun Dis Rep 2018;44(9):215–9. https://doi.org/10.14745/ccdr.v44i09a05

Keywords: Rat bite fever, zoonotic infection, *Streptobacillus moniliformis*, *Spirillium minus*

Introduction

Rat bite fever (RBF) is a rare zoonotic infection caused by gram-negative *Streptobacillus moniliformis* and *Spirillium minus* (1,2). These bacteria are part of the commensal flora (i.e., the normal flora of the mouth) of healthy domesticated or laboratory rats (3). *S. moniliformis* is the predominant pathogen throughout North America, whereas *S. minus* is more prevalent in Asia where RBF is also known as "sodoku" (4,5). RBF is aptly named as the classical cause of infection occurs through rodent bites; however, it can also occur through scratches or mucocutaneous contact with rodent saliva, urine or feces (4). Historically, the populations at risk for developing RBF were limited to laboratory personnel and those of low socioeconomic status (6). The domestication of rodents has led to a broadening of the epidemiology of RBF to include pet rodent owners and pet store employees (6,7) and, with an increase in rodent handling, there has been a concomitant increase in rat bites. One report estimated 40,000 rat bites per year in the United States, of which, 2% caused infection (8). Previous studies have noted that RBF represents a significant and potentially growing public health concern and consequently, there exists a need to better understand RBF clinically (5,9).

Clinical presentation, diagnosis and treatment

Following inoculation of the pathogen, the incubation period for *S. moniliformis* is typically fewer than seven days but ranges from three days to three weeks (4). RBF is classically characterized by overt symptoms of fever, rigors, rash and polyarthralgia. Additional symptoms may include fatigue, emesis, myalgia, headache and pharyngitis (10). As symptoms are non-specific and variable, the clinical diagnosis of RBF is often missed if the history of rodent exposure is not identified. Infections by *S. minus* have a slightly different clinical presentation, with induration and possible ulceration of the bite site and associated adenopathy after a 14- to 18-day incubation (4). Complications of untreated RBF include the development of myocarditis, pericarditis, meningitis, amnionitis and abscesses in a variety of organs, as well as mortality in up to 13% of cases (11–14).

Recognition of RBF within the microbiology laboratory is often difficult and delayed given the fastidious nature of both *S. moniliformis* and *S. minus* (1,4). The organisms are slow to cultivate and growth may be inhibited by substances within the culture media. Fortunately, the organisms are typically susceptible to a variety of antibiotics including beta-lactam antibiotics, clindamycin, erythromycin and tetracycline (3,4). Among these, the recommended treatment is penicillin (15).

Canadian context

Case reports of RBF in Canada were rarely documented until 2002 (16), although cases have been described in Canada since the early half of the 20th century (17,18). Subsequently, a total of seven cases of *S. moniliformis* infections were reported across Canada, predominantly in Ontario and Quebec (16,19–21). Most recently in 2013, a single case report from Vancouver Island was reported (22). Including that recent case, we have observed several confirmed cases of RBF on Vancouver Island since 2010.

The objective of this case series is to describe the etiology, epidemiology and clinical features of RBF amongst the population on Vancouver Island between 2010 and 2016. Secondary objectives are to examine patient outcomes, including the length of hospital stay, treatment and consequent sequelae.

Methods

Setting and population

Island Health is a regional health authority that provides inpatient and emergency patient care to all 765,000 residents of Vancouver Island. RBF cases were identified through queries of the Island Health's Enterprise Data Warehouse. Specifically, the queries were placed against the Discharge Abstract Database for admitted patients using ICD-10-CA (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada) diagnosis codes for "Streptobacillosis" (A25.1) or "Rat-bite fever, unspecified" (A25.9), and against the microbiology laboratory information system for *S. moniliformis* or *S. minus* between January 2010 and December 2016. Patients with microbiological confirmation of either *S. moniliformis* or *S. minus*, or those with a history of rodent exposure and a compatible clinical syndrome, were included in this case series. Data was collected through retrospective chart reviews of identified cases regarding the clinical features upon presentation, treatment course provided and health outcomes. Institutional research ethics approval was sought and received for this study.

Data collection and analysis

Epidemiological and clinical details from identified cases were collected from hospital electronic medical records and paper charts. In particular, an attempt was made to record, where documented, any information regarding exposure source, including the context of interaction, such as bites, scratches or contact with either domestic, laboratory or wild rodents. The population data was analyzed using descriptive statistics to estimate the epidemiology, clinical features and outcomes between patients.

Results

Eleven cases of RBF were identified from Vancouver Island between 2010 and 2016 (**Table 1**). The median age of patients at diagnosis was 20 years old and ranged from five to 57 years of age. The cases were divided without significant gender bias, withfive male patients and six female patients. Nine patients reported a history of rodent exposure (82%), all of which were from pet rats. Among the five cases with documented scratches and/or bites, three provided a date of the bite or scratch. The time between exposure and presentation to health care providers were seven, eight and 19 days.

Table 1: Reported cases of rat bite fever on Vancouver Island from 2010 to 2016

Age (years) /sex	Rat exposure[a]; route of inoculation	Incu-bation	Diagnostics; pathogen	Clinical features and compli-cations	Treatment regimen	Days of antibiotic therapy[b]
5/M	+ ; NR	Unknown	Culture -, 16S RNA +; *S. moniliformis*	Fever, emesis	Ceftriaxone, penicillin	7 (4d IV)
7/F	+ ; NR	Unknown	Culture -, 16S RNA -; unknown	Fever, rash, polyarthralgia, emesis, joint effusion, sepsis	Gentamicin, penicillin	14 (7d IV)
14/F	+ ; Bite and scratch	7 days	Culture +; *S. moniliformis*	Fever, myalgia, rigors	Ceftriaxone, amoxicillin	16 (6d IV)
17/F	NR ; NR	Unknown	Culture +; *S. moniliformis*	Fever, back pain	Ceftriaxone	Unknown
17/M	+ ; Scratch	Unknown	Culture +, 16S RNA +; *S. moniliformis*	Fever, polyarthralgia, joint effusion	Ceftriaxone	42 (42d IV)
20/M	NR ; NR	Unknown	Culture +; *S. moniliformis*	Fever, rash, polyarthralgia, back pain	Ceftriaxone, penicillin	14 (7d IV)
21/F	+ ; Bite	Unknown	Culture +; *S. moniliformis*	Fever, joint effusion	Ceftriaxone, penicillin	11 (4d IV)
21/M	+ ; NR	Unknown	Culture +; *S. moniliformis*	Fever, myalgia	Doxycycline	14 (no IV)
28/F	+ ; NR	Unknown	Culture +; *S. moniliformis*	Fever, rash, polyarthralgia, emesis, diarrhea, pharyngitis	Penicillin	21 (3d IV)
30/F	+ ; Scratch	8 days	Culture +; *S. moniliformis*	Fever, polyarthralgia, emesis, headaches query erythema nodosum	Ceftriaxone	28 (28d IV)
57/M	+ ; Bite	19 days	Culture -, 16S RNA +; *S. moniliformis*	Fever, rigors	Ceftriaxone, doxycycline	38 (28d IV)

Abbreviations: d, days; F, Female; IV, intravenous; M, male; NR, none reported; RNA, ribonucleic acid; *S. moniliformis*, *Streptobacillus moniliformis*; -, negative; +, positive
[a] All exposures were from pet rats
[b] Duration of intravenous therapy in parenthesis

Signs and symptoms documented at initial presentation were included for all 11 cases. Fever, at least intermittently, was reported in all cases (100%). Pronounced signs and symptoms included polyarthralgia in five cases (45%), rashes in three cases (27%) and joint effusions in three cases (27%). Other common symptoms included emesis (36%), myalgia (18%), rigors (18 %) and back pain (18%). Two cases (18%) reported to have complications or potential complications; one had sepsis and the other was suspected to have erythema nodosum, although no further information was subsequently documented.

Ten (91%) of the 11 cases were confirmed by microbiology diagnosis, and the remaining case was diagnosed clinically based on history and symptoms. Blood cultures were performed on all cases using routine blood culture media, BD BACTEC Plus Aerobic and BD BACTEC Lytic Anaerobic (Becton Dickinson, Sparks, Maryland). Eight (73%) were culture-positive for *S. moniliformis*. Two additional cases were identified based on the presence of *S. moniliformis* 16S ribonucleic acid (RNA) within the culture-negative blood culture media or from a joint aspirate. In one case with positive blood cultures, *S. moniliformis* was also

successfully identified by 16S RNA analysis of fluid collected from an effused knee joint fluid. With the four most recent cases with positive blood cultures, the blood culture bottles signalled positive within 24 hours of incubation and subcultures of these on solid media demonstrated pinpoint growth of colonies within 48 hours. *S. moniliformis* was identified by Matrix Assisted Laser Desorption/Ionization Time-of-Flight (MALDI-ToF) mass spectrometry (Bruker Daltonics, Billerica, Massachusetts) in these four cases. Non-standardized susceptibility testing found the organisms in these four cases to be susceptible to penicillin and ceftriaxone.

Seven cases required hospitalization; the median length of stay was five days, and the range was three to 17 days. Complete treatment regimens were documented for all cases with the exception of one, which identified the antibiotic but did not describe the length of treatment (Table 1). Ten cases (91%) used intravenous beta-lactam antibiotics as part of the initial treatment regimen, with ceftriaxone as the most frequently used antibiotic in both the inpatient and outpatient settings. The remaining case used solely oral doxycycline, i n part due to the patient's documented penicillin allergy. In nine cases (82%), treatment was initiated with single-agent antibiotics, while in two cases (18%), combination antibiotics were used as empiric therapy before adjusting antibiotics based on sensitivities. The median and average total duration of antibiotic therapy was 14 days, but the range varied from seven to 42 days. For all patients who were treated with antibiotics, treatment included a course of outpatient antibiotics with either intravenous or oral stepdown therapy.

Discussion

This is the largest single case series of RBF published in Canada. A case series from San Diego County, which had a population of 3,095,313 people in 2010, recorded 17 cases of RBF between 2000 and 2012 (23). Interestingly, in Vancouver Island, which had a population of only 746,058 people in 2010, 11 cases were documented between 2010 and 2016. Thus, the estimated population-corrected annual incidence of RBF on Vancouver Island was 1.34 per million inhabitants per year, compared with San Diego at 0.42 per million inhabitants per year.

There may be several reasons to account for the apparent higher incidence on Vancouver Island. The prevalence of pet rodent ownership may be greater on Vancouver Island, thereby increasing rodent exposure. It is possible that, given the large variability in mucosal colonization by *S. moniliformis* (3), its prevalence as commensal flora of rats could be higher on Vancouver Island. Alternatively, having all the relevant data from the region centralized within Island Health's Enterprise Data Warehouse may have contributed to a more comprehensive case finding.

On Vancouver Island, *S. moniliformis* is the only identified causative pathogen of RBF. Within this case series, fever was a feature of all documented cases; however, the other classic RBF findings of rash and polyarthralgia were documented in only three (27%) and five (45%) cases, respectively. After fever and polyarthralgia, emesis was the third most common symptom afflicting four (36%) of cases. The remaining signs and symptoms, including myalgia, headaches and pharyngitis, were seen in fewer than one-third of the cases; consistent with a previous meta-analysis of case reports (4). Further signs and symptoms such as joint effusions, back pain, rigors and diarrhea were also documented.

Despite the broad susceptibility of *S. moniliformis* to many classes of antibiotics, current recommendations for treatment of RBF is penicillin (3,15). In this case series, ceftriaxone was the most common empiric antibiotic choice and was a component of therapy in eight (73%) of cases; however, penicillin was the most common stepdown therapy (Table 1). Alternatives, including gentamicin, doxycycline and amoxicillin, were used without complications. Of note, one patient responded to a 14-day course of oral doxycycline alone.
While RBF carries roughly a 10% mortality in those who do not receive treatment (7,10,24), no mortality was observed in this case series as timely treatment was provided in all cases. Similarly, previously published studies have shown that the outcomes of RBF are favorable when treatment was provided and no long-term morbidity or mortality were identified. This further supports the idea that awareness, recognition and judicious antibiotic treatment are significant contributors to positive patient outcomes.

There are several limitations to this retrospective study that are related to the breadth and depth of information. Despite a comprehensive search for RBF cases within Island Health, cases may be missed: patients who were diagnosed as outpatients and their blood cultures were negative or were not performed; patients from Vancouver Island who were diagnosed and managed outside of Vancouver Island; and patients for whom detailed information about rodent exposure was not recorded. Moving forward, efforts should be made to estimate the risk of developing RBF upon a scratch, bite or other significant exposure to rat saliva, urine or feces. In one case, it was noted that the patient had been bitten and scratched by his or her pet rat numerous times in the preceding months before subsequently developing RBF. Next steps in the research into RBF should include a province-wide analysis to determine if the rates of RBF on Vancouver Island are higher than the remainder of British Columbia as this may point to either a failure to recognize RBF elsewhere in the province or a local factor or factors contributing to higher prevalence on Vancouver Island.

Conclusion

This study represents the largest single case series of RBF in Canada to date. It also suggests a higher than expected incidence of RBF on Vancouver Island. RBF is a rare disease, but may be underreported due to the non-specific presentation and challenges with laboratory diagnosis. To detect RBF, a high index of suspicion is needed that would lead to an inquiry regarding a patient's exposure to rodents in those with symptoms of fever with rash, polyarthralgia, emesis, myalgia or joint effusions. Blood culture is needed to confirm the diagnosis.

Rat bite fever remains a serious and under recognized infection. Further study may assist in getting an accurate picture of the epidemiology of RBF in Canada.

Authors' statement

The authors contributed equally to this manuscript

BH – Conceptualization, methodology, investigation, writing-original draft, review and editing
CW – Conceptualization, methodology, investigation, writing-original draft, review and editing
KT – Conceptualization, methodology, resources, writing-review and editing

The views expressed in the submitted article are those of the authors and are not an official position of the University of British Columbia.

Conflict of interest

None.

Acknowledgements

We would like to thank the clinicians and allied-health care teams involved in providing care to the patients infected with RBF. Further, we would like to thank Rebecca Raworth, Island Medical Program Librarian, for her support in the literature review process.

Funding

None.

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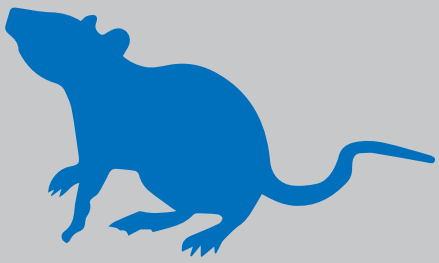
Canada Communicable Disease Report
CCDR
VISUAL ABSTRACT

RAT BITE FEVER (RBF) ON VANCOUVER ISLAND: RARE BUT HIGHER THAN EXPECTED

Rat bite fever is rare

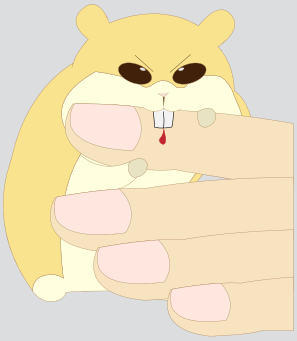
Rate bite fever (RBF) is a rare infection caused by bacteria and is part of the normal flora in the mouths of rodents (rats, mice, gerbils, etc.).



RBF is caused by bites, scratches, and contact with rodent urine or feces. Symptoms include fever, chills, rash, muscle aches, and joint pain.

More cases than expected

There were 11 cases reported on Vancouver Island between 2010–2016.* Seven cases required hospitalization.



As more people have rodents as pets, exposure and risk of contracting the disease has increased.

RBF is treatable and preventable

TREATMENT

Rat bite fever is easily treated with antibiotics; it can be a serious illness if left untreated.

PREVENTION

If you have a rodent as a pet, wash your hands thoroughly after handling it. If you suffer any symptoms after a bite or scratch, report it to a doctor.

*Reference: Hryciw BN, Wright CP, Tan K. Rat bite fever on Vancouver Island. Can Commun Dis Rep 2018;44(9):215–9. https://doi.org/10.14745/ccdr.v44i09a05

Summary of the NACI Update on Herpes Zoster Vaccines

R Warrington[1,2], S Ismail[3] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Steep increases in herpes zoster (HZ) incidence, hospitalization due to HZ and the risk of post-herpetic neuralgia as a complication of HZ occur in people over 50 years of age. Two HZ vaccines are currently authorized for use in those 50 years of age and older in Canada: a live attenuated zoster vaccine (LZV) authorized in 2008; and a recombinant subunit vaccine (RZV) authorized in October 2017.

Objectives: To review current evidence and develop guidance on whether the previously authorized LZV (Zostavax®) and/or the recently authorized RZV (Shingrix®) vaccine should be offered to Canadians 50 years of age and older: 1) at a population-level, in publicly funded immunization programs; and 2) at an individual-level, to individuals wishing to prevent HZ, or by clinicians wishing to advise individual patients about preventing HZ.

Methods: The National Advisory Committee on Immunization (NACI) Herpes Zoster Working Group developed a predefined search strategy to identify all eligible studies, assessed their quality, and summarized and analyzed the findings. A Cost Utility Analysis of LZV and RZV was also conducted from a health care system perspective. Recommendations were proposed according to NACI's evidence-based process. The strength of these recommendations was defined, and the Grade of evidence supporting them was identified. In light of the evidence, the recommendations were then considered and approved by NACI.

Results: Five recommendations were developed for public health and individual-level decision-making. 1) RZV *should be offered* to populations/individuals ≥50 years of age without contraindications (Strong NACI Recommendation, Grade A evidence). 2) RZV *should be offered* to populations/individuals ≥50 years of age without contraindications who have previously been vaccinated with LZV (Strong NACI Recommendation, Grade A evidence). Re-immunization with two doses of RZV may be considered one year after LZV (Discretionary NACI Recommendation, Grade I evidence). 3) RZV *should be offered* to populations/individuals ≥50 years of age without contraindications who have had a previous episode of HZ (Strong NACI Recommendation, Grade B evidence). Immunization with two doses of RZV may be considered one year after the HZ episode (Discretionary NACI Recommendation, Grade I evidence). 4) LZV *may be considered* for immunocompetent populations/individuals ≥50 years of age without contraindications when RZV vaccine is contraindicated, unavailable or inaccessible (Discretionary NACI Recommendation, Grade A evidence). 5) RZV vaccine (not LZV) *may be considered* in immunocompromised adults ≥50 years of age on a case-by-case basis (Discretionary NACI Recommendation, Grade I evidence).

Conclusion: Both vaccines have been shown to be safe and immunogenic and to reduce the incidence of HZ and post-herpetic neuralgia. Vaccine efficacy of LZV against HZ decreases with age at, and time since vaccination. The vaccine efficacy of RZV remains higher and appears to decline more slowly than vaccine efficacy of LZV across all age groups. Both vaccines are cost-effective in those 50 years of age and older compared with no vaccination, especially in those 65–79 years of age. RZV is more cost-effective than LZV.

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Suggested citation: Warrington R, Ismail S. Summary of the NACI Update on Herpes Zoster Vaccines. Can Commun Dis Rep 2018;44(9):220-5. https://doi.org/10.14745/ccdr.v44i09a06

Keywords: National Advisory Committee on Immunization, varicella zoster, vaccine, shingles

Introduction

Herpes zoster (HZ), or shingles, is characterized by neuropathic pain and dermatomal vesicular rash. It results from reactivation of varicella zoster virus (VZV), which occurs with reduced cellular immune response associated with aging or immune suppression. The most frequent and often debilitating complication of HZ is post-herpetic neuralgia. Nearly one in three Canadians develops HZ during their lifetime (1). Age is the predominant risk factor for the development of HZ, as well as post-herpetic neuralgia and

hospitalization among HZ cases, with steep increases occurring over 50 years of age (2–7). Peak hospitalization rates for HZ and post-herpetic neuralgia risk per HZ case are observed among those 65 years of age and older (1,4,7–9).

In Canada in 2008, a live attenuated vaccine against HZ (LZV, Zostavax®) was approved for use among those 60 years of age and older, and in 2011 it was approved for use in those 50 years of age and older. In 2010 and 2014, Canada's National Advisory Committee on Immunization (NACI) published evidence-based recommendations on the use of LZV in immunocompetent individuals 60 years of age and older (10,11). NACI also recommended that LZV *may be used* in patients 50–59 years of age because, while it was shown to be safe and efficacious in this age group, the duration of protection from the vaccine was unknown beyond five years, and it was uncertain whether protection would persist at older ages when the burden of HZ is greatest. In May 2014, the Canadian Immunization Committee recommended that LZV be routinely offered to immunocompetent adults aged 60–65 years of age without contraindications on the basis of the epidemiology of VZV, vaccine characteristics, disease modeling and economic analysis, as well as on the feasibility and acceptability of immunization programs for HZ (12). While LZV has been available for private purchase, no publicly-funded immunization program has been offered in Canada until Ontario offered the vaccine to individuals 65–70 years of age in September 2016 (13).

In October 2017, Canada was the first country to authorize the use of a recombinant subunit HZ vaccine (RZV, Shingrix®) containing VZV glycoprotein E and the novel $ASO1_B$ adjuvant system. This triggered the need for an updated NACI Advisory Committee Statement on the Use of Herpes Zoster Vaccines. The primary objective of this statement is to review current evidence and develop guidance on the use of RZV, as well as whether the previously authorized LZV and/or the recently authorized RZV vaccine should be offered to Canadians ≥50 years of age at a population-level, in publicly-funded immunization programs and at an individual-level, to individuals wishing to prevent HZ or by clinicians wishing to advise individual patients about preventing HZ, with vaccines that may not currently be included in public health immunization programs. Complete details can be found in the *National Advisory Committee on Immunization Update on the Use of Herpes Zoster Vaccines* (14). The objective of this article is to summarize the main findings of the update.

Methods

The NACI Herpes Zoster Working Group (HZWG) performed literature reviews and reviewed vaccine manufacturer-provided data on the topic of HZ and HZ vaccines. All evidence was rated, critically appraised and reported in evidence tables. Studies on RZV vaccine immunogenicity, safety and efficacy in various immunocompromised groups ≥18 years of age with various dosing schedules were ongoing at the time of NACI deliberations; therefore, they were not included for this review.

The NACI will monitor and review the evolving evidence on HZ vaccines in those who are immunocompromised in a separate advisory committee statement.

A knowledge synthesis was performed, the evidence was critically appraised and the HZWG proposed specific evidence-based recommendations according to NACI's evidence-based process for developing recommendations (15). This included elucidating the rationale and relevant considerations. New terminology has recently been developed to define the strength of NACI Recommendations:

- A *strong recommendation* applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.
- A *discretionary recommendation* may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Results

Both LZV and RZV have been shown to be safe, immunogenic and effective in reducing the incidence of HZ and its complications, such as post-herpetic neuralgia. With LZV, vaccine efficacy against HZ decreases with age at, and time since, vaccination. The vaccine efficacy of RZV remains higher and appears to decline more slowly than vaccine efficacy of LZV across all age groups. The RZV vaccine efficacy against incident HZ and post-herpetic neuralgia in the three years after immunization appears to be double that observed for LZV. Significant waning of protection has been observed one year after immunization with LZV. In contrast, vaccine efficacy of RZV against incident HZ in the four years post-immunization remains consistent, with no significant decreases observed over time. LZV is significantly less effective in adults over 70 years of age compared with adults 50–59 years of age, whereas differences in four year vaccine efficacy of RZV against HZ are non-significant across different age groups. RZV is more reactogenic than LZV due to the adjuvant in RZV, which induces a high cellular immune response to help address the natural age-related decline in immunity. While both vaccines are cost-effective in those 50 years of age and older compared with no vaccination especially in those 65–79 years of age, RZV is more cost-effective than LZV from a health care system perspective. The review of the literature on the use of HZ vaccines and current HZ vaccine recommendations are published in the full NACI statement update (14) and the HZ chapter of the *Canadian Immunization Guide* (16).

Recommendations and rationale

The NACI approved five recommendations for public health level and individual level decision-making with the following rationales.

1. **RZV *should be offered* to populations/individuals ≥50 years of age without contraindications (Strong NACI Recommendation, Grade A evidence).**

Both LZV and RZV are safe, immunogenic and effective in preventing HZ and post-herpetic neuralgia. On the balance, NACI felt that the higher efficacy of the RZV vaccine in adults 50 years of age and older, minimal waning of protection and cost-effectiveness supports a public health program level recommendation to vaccinate populations ≥50 years of age, who are at higher risk of HZ and post-herpetic neuralgia and will likely continue to be protected with RZV at older ages as the risk of HZ and post-herpetic neuralgia continues to increase. From a

public health program level perspective, RZV has been shown to be more cost effective than LZV. Programs will require strategies (e.g., education, recalls/reminders) to ensure adherence to the two dose schedule for RZV (as vaccine efficacy and duration of protection is unclear after only one dose), and provide counseling on short term reactogenicity of the vaccine. If, due to operational constraints, prioritization of targeted immunization programs is required for implementation, jurisdictions may wish to consider the relative merits of vaccinating different age cohorts (with respect to epidemiology and cost-effectiveness). From an individual level perspective, individuals wishing to prevent HZ or clinicians wishing to advise patients may consider the individual cost of RZV vs LZV vaccines. Individuals should be prepared to adhere to a two dose schedule for the RZV vaccine (as vaccine efficacy and duration of protection is unknown after only one dose) and to understand that they may experience more short term reactogenicity from the RZV vaccine.

2. **RZV *should be offered* to populations/individuals ≥50 years of age without contraindications who have previously been vaccinated with LZV (Strong NACI Recommendation, Grade A evidence).**

2a. **Re-immunization with two doses of RZV may be considered one year after LZV (Discretionary NACI Recommendation, Grade I evidence).**

Prior recipients of LZV vaccine will derive additional protection from completion of the two dose series of RZV given higher and more durable vaccine efficacy across age groups. Comparable safety, reactogenicity and immunogenicity have been demonstrated between those who have previously been vaccinated with LZV and those who have not. For those who have previously been vaccinated with LZV, consideration of the interval between LZV and RZV vaccination will depend on age of vaccination with LZV (since vaccine efficacy decreases with age), as well as time since LZV vaccination (since efficacy wanes after the first year). Based on limited evidence, NACI suggests re-immunization with two doses of RZV after one year post-LZV administration due to rapidly declining LZV effectiveness after the first year post-vaccination. While the only published study to date investigating immunization with RZV following LZV used an interval of at least five years, there is no reason to believe that a shorter interval would be harmful.

3. **RZV *should be offered* to populations/individuals ≥50 years of age without contraindications who have had a previous episode of HZ (Strong NACI Recommendation, Grade B evidence).**

3a. **Immunization with two doses of RZV may be considered one year after the HZ episode (Discretionary NACI Recommendation, Grade I evidence).**

Similar to its 2014 recommendation for LZV, NACI recommends immunization with RZV in individuals with a prior episode of HZ. Individuals with a prior episode of HZ are still at risk of HZ, and a history of HZ is unreliable; therefore, vaccination with RZV in those who report a prior history of HZ will be beneficial. Furthermore, one study has shown no differences in safety or immunogenicity of RZV in individuals with a prior episode of HZ. In the absence of evidence on an appropriate interval, NACI maintains its previous suggestion of waiting at least one year post HZ episode prior to the administration of herpes zoster vaccine.

4. **LZV *may be considered* for immunocompetent populations/individuals ≥50 years of age without contraindications when RZV vaccine is contraindicated, unavailable or inaccessible (Discretionary NACI Recommendation, Grade A evidence).**

The NACI concludes (as it has in previous HZ advisory committee statements) that there is good evidence to recommend immunization with LZV in adults aged ≥60 years (Grade A evidence). However, the recommendation on the use of this vaccine in immunocompetent populations ≥60 years of age is now "Discretionary" due to the comparative evidence on higher efficacy, longer duration of protection, and relative cost effectiveness of the newly authorized RZV vaccine. Although LZV is safe and efficacious in 50–59 year olds and was previously recommended by NACI on a discretionary basis for this age group, waning protection of the vaccine means that it may not provide optimal ongoing protection at older ages where the risk of HZ and post-herpetic neuralgia is greatest. With the newly authorized RZV vaccine and its higher efficacy and longer duration of protection in this age group, NACI now strongly recommends that RZV be used in adults 50–59 years in addition to adults ≥60 years, without contraindications. LZV vaccine may still be considered in individuals in whom RZV vaccine is contraindicated (i.e., known hypersensitivity to any component of the vaccine), or if RZV is not available or inaccessible due to cost. LZV has been authorized in Canada since 2008 and has been shown to be safe, immunogenic and effective.

5. **RZV vaccine (not LZV) *may be considered* in immunocompromised adults ≥50 years of age on a case by case basis (Discretionary NACI Recommendation, Grade I evidence).**

Unlike with LZV, immuncompromise is not a contraindication for RZV. Based on the burden of illness of HZ in immunocompromised individuals and general guidance on the use of inactivated vaccines versus live vaccines in those who are immunocompromised, NACI feels that the benefits of considering vaccination with RZV (instead of LZV) in immunocompromised individuals on a case by case basis outweighs the risks at this time. NACI will monitor the evidence as it evolves and will reassess individual level and public health program level recommendations in different immunocompromised individuals and populations ≥18 years of age as soon as the evidence from ongoing trials becomes available.

Table 1 provides a summary of NACI's updated recommendations on the use of LZV and RZV for public health program level decision-making that is applicable to provincial and territorial authorities who are making decisions for publicly funded immunization programs. The strength of each recommendation and the grading of the body of evidence supporting the recommendation are included.

Table 2 provides a summary of NACI's updated recommendations on the use of LZV and RZV for individual level decision-making that is applicable to individuals wishing to prevent HZ, or clinicians wishing to advise individual patients about preventing HZ with vaccines that may not currently be included in public health immunization programs. The strength of each recommendation and the grading of the body of evidence supporting the recommendation is included.

Table 1: Summary of 2018 NACI recommendations on the use of herpes zoster vaccines for public health program level decision-making[a]

Vaccine type	NACI Recommendation (Strength of recommendation)	Grade of evidence supporting recommendation
RZV	1. NACI recommends that RZV should be offered to populations ≥50 years of age without contraindications. (Strong NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
	2. NACI recommends that RZV should be offered to populations ≥50 years of age without contraindications who have previously been vaccinated with LZV. (Strong NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
	2a. NACI recommends that for adults ≥50 years of age who have previously been immunized with LZV, re-immunization with two doses of RZV may be considered one year after LZV. (Discretionary NACI Recommendation; based on expert opinion)	NACI concludes that there is insufficient evidence to recommend an interval between LZV and RZV. (Grade I evidence)
	3. NACI recommends that RZV should be offered to populations ≥50 years of age without contraindications who have had a previous episode of HZ. (Strong NACI Recommendation)	NACI concludes that there is fair evidence to recommend immunization. (Grade B evidence)
	3a. NACI recommends that for adults ≥50 years of age who have had a previous episode of HZ, immunization with two doses of RZV may be considered at least one year after the HZ episode. (Discretionary NACI Recommendation; based on expert opinion)	NACI concludes that there is insufficient evidence to recommend an interval between a previous episode of HZ and vaccination with RZV. (Grade I evidence)
LZV	4. NACI recommends that LZV *may be considered* for immunocompetent populations ≥50 years of age without contraindications when RZV is contraindicated or unavailable. (Discretionary NACI Recommendation)	NACI concludes that there is good evidence to recommend (Grade A evidence)
RZV vs LZV in immuno-compromised populations	5. NACI recommends that RZV (not LZV) *may be considered* in immunocompromised adults ≥50 years of age on a case by case basis. (Discretionary NACI Recommendation; based on expert opinion) NACI will review the evidence as it evolves and reassess recommendations.	NACI concludes that there is insufficient evidence at this time to recommend immunization. (Grade I evidence)

Abbreviations: HZ, herpes zoster; NACI, National Advisory Committee on Immunization; LZV, live attenuated zoster vaccine; RZV, recombinant subunit vaccine
[a] In considering these recommendations, provinces and territories may take into account other local operational factors (e.g. current immunization programs, resources), and may wish to review differences between age cohorts (e.g., with respect to epidemiology and cost-effectiveness) outlined in the 2018 NACI Statement if prioritization of targeted immunization programs is required for implementation

Table 2: Summary of 2018 NACI recommendations on the use of herpes zoster vaccines for individual level decision-making[a]

Vaccine type	NACI Recommendation (Strength of recommendation)	Grade of evidence supporting recommendation
RZV	1. NACI recommends that RZV *should be* offered to individuals ≥50 years of age without contraindications. (Strong NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
	2. NACI recommends that RZV *should be* offered to individuals ≥50 years of age without contraindications who have previously been vaccinated with LZV. (Strong NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
	2a. NACI recommends that for adults ≥50 years of age who have previously been immunized with LZV, re-immunization with two doses of RZV may be considered one year after LZV. (Discretionary NACI Recommendation; based on expert opinion)	NACI concludes that there is insufficient evidence to recommend an interval between LZV and RZV. (Grade I evidence)
	3. NACI recommends that RZV *should be* offered to individuals ≥50 years of age without contraindications who have had a previous episode of HZ. (Strong NACI Recommendation)	NACI concludes that there is fair evidence to recommend immunization. (Grade B evidence)
	3a. NACI recommends that for adults ≥50 years of age who have had a previous episode of HZ, immunization with two doses of RZV may be considered one year after the HZ episode. (Discretionary NACI Recommendation; based on expert opinion)	NACI concludes that there is insufficient evidence to recommend an interval between a previous episode of HZ and vaccination with RZV. (Grade I evidence).
LZV	4. NACI recommends that LZV *may be considered* for immunocompetent individuals ≥50 years of age without contraindications when RZV is contraindicated unavailable, or inaccessible. (Discretionary NACI Recommendation)	NACI concludes that there is good evidence to recommend immunization. (Grade A evidence)
RZV vs LZV in immune-compromised populations	5. NACI recommends that RZV (not LZV) *may be considered* in immunocompromised adults ≥50 years of age on a case by case basis. (Discretionary NACI Recommendation; based on expert opinion) NACI will review the evidence as it evolves and reassess recommendations.	NACI concludes that there is insufficient evidence at this time to recommend immunization (Grade I evidence)

Abbreviations: HZ, herpes zoster; NACI, National Advisory Committee on Immunization; LZV, live attenuated zoster vaccine; RZV, recombinant subunit vaccine
[a] In considering these recommendations, individuals/clinicians may wish to review the decision points with respect to vaccine and age at vaccination outlined in the 2018 NACI Statement

Conclusion

The NACI has concluded that both the RZV and LZV vaccines are safe, immunogenic and cost-effective and reduce the incidence of HZ and post-herpetic neuralgia; however, while vaccine efficacy of LZV decreases with age at, and time since, vaccination, vaccine efficacy of RZV remains higher and appears to decline more slowly than vaccine efficacy of LZV across all age groups. RZV vaccine efficacy against incident HZ and post-herpetic neuralgia in the three years post-immunization appears to be double that observed for LZV. RZV vaccine efficacy against incident HZ in the four years post-immunization remains consistent, with no significant decreases observed over time; in contrast, significant waning of protection has been observed one-year post-immunization with LZV. Differences in RZV four-year vaccine efficacy against incident HZ are non-significant across different age groups; in contrast, LZV is significantly less effective in adults over 70 years of age compared with adults 50–59 years of age. Due to the adjuvant in RZV, which induces a high cellular immune response to help address the natural age-related decline in immunity, this vaccine is more reactogenic than LZV. However, this reactogenicity is transient, and education to improve adherence to the second dose of the RZV vaccination schedule will be important.

Both vaccines are cost-effective in those 50 years of age and older compared with no vaccination, especially in those 65–79 years of age because of the increased burden of illness with age (increased risk of hospitalization and post-herpetic neuralgia per HZ case especially in those 65 years of age and older) and the likeliness that the vaccine will be effective during the years when burden of illness is high (unless vaccine efficacy wanes quickly). In addition, the benefits of vaccination accrue over a longer period of time due to the longer life expectancy in this age cohort compared to those 80 years of age and older. From a public health perspective, the HZ vaccine may be simultaneously administered with other adult vaccines to improve coverage and reduce operational costs. For all age cohorts considered, RZV is more cost-effective than LZV.

Based on the evidence reviewed, NACI recommends immunization against herpes zoster.

Authors' statement

RW – Writing original summary draft – review and editing
SI – Writing original summary draft – review and editing

This is a summary of the NACI Herpes Zoster Statement, which was prepared by S Ismail, M Tunis, O Baclic, K Eng, MK Doll, J Hu, S Duchesne-Belanger, R Warrington and was approved by NACI.

Conflict of interest

None.

Acknowledgements

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NACI gratefully acknowledges the contribution of the following groups: The team from University of Laval, Centre de recherche du Centre hospitalier universitaire (CHU) de Québec, and Institut national de santé publique du Québec (INSPQ) for contributions to the economic analysis including M Brisson, Z Zhou, M Drolet, C Sauvageau, P DeWals, V Gilca, JF Laprise, and R Amini. This team, however, are not the authors of the economic section in the Statement. L Gamble (Health Library, HC) for supporting the immunogenicity search strategy, and the MAGIC team for their contribution to the safety, effectiveness, and efficacy analysis including AC Tricco, SE Straus, W Zarin, R Cardoso, AA Veroniki, PA Khan, V Nincic, M Ghassemi, R Warren, J Sharpe and A Page. The safety, effectiveness, efficacy literature search strategy was developed and peer-reviewed by librarians E Cogo and J McGowan

Funding

The work of NACI is supported by the Public Health Agency of Canada.

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RAPID COMMUNICATION

Updated NACI recommendations for measles post-exposure prophylaxis

MC Tunis[1], MI Salvadori[2], V Dubey[3], O Baclic[1] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Human immune globulin (Ig) products are currently recommended as post-exposure prophylaxis (PEP) for measles in certain susceptible groups. However, successful measles vaccination programs in North America have led to low circulation of measles virus and most blood donors now have vaccine-derived immunity. Concurrently, the concentrations of anti-measles antibodies in human Ig products have shown trends of gradual decline and previously recommended doses and routes of administration may no longer be optimally protective.

Objectives: To review the literature and update recommendations on post-exposure prophylaxis for measles, including dosing and route of administration, for measles Ig PEP in susceptible infants and in individuals who are immunocompromised or pregnant, in order to prevent severe disease.

Approach: The National Advisory Committee on Immunization (NACI) Measles, Mumps, Rubella, Varicella Working Group reviewed key literature, international practices, and product information for current Ig products pertaining to the optimal dosage and routes of Ig administration for measles PEP. It then proposed evidence-based changes to the PEP recommendations that were considered and approved by NACI.

Results: NACI continues to recommend that susceptible immunocompetent individuals six months of age and older, who are exposed to measles and who have no contraindications be given measles-mumps-rubella (MMR) vaccine within 72 hours of the exposure. NACI recommends that for susceptible infants younger than six months of age, if injection volume is not a major concern, intramuscular immunoglobulin (IMIg) should be provided at a concentration of 0.5 mL/kg, to a maximum dose of 15 mL administered over multiple injection sites. Susceptible infants six to 12 months old who are identified after 72 hours and within six days of measles exposure should receive IMIg (0.5 mL/kg) if injection volume is not a major concern. For susceptible contacts who are pregnant or immunocompromised, if injection volume is not a concern, IMIg can be provided at a concentration of 0.5 mL/kg understanding that recipients 30 kg or more will not receive the measles antibody concentrations that are considered to be fully protective. Alternatively, in cases where injection volume is a major concern or for recipients 30 kg or more, intravenous immunoglobulin (IVIg) can be provided at a dose of 400 mg/kg.

NACI does not recommend that susceptible immunocompetent individuals older than 12 months of age receive Ig PEP for measles exposure due to the low risk of disease complications and the practical challenges of administration for case and contact management.

Conclusion: NACI has updated the recommendations for measles PEP to reflect current evidence and best practices in order to prevent severe disease in Canada. Consistent with recommendations in other countries, this includes consideration of off-label use of IVIg in some instances.

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Suggested citation: Tunis MC, Salvadori MI, Dubey V, Baclic O, on behalf of the National Advisory Committee on Immunization (NACI). Updated NACI recommendations for measles post-exposure prophylaxis. Can Commun Dis Rep 2018;44(9):226-30. https://doi.org/10.14745/ccdr.v44i09a07

Keywords: measles outbreak, measles vaccine, post-exposure prophylaxis, NACI recommendations, intravenous immunoglobulin, intramuscular immunoglobulin, Canada

Introduction

Although Canada has maintained measles elimination status since 1998, sporadic measles activity continues to occur on occasion, typically among susceptible individuals. Recent measles activity in Canada and the declining potency of immune globulin (Ig) products over time has led to a review of the National Advisory Committee on Immunization (NACI) recommendations for measles post-exposure prophylaxis (PEP).

Intramuscular immunoglobulin (IMIg) products have previously been recommended by NACI for measles PEP in susceptible

contacts who are pregnant or immunocompromised, children younger than six months of age and susceptible immunocompetent contacts six months or older who present to a health care professional more than 72 hours but within six days after measles exposure (1). Susceptible individuals are those who do not meet the criteria for measles immunity outlined in the Canadian Immunization Guide in guidelines for the prevention and control of measles outbreaks in Canada (1).

Over the past fifty years, successful measles vaccination programs in North America have led to low circulation of measles virus and absence of natural infection. Concurrently, the concentrations of anti-measles antibodies in human Ig products have shown trends of gradual decline and are no longer considered optimally protective, using the previously recommended doses and routes of administration (2).

Although the exact protective level of anti-measles antibody is not known, an anti-measles titre of >120 milli International Units per millilitre (mIU/mL) of serum is generally considered to be protective and has been associated with protection in healthy young adults (3). Human Ig products are authorized in Canada for use as measles PEP based on compliance with the Center for Biologics Evaluation and Research (CBER) reference standard that was issued from the United States of America (USA) Food and Drug Administration (FDA) in 2006 (4,5). In light of this product information, NACI reviewed key evidence sources in order to revise recommendations on measles PEP dosage and routes of administration.

The objective of this update is to revise recommendations on measles PEP in response to recent measles activity in Canada and the declining potency of Ig products over time. There is no full NACI Statement on this topic, but changes are reflected in the Canadian Immunization Guide (6) and NACI will provide a comprehensive review of measles PEP in a future statement.

Methods

The NACI Measles, Mumps, Rubella, Varicella Working Group (MMRVWG) reviewed key literature, international practices, and evidence from manufacturers pertaining to the optimal dosage and routes of Ig administration for measles PEP. Key literature was identified through an environmental scan of international recommendations and practices, including National Immunization Technical Advisory Groups from the USA (Advisory Committee on Immunization Practices), the United Kingdom (UK) (Joint Committee on Vaccination and Immunization), Germany (Standing Committee on Vaccination), Australia (Australian Technical Advisory Group on Immunization), France (Technical Vaccination Committee), New Zealand and Ireland. Once key studies were identified, their references were searched for additional pertinent studies. In total, six relevant reference studies were identified (3,4,7–9). In addition, data were presented to the MMRVWG from the intramuscular immunoglobulin (IMIg) manufacturer, Grifols, on the state of anti-measles concentration in products over the years, as well as available evidence on anti-measles antibody concentrations in recipients of the Ig products at different dosages and routes of administration.

Results

Following a review of international practices, product information for current Ig products and key literature, the MMRVWG considered the effectiveness, appropriate dosing and optimal administration routes for Ig products to protect against measles in vulnerable and susceptible populations. Results are presented below as they pertain to the route of administration: intramuscular or intravenous.

In order to interpret key effectiveness literature, each study had to be evaluated in relation to the concentration of anti-measles antibodies in today's Ig products according to a common reference standard. The current minimum concentration requirement for anti-measles antibodies in Ig preparations is 0.60 x CBER Reference Standard #176 (42 IU/mL) (4), which is equivalent to 25 IU/mL. Data presented to the NACI MMRVWG by Grifols, the manufacturer of both the IMIg product GammaSTAN® (10) and the intravenous immunoglobulin (IVIg) product Gamunex® (11), suggested that the anti-measles antibody levels are declining over years but are still well above the minimum regulatory threshold. Recent measurements (2015–2016) have been in the range of 0.79 x CBER Reference Standard, which is equivalent to 33 IU/mL. Although not all IVIg manufacturers presented data, all Ig preparations available in Canada contain pooled plasma from USA donors, except IGIVnex®, which contains plasma from Canadian donors. Therefore, it can be reasonably assumed, that trends in antibody concentration would be reflected across products.

There is no simple or reliable way to predict serum anti-measles titres based on the PEP dosage administered. Previous attempts have used mathematical estimations and modelling, including those outlined by Audet et al. in 2006, to establish the CBER reference standard in relation to a threshold of 120 mIU/mL (4). Real world effectiveness studies for IMIg measles PEP are more useful, but there are very few relevant effectiveness studies (7–9).

Intramuscular immunoglobulin

Available evidence and product information was reviewed concerning IMIg, which has previously been recommended by NACI for measles PEP at a dose of 0.25 mL/kg for susceptible pregnant women and infants or 0.5 mL/kg for immunocompromised individuals, or for other susceptible contacts who presented between 72 hours and six days post-exposure. GammaSTAN (10) is the only IMIg preparation in Canada, and it is indicated for use as measles PEP. When effectiveness studies were examined based on the relative anti-measles antibody concentrations in current Ig products, it was apparent that IMIg doses exceeding the CBER Reference Standard with current protein concentrations of 0.442 mL/kg, 0.393 mL/kg or 0.335 mL/kg, would result in 100%, 100% and 83% effectiveness respectively against measles up to two weeks post-injection (9). Dosing equivalent to 0.297 mL/kg in current products would result in an estimated 69% effectiveness (7), while dosing equivalent to 0.157 mL/kg showed only 42.9% effectiveness against measles up to two weeks post-injection (9). A study by Sheppeard et al. found that a dose of 0.19ml/ kg by today's equivalent products would result in effectiveness of 75.8%, but this study was considered to have a high risk of effectiveness overestimation based on a broad definition

of exposure to measles cases (8). It should be noted that the sample sizes for all of these studies were small; ranging from 1–55 subjects receiving various dosages of IMIg.

Despite the limited evidence, it is assumed that IMIg at the previously recommended dosing of 0.25 mL/kg for susceptible pregnant women and infants is not fully protective against measles, even though these products do exceed the current CBER Reference Standard. Given the available effectiveness data and the emerging trend towards diminishing concentration of anti-measles antibodies within North American products, the MMRVWG determined that an IMIg dose of 0.5 mL/kg would be appropriate to provide immediate protection at current product concentrations of anti-measles antibody, and also to mitigate against future declining potency of the Ig products. IMIg can be provided up to a maximum volume of 15 mL, therefore anyone weighing 30 kg or more will not receive an optimal dose of IMIg at 0.5 mL/kg. Large volumes (greater than 2 mL for children or 3–5 mL for adults) should be divided and injected at two or more sites (12); therefore, anyone receiving 15 mL of IMIg would be subject to multiple injections. Multiple injections may not be acceptable to all patients, and IVIg may therefore be preferred.

Intravenous immunoglobulin

Although IVIg preparations are not indicated in Canada for use as measles PEP, the MMRVWG considered the use of IVIg as an alternative strategy based on international practices and the lack of alternative prophylaxis strategies. Gamunex IVIg is in fact indicated for measles PEP by the FDA in the USA. Moreover, several countries routinely use IVIg preparations for measles PEP in immunodeficient or immunosuppressed populations, or in circumstances where a large dose would be required, including the USA (13), UK (14), New Zealand (15), Ireland (16) and France (17). Although IVIg is not indicated for measles PEP in Canada, NACI determined that it is an important strategy to prevent post-exposure measles disease in susceptible and vulnerable groups, particularly individuals weighing more than 30 kg. Subcutaneous dosing is rarely used, and following discussion NACI identified significant logistical barriers to subcutaneous administration, including an infusion pump and advanced training.

For IVIg administration, 400 mg/kg is a standard dosage that is within the indicated range of Ig replacement therapy for patients with primary immunodeficiency according to Canadian product monographs for Gammagard® (18,19), Gamunex (11), IGIVnex (20), Privigen® (21) and Panzyga® (22) which are the IVIg products available in Canada through Canadian Blood Services (CBS). Although there is no maximum infusion volume listed in the product monographs, reactions can be prevented in many cases by slowing the infusion rate (23). Maximum infusion rates have been summarized by CBS (24).

Unpublished data on file from Grifols indicates that the serum levels of anti-measles antibodies in 10 children aged 2–16 years with primary immunodeficiency who received Gamunex IVIg at doses ranging from 300–600 mg/mL were all more than four-fold higher than the 120 mIU/mL protective level for measles. Individuals already receiving replacement IVIg at 400 mg/kg of body weight or higher are therefore considered protected against measles and do not require Ig if the last dose of IVIg was received within three weeks prior to measles exposure.

IVIg necessitates administration in the hospital and active patient monitoring over several hours of infusion, performed by appropriately-trained staff (23). In remote settings, IVIg administration can require evacuation by air to a larger medical centre. Although there are implementation barriers to intravenous administration, it may be preferable in some cases as an alternative to multiple IM injections or to ensure an optimal protective dose for susceptible vulnerable individuals who require more than 15 mL of IMIg.

CBS is the supplier of IMIg and IVIg blood products in Canada. It is advisable that providers review the respective product monographs and CBS guidelines (23,24) prior to administering IVIg products for information on administration practices, adverse events and repeated administration. The safety of these products is monitored and reviewed by Health Canada, CBS (25), and Public Health Agency of Canada (PHAC) Blood Safety Contribution Program, which includes the Transfusion Transmitted Injuries Surveillance System (27). Further information on the administration of passive immunizing agents can be found in the Canadian Immunization Guide.

Recommendations

NACI continues to recommend that susceptible immunocompetent individuals six months of age and older who are exposed to measles and who have no contraindications, be given measles-mumps-rubella (MMR) vaccine within 72 hours of the exposure. NACI recommends that for susceptible infants younger than six months of age, if injection volume is not a major concern, IMIg should be provided at a concentration of 0.5 mL/kg, to a maximum dose of 15 mL administered over multiple injection sites. Susceptible infants six to 12 months old who are identified after 72 hours and within six days of measles exposure should receive IMIg (0.5 mL/kg) if injection volume is not a major concern. For susceptible contacts who are pregnant or immunocompromised, if injection volume is not a concern, IMIg can be provided at a concentration of 0.5 mL/kg, understanding that recipients weighing 30 kg or more will not receive the measles antibody concentrations that are considered to be fully protective. In cases where injection volume is a major concern or for recipients weighing 30 kg or more, IVIg can be provided alternatively at a dose of 400 mg/kg.

NACI does not recommend that susceptible immunocompetent individuals older than 12 months of age receive Ig PEP for measles exposure due to low risk of disease complications and the practical challenges of administration for case and contact management. **Table 1** includes an updated summary of recommended measles PEP strategies.

Table 1: Summary of updated measles post-exposure prophylaxis recommendations for susceptible contacts

Population	Time since exposure to measles[a]	
	≤ 72 hours	73 hours–six days
Susceptible infants 0–6 months of age[b]	IMIg (0.5 mL/kg)[c]	
Susceptible immunocompetent infants 6–12 months of age	MMR vaccine[d]	IMIg (0.5 mL/kg)[b,e]

Table 1: (continued) **Summary of updated measles post-exposure prophylaxis recommendations for susceptible contacts**

Population	Time since exposure to measles[a]	
	≤ 72 hours	73 hours–six days
Susceptible immunocompetent individuals 12 months of age and older	MMR vaccine series[e]	
Susceptible pregnant individuals[f]	IVIg (400 mg/kg) or IMIg (0.5 mL/kg), limited protection[g]	
Immunocompromised individuals six months of age and older	IVIg (400 mg/kg) or IMIg (0.5 mL/kg), limited protection if 30 kg or more[g]	
Individuals with confirmed measles immunity	Not applicable	

Abbreviations: IMIg, intramuscular immunoglobulin; IVIg, intravenous immunoglobulin; MMR, measles-mumps-rubella
[a] Ig should only be provided within six days of measles exposure. Individuals already receiving replacement IVIg (400 mg/kg of body weight or higher) are considered protected against measles and do not require Ig if the last dose of IVIg was received within three weeks prior to measles exposure
[b] Two doses of measles-containing vaccine are still required after the first birthday for long-term protection
[c] If injection volume is a major concern, IVIg can be provided at a concentration of 400 mg/kg
[d] Two additional doses of MMR vaccine provided after 12 months of age are required for long term protection
[e] MMR vaccine will not provide PEP protection after 72 hours of exposure, however, starting and completing a two dose series should not be delayed to provide long term protection
[f] Provide two doses of MMR vaccine postpartum for long-term protection
[g] For individuals weighing 30 kg or more, IMIg will not provide complete protection but may provide partial protection

Discussion and conclusion

NACI has updated the recommendations for measles PEP to reflect current evidence and best practices in order to prevent severe disease. NACI continues to recommend that PEP should be considered for select susceptible or vulnerable groups within six days of measles exposure. Susceptible individuals who are not infants, pregnant or immunocompromised, are no longer recommended to receive Ig following measles exposure. Although IVIg products are not indicated for use as measles PEP in Canada, NACI now recommends them as an alternative to IMIg because there are no comparable appropriate prophylaxis strategies in some situations.

NACI provides PHAC with ongoing and timely medical, scientific and public health advice relating to immunization. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. People administering the vaccine should also be aware of the contents of the relevant product monographs. Recommendations for use and other information set out herein may differ from that set out in the product monographs of the Canadian manufacturers of the vaccines. Manufacturers have sought approval of the products and provided evidence as to its safety and efficacy only when it is used in accordance with the product monographs.

Authors' statement

MCT – Writing – original draft, writing – review and editing
MIS – Writing – original draft, writing – review and editing
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This summary was prepared by the authors and approved by NACI.

Conflict of interest

None. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

Acknowledgements

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NACI acknowledges and appreciates the contribution of A House, S Duchesne-Belanger, J Chor, K Young and Canadian Blood Services.

Funding

The work of NACI is supported by the Public Health Agency of Canada.

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