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RESPIRATORY SYNCYTIAL VIRUS (RSV)

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RESPIRATORY SYNCYTIAL VIRUS (RSV)

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OVERVIEW

Burden of disease of respiratory syncytial virus in infants, young children and pregnant women and people

Elissa M Abrams[1,2,3], Pamela Doyon-Plourde[1], Phaedra Davis[1,4], Nicholas Brousseau[5], Andrea Irwin[6], Winnie Siu[1,4], April Killikelly[1]*

Abstract

Background: Passive immunization products for infants and pregnant women and people have sparked interest in understanding Canada's respiratory syncytial virus (RSV) burden. This rapid review examines RSV burden of disease in infants, young children and pregnant women and people.

Methods: Electronic databases were searched to identify studies and systematic reviews reporting data on outpatient visits, hospitalizations, intensive care unit admissions, deaths and preterm labour associated with RSV. We also contacted Canadian respiratory virus surveillance experts for additional data.

Results: Overall, 17 studies on infants and young children and 10 studies on pregnant women and people were included, in addition to primary surveillance data from one Canadian territory (Yukon). There were higher rates of medical utilization for infants than older children. Hospitalization rates were highest in infants under six months (more than 1% annually), with 5% needing intensive care unit admission, but mortality was low. Severe outcomes often occurred in healthy full-term infants and burden was higher than influenza. Respiratory syncytial virus attack rate was 10%–13% among pregnant women and people. Only one study found a higher hospitalization rate in pregnant women and people compared to non-pregnant women and people. Limited evidence was found on intensive care unit admission, death and preterm birth for pregnant women and people.

Conclusion: While risk of severe outcomes is larger in high-risk infants and children, healthcare burden is greatest in healthy term infants. The RSV severity for pregnant women and people appears to be similar to that for non-pregnant women and people.

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Introduction

Respiratory syncytial virus (RSV) is a common respiratory virus, affecting nearly all children younger than two years of age (1). Globally, RSV contributes to 31% of pneumonia cases, causing 33 million acute respiratory infections (ARI), 3.1 million hospitalizations and 118,200 deaths annually (2). Respiratory syncytial virus ranks as the third leading cause of lower respiratory deaths in children younger than five years of age, after *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (3).

The RSV vaccine landscape has evolved. Previously, only one passive immunization product (palivizumab; a monoclonal antibody) was available for high-risk infants. Canada anticipates at least two new products; nirsevimab, a long-acting monoclonal

antibody, and an RSV stabilized pre-fusion subunit protein vaccine for pregnant women and people (Pfizer RSVpreF vaccine, Abrysvo), offering both active and passive immunity for newborns. As the indication for the new passive immunization product includes healthy infants, and as the vaccine for pregnant individuals would protect both healthy and higher-risk infants, there is a need for an understanding of RSV's burden in infants, young children and pregnant women and people.

Throughout this article we will refer to "pregnant women and people" and intend it to be an inclusive term to include people of all gender identities who are pregnant. We recognize this language is evolving and our aim is to use language that removes barriers to care.

While a recent review focused on high-risk infants (including prematurity, cardiopulmonary disease and immunocompromised), less data exists on RSV's burden in healthy infants and young children in Canada (4). To inform recommendations for RSV prevention, we conducted literature reviews on RSV's burden focusing on healthy infants (younger than 12 months of age) and young children (12–24 months of age). Since one approach involves vaccinating pregnant women and people, we also explored RSV's burden in this group. This rapid review aims to summarize the available evidence on RSV burden of disease in infants, young children and pregnant women and people in Canada and other high-income countries.

Methods

Search strategies

Three search strategies were developed by a research librarian from Health Canada and the Public Health Agency of Canada. One focused on systematic reviews (SR) of RSV burden in infants and young children (**Supplemental material S1**). Two targeted RSV burden in pregnant women and people, with one concentrating on primary evidence studies and the other on SRs (**Supplemental material S2**). Embase, MEDLINE, Global Heath and ProQuest Public Health databases were searched for studies published from January 1, 1995, to April 10, 2023. We also contacted Canadian respiratory virus surveillance experts for additional data. After removal of duplicates, references were uploaded in DistillerSR online software (Evidence Partners, Ottawa, Ontario).

Study selection

Two reviewers (for pregnant women and people and for infants and young children) screened titles and abstracts for study eligibility. The articles pertaining to infants and young children focused on healthy infants younger than 12 months and healthy young children 12–24 months of age but did not exclude articles that captured high-risk infants. Full texts of selected articles were then evaluated. A second independent reviewer assessed citations marked for exclusion, with disagreements resolved through discussion. The reference lists of included studies were also screened for relevant articles on RSV burden in high-income countries including Canada and the United States (US) for infants and young children; due to a paucity of data, we did not restrict articles pertaining to pregnant women and people to high income countries.

Eligibility criteria

Observational studies, randomized controlled trials (RCTs) and SRs that met the criteria outlined in **Table 1** were included. Inclusion was limited to studies conducted after 1995 to capture the most recent evidence. The evaluation of RSV burden focused on clinical outcomes of interest in infants, young children and pregnant women and people and considered emergency department (ED) or outpatient visits, hospitalizations, intensive care unit (ICU) admissions, death and preterm labour associated with RSV.

Table 1: Study inclusion and exclusion criteria

PICOS	Inclusion	Exclusion
Population	Infants and children (focus on 24 months of age and younger) Pregnant women and people	Adults only
Intervention	N/A	N/A
Control	N/A	N/A
Outcome	Emergency department or other ambulatory visits due to RSV Hospitalization due to RSV-associated disease ICU admission due to RSV-associated disease RSV-associated death Preterm labour associated with RSV	Outcome not associated with RSV infection
Study design	Systematic reviews and/or meta-analyses Any primary evidence studies (i.e., experimental, quasi and non-experimental studies)	Narrative reviews Guidelines Editorials, commentaries Conference abstracts

Abbreviations: ICU, intensive care unit; N/A, not applicable; PICOS, population, intervention, control, outcome and study design; RSV, respiratory syncytial virus

Data extraction and data synthesis

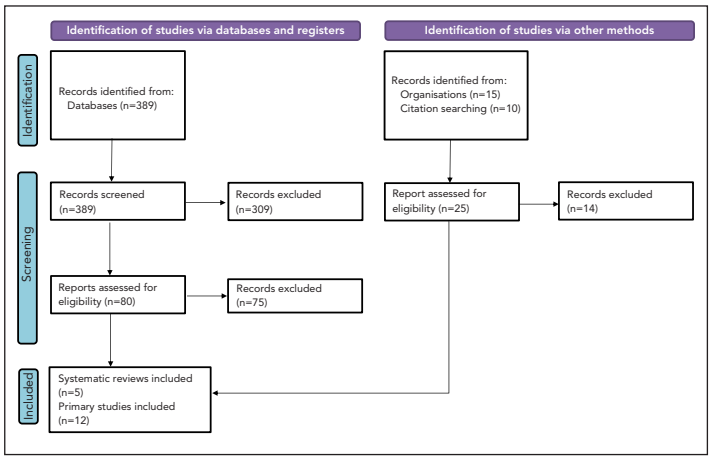
One reviewer extracted data from each article, verified by a second reviewer. Disagreements were resolved through discussion. Data included event number, sample size and effect measures. Results were synthesized narratively based on the study population and outcomes. Due to the value of Canadian data on RSV's burden in healthy infants and young children, surveillance data from one territory (Yukon Communicable Disease Control) were included in this literature review.

Results

Infants and young children

Study selection: After deduplication, 389 references underwent screening (**Figure 1**). Seventeen articles, including five SRs, were incorporated into the narrative synthesis of RSV burden in infants and young children (**Table 2**).

Figure 1: Study selection PRISMA flow diagram of infants and young children



Medically attended RSV respiratory tract infection: Three prospective observational studies demonstrated a high incidence of medically attended RSV infections. A US-based surveillance system from 2002 to 2004 found that RSV accounted for 18% of ED visits and 15% of office visits for ARI from November through April with higher rates in infants (5). More than 70% of the outpatients were previously healthy. Another US study from 2003 to 2005 reported 21.5 RSV-related ED visits per 1,000, higher than influenza (n=10.2 per 1,000), particularly in children younger than 24 months (n=64.4 visits per 1,000) (6). A European birth cohort in healthy term infants from 2017 to 2020 found a 26.2% (95% confidence interval [CI]: 24.0–28.6) RSV infection incidence and 14.1% (95% CI: 12.3–16.0) medically attended RSV incidence during the first year of life (7). Global data for children younger than five years aligned with these findings, reporting 38.5 (95% CI: 21.6–68.8) RSV-associated ARI per 1,000 children younger than one year of age in high-income countries (8).

Over five respiratory seasons, from 2018 to 2023, in Yukon, there were a total of 73 RSV infections in children 24 months and younger, which was higher than the number of influenza infections (n=20). Among infants younger than 12 months of age, the highest number of RSV infections occurred in those younger than three months of age. In summary, medically attended RSV infections are significant during infancy and early childhood, with approximately 10%–20% of infants seeking care for RSV in a season, surpassing medically attended influenza.

Hospitalization associated with RSV respiratory tract infection: Several Canadian studies highlight a substantial incidence of RSV-related hospitalizations in infants and young children. Schanzer *et al.*'s pan-Canadian study showed RSV as a major cause of hospitalization (n=130 per 100,000), with the highest rates in infants younger than six months (9). Papenburg *et al.*'s Québec-based study found RSV was the most common virus (63.6%) in children hospitalized for ARI, with higher severity linked to age under six months and prematurity (10). In Nunavik, RSV hospitalization rates were higher in high-risk infants (147.6 per 1,000 live births) compared to healthy term infants (n=64.8 per 1,000) (11). An Ontario study by Pisesky *et al.* reported RSV hospitalization rates of 10.2 per 1,000 children younger than one year and 4.8 per 1,000 in children one to three years of age (12). Buchan *et al.*'s Ontario cohort study revealed varying RSV hospitalization rates across age groups, with the highest in one-month-olds (n=29.55 per 1,000) and declining with age, with rates highest among children born at younger gestational ages (13). Over five respiratory seasons from 2018 to 2023 in Yukon, there were 27 severe RSV cases (non-ICU hospitalizations, ICU admissions and deaths), of which 18 were non-ICU hospitalizations. During that same time period, in children 24 months and younger, the number of severe RSV (n=27) cases was higher than the number of severe influenza cases (n=7).

Authors of systematic reviews and meta-analyses have also examined RSV hospitalization rates in infants and young children. McLaughin *et al.* reported US rates of 26.2 (95% CI: 24.2–28.2) and 19.4 (95% CI: 17.9–20.9) per 1,000 infants younger than six months and younger than 12 months, respectively (14). Stein *et al.* found rates of 20.01 (95% CI: 9.65–41.31) and 19.19 (95% CI: 15.04–24.48) per 1,000 children-years in the same groups (15). United States national studies reported annual RSV hospitalization rates ranging from 11.6 to 50.1 per 1,000 among infants (16). A rapid review showed varying incidence rates, from 1.2% in healthy term infants to 2.8%–5.1% in preterm infants (4). Global analysis found similar rates in high-income countries, with 28.4 (95% CI: 20.2–40.0) and 22.0 (95% CI: 17.1–28.4) per 1,000 in infants younger than six months and 12 months, respectively (8). A systematic review identified that RSV was associated with 19%–81% of all viral ARI causing hospitalization (17). While rates varied by a factor of 2–3 over seasons, they decreased significantly with increasing age. The majority (more than 70%) of children hospitalized had no underlying risk factors. Compared to influenza, RSV caused up to 16 times more hospitalizations in children younger than five years of age (17).

Table 2: Summary of included studies on the burden of disease of respiratory syncytial virus in infants and young children

Author, year (reference), country	Study design	Study period	Population	Outcome definition	Results
Medically attended RSV respiratory tract infection					
Hall *et al.*, 2009 (5) US	Prospective population-based surveillance study (NVSN)	October 2000 to September 2004, during the winter months (November–April)	Children under five years of age and had received a diagnosis of acute respiratory infection (n=5,067)	Specimens were defined as positive if RSV was detected by viral isolation or by duplicate RT-PCR assays	Of 5,067 participants, 1,014 (20%) were treated in ED and 1,161 (23%) were treated in paediatric offices: • 919 (18%) were infected with RSV • 564 (61%) were hospitalized • 355 (39%) were outpatient • 184 (52%) were treated in ED • 171 (48%) were treated in paediatric office 18% of ED visits (184/1,014) and 15% of paediatric office visits (171/1,161) were RSV-associated
Bourgeois *et al.*, 2009 (6) US	Prospective cohort study	2003–2005	Children seven years of age and younger and treated in the ED for an acute respiratory infection (n=895)	Nasopharyngeal specimens were considered RSV-positive if RSV was detected through direct immunofluorescent antibody stain and/or RT-PCR	ED visit rates: • 10.2 per 1,000 ED visits attributable to influenza • 21.5 per 1,000 ED visits attributable to RSV Children 0–23 months: 64.4 ED visits per 1,000 attributable to RSV
Wildenbeest *et al.*, 2023 (7) Europe (Spain, Finland, England, Scotland and the Netherlands)	Multicentre, prospective birth cohort study	2017/07/01–2020/07/31 October 1 to May 31, parents were contacted weekly to reported ARI symptoms of their child	Healthy term infants, defined as children born at 37 weeks or more of gestation with no evidence of significant disorders[a], were included in the active surveillance cohort (n=993)	An RSV-positive ARI episode was defined as a positive test result from either in-house RT-qPCR or POCT or both	Medically attended RSV-positive ARI: • Incidence: 14.1% (12.3–16.0), n=129 infants • Incidence rate per 1,000 infant-months: 12.1 (10.2–14.3), n=131 events RSV-positive ARI: • Incidence: 26.2% (24.0–28.6), n=249 infants • Incidence rate per 1,000 infant-months: 23.7 (21.0–26.7), n=262 events
Li *et al.*, 2022 (8) World Bank income regions (data reported for high income)	Systematic review of studies published 2017/01/01–2020/12/31	2019 or before (i.e., before the onset of the COVID-19 pandemic)	Children 0–60 months of age	RSV-associated acute lower respiratory infection was defined as acute lower respiratory infection with lab-confirmed RSV infection RSV-attributable acute lower respiratory infection was defined as acute lower respiratory infection that could be causally attributable to lab-confirmed RSV-infection	Incidence rate (UR) of RSV-associated acute lower respiratory infection in high-income regions (number of studies): • 0–3 months: 19.6 (6.5–59.7), n=3 • 3–6 months: 17.9 (4.8–66.7), n=3 • 0–6 months: 29.0 (12.9–65.0), n=4 • 6–12 months: 32.5 (19.9–53.0), n=4 • 0–12 months: 38.5 (21.6–68.8), n=5 • 0–60 months: 24.3 (13.8–42.7), n=7
RSV respiratory tract infection with hospitalization					
Schanzer *et al.*, 2006 (9) Canada	Retrospective population-based study	September 1994 to August 2000 (six influenza seasons, 1994/1995–1999/2000)	Hospitalized children younger than 19 years old	Diagnostic codes (ICD-9) selected based on their association with viral respiratory illness in children. RSV-attributable bronchiolitis admissions provided a better proxy for RSV activity than RSV positive specimens alone	RSV rates were highest in infants younger than six months of age at approximately 2,000 per 100,000

Table 2: Summary of included studies on the burden of disease of respiratory syncytial virus in infants and young children (*continued*)

Author, year (reference), country	Study design	Study period	Population	Outcome definition	Results
RSV respiratory tract infection with hospitalization (*continued*)					
Papenburg *et al.*, 2012 (10) Canada (QC)	Prospective cohort study	Four consecutive winter seasons (2006/07–2009/10)	Children aged 0–35 months presenting as outpatients to paediatric clinic or hospitalized for RTI (n=1,039 episodes; 305 in the clinic and 734 in the hospital)	PCR/DNA microarray hybridization assay Hospitalization was defined as admission for more than 24 hours to a short-stay unit, paediatric ward or PICU	RSV was the most frequently identified virus in infants and young children in hospital (n=467/734, 63.6%) with age younger than six months and prematurity associated with severe RSV cases among hospitalized children
Gilca *et al.*, 2020 (11) Canada (QC; Nunavik)	Retrospective cohort study	2012/11/01–2019/06/30 Children were followed up to one year of age or until 2019/06/30	Nunavik infants less than one year of age hospitalized for a respiratory illness (ICD-10 codes J00-J22 at any point, n=354)	RSVH was defined as hospitalization lasting 24 hours or longer with at least one positive RSV specimen collected during hospitalization or within four days prior to admission	113 (25%) of 458 episodes had RSV; annual average was 2.5 RSV-positive hospitalizations in high-risk infants and 16 RSV-positive hospitalizations in healthy full-term infants The overall RSVH rate per 1,000 live births in children younger than one year of age (adjusted for missed cases): • High-risk infants: 147.6 • Healthy full-term infants: 64.8 • Overall: 72.6
Piesky *et al.*, 2016 (12) Canada (ON)	Retrospective chart review	2010/01/01–2011/12/31	Children younger than three years of age residing within the Ottawa region potentially hospitalized for RSV (true positive cohort: n=1,119, and annual incidence estimates: n=19,815)	RSV hospitalization was defined as a positive test for RSV within 72 hours of admission and if the signs and symptoms responsible for hospital admission were consistent with RSV pathophysiology	Hospital admissions in children attributable to RSV: • Younger than one year of age: 8.8% • 1–2 years of age: 4.5% • 2–3 years of age: 2.7% Incidence of RSV hospitalization per 1,000 children from 2005 to 2012: • Younger than one year of age: 10.2 • 1–3 years of age: 4.8
Buchan *et al.*, 2023 (13) Canada (ON)	Population-based birth cohort study	First hospitalization in children born between 2009/05–2019/06	Children born May 2009 to June 2015 (n=826,140)	RSV hospitalizations were identified using a validated algorithm based on ICD-10 codes and/or laboratory-confirmed outcomes	12,573 (1.4%) incident cases of RSV hospitalization Rate of RSV-hospitalization per 1,000 patient-year (95% CI): • Range: from 29.55 (28.29–30.87) in children one month of age to 0.52 (0.47–0.57) in those 36–59 months of age • Overall: 4.23 (4.16–4.30) RSV hospitalization rates varied inversely with gestational age
McLaughlin *et al.*, 2022 (14) US	Systematic review and meta-analysis	Studies identified were published 2000–2020, and reported and collected 1989–2016	Children younger than five years of age (n=25 studies gave 31 estimates)	RSV hospitalization: • 13% (n=4/31) etiologic confirmation of RSV • 10% (n=3/31) clinician-directed standard-of-care medical and laboratory records • 65% (n=20/31) administrative claims data using RSV-specific ICD-9 codes • 13% (n=4/31) combined ICD-9 claims and etiologic surveillance data	Pooled rate of RSV-associated hospitalization per 1,000 (95% CI), n=31: • Younger than six months of age: 26.2 (24.2–28.2) • Younger than one year of age: 19.4 (17.9–20.9) • Younger than five years of age: 5.2 (4.8–5.6)

Table 2: Summary of included studies on the burden of disease of respiratory syncytial virus in infants and young children (*continued*)

Author, year (reference), country	Study design	Study period	Population	Outcome definition	Results
RSV respiratory tract infection with hospitalization (*continued*)					
Stein *et al.*, 2017 (15) 32 countries (26 countries reported data on RSV-associated severe ARI hospitalization)	Systematic review and meta-analysis	Studies published 2000–2015	Children younger than five years of age not receiving RSV immunoprophylaxis with palivizumab (n=55 studies, of those 34 reported on hospitalization for severe RSV-ARI)	Case of severe ARI included hospitalized ARI or hospitalized lower or acute lower respiratory infection, pneumonia, and bronchitis	RSV-associated ARI hospitalization per 1,000 children-year (95% CI), (number of studies): • Younger than six months: 20.01 (9.65–41.31), n=6 • Younger than 12 months: 19.19 (15.04–24.48), n=18 • Younger than five years: 4.37 (2.98–6.42), n=15
Suh *et al.*, 2022 (16) US	Systematic review	Studies published 2000/01/01–2021/06/11 (data 1979–2020)	Studies of US infants younger than one year of age with clinical sequelae of RSV, and bronchiolitis (n=141 studies)	Lab-confirmed or ICD diagnostic codes for RSV hospitalization or bronchiolitis hospitalization	Five studies provided nationally representative data on annual average RSVH rates per year ranging from 11.6 (95% CI: 6.9–16.3) per 1,000 per year among infants 6–11 months of age to 50.1 (95% CI: 35.6–64.6) per 1,000 per year among infants 0–2 months of age
Wingert *et al.*, 2021 (4) OECD countries	Rapid review	Studies published 2014/01/01–2018/09/06	Children 24 months of age and younger, with or without a risk factor of interest, or immunocompromised children 18 years of age and younger without palivizumab prophylaxis with lab-confirmed RSV infection (n=29 cohort studies)	Lab-confirmed RSV-hospitalization, ICU admission, oxygen support, mechanical ventilation, extracorporeal membrane oxygenation, case fatality and complications from RSV infections (e.g., secondary infection)	RR (95% CI) RSV-hospitalization, (number of studies): • 29–32 wGA vs. 33–36 wGA: 1.20 (0.92–1.56), n=1 • 33–36 wGA vs. ≥37 wGA: 2.05 (1.89–2.22), n=1 • Fewer than 33 wGA vs. 39–41 wGA: 3.88 (1.13–13.30), n=1
Li *et al.*, 2022 (8) World Bank income regions (data reported for high income)	Systematic review of studies published 2017/01/01–2020/12/31	2019 or before (i.e., before the onset of the COVID-19 pandemic)	Children 0–60 months of age	RSV-associated acute lower respiratory infection was defined as acute lower respiratory infection with lab-confirmed RSV infection RSV-attributable acute lower respiratory infection was defined as acute lower respiratory infection that could be causally attributable to lab-confirmed RSV-infection	Hospital admission rate per 1,000 children per year due to RSV-associated acute lower respiratory infection in high income countries (number of studies): • 0–3 months (n=19): 34.7 (21.5–56.2) • 3–6 months (n=21): 20.7 (13.5–31.6) • 0–6 months (n=27): 28.4 (20.2–40.0) • 6–12 months (n=27): 11.2 (7.5–16.7) • 0–12 months (n=41): 22.0 (17.1–28.4)
Bont *et al.*, 2016 (17) Western Countries (Canada, the US, and Europe)	Systematic review	Studies published 1995/01/01–2015/12/31	Children 18 years or younger	Hospitalization for RSV-related ARI or RSV-related bronchiolitis	RSV was associated with 19%–81% of all viral ARIs causing hospitalization Annual hospitalization rates per 1,000 children per year for RSV-associated ARIs: • 0–12 months: ranging from 3.2–42.7 • 1–4 years: ranging from 0.6–1.78 More than 70% of children hospitalized with RSV-associated ARIs had no underlying medical conditions Compared to influenza, RSV causes up to 16 times more hospitalizations and ED visits in children younger than five years

Table 2: Summary of included studies on the burden of disease of respiratory syncytial virus in infants and young children (*continued*)

Author, year (reference), country	Study design	Study period	Population	Outcome definition	Results
RSV respiratory tract infection with intensive care unit admissions					
Papenburg *et al.*, 2012 (10) Canada (QC)	Prospective cohort study	Four consecutive winter seasons (2006/07–2009/10)	Children aged 0–35 months presenting as outpatients to paediatric clinics or hospitalized for RTI (n=1,039 episodes; 305 in the clinic and 734 in the hospital)	PCR/DNA microarray hybridization assay Hospitalization was defined as admission for more than 24 hours to a PICU	63.6% (n=467) were RSV-positive hospitalization 5.2% (n=24/460) of hospital admissions for RSV had ICU admission (similar for hMPV)
Piesky *et al.*, 2016 (12) Canada (ON)	Retrospective chart review	2010/01/01–2011/12/31	Children younger than three years of age residing within the Ottawa region potentially hospitalized for RSV (true positive cohort: n=1,119)	RSV hospitalization was defined as a positive test for RSV within 72 hours of admission and if the signs and symptoms responsible for hospital admission were consistent with RSV pathophysiology	Of hospitalized cohort, 5.6% (95% CI: 5.2–5.9) were admitted to PICU and 3.1% (95% CI: 2.9–3.3) were intubated
Buchan *et al.*, 2019 (18) Canada (ON)	Retrospective multicentre cohort study	2009/05/01–2014/05/31	Hospitalized children aged 0–59 months tested for respiratory viruses including RSV (n=6,364)	Monoplex or multiplex PCR, viral culture or direct immunofluorescence	ICU admission: • 5% (n=192/3,569) with no comorbidities • 10% (n=275/2,795) if one or more comorbidity
Buchan *et al.*, 2023 (13) Canada (ON)	Population-based birth cohort study	First hospitalization in children born 2009/05–2019/06	Children born between May 2009 and June 2015 (n=826,140)	RSV hospitalizations were identified using a validated algorithm based on ICD-10 codes, and/or laboratory-confirmed outcomes	8.1% required intensive care during their hospitalizations (from 22% in those fewer than 28 weeks to 7% in those 37 weeks or more gestational age)
Amini *et al.*, 2019 (19) Canada (QC)	Prospective surveillance study	Peak weeks of five influenza seasons (2012/2013, 2014/2015–2017/2018)	Children younger than 24 months hospitalized with respiratory symptoms (n=546)	Multiplex PCR Hospitalization for 24 hours or longer for fever/feverishness or cough or sore throat	ICU admissions rates (p=0.07): • RSV: 3.6% • Influenza: 0%
Wildenbeest *et al.*, 2023 (7) Europe (five sites in Spain, Finland, England, Scotland and the Netherlands)	Multicentre, prospective birth cohort study	2017/07/01–2020/04/01	Healthy term infants, defined as children born 37 weeks or more of gestation with no evidence of significant disorders[a], were included in the active surveillance cohort (n=993)	Parental questionnaire and hospital chart reviews, active RSV surveillance in nested cohort	Eight PICU admissions, corresponding to 5.5% of 145 RSV-associated hospitalizations and 0.09% of the total cohort Six of eight infants admitted to the ICU were younger than three months of age (median one month)
Suh *et al.*, 2022 (16) US	Systematic review	Studies published 2000/01/01–2021/06/11 (data 1979–2020)	Studies of US infants younger than one year of age with RSV, clinical sequelae of RSV and bronchiolitis (n=141 studies)	RSV and bronchiolitis defined as lab-confirmed and/or ICD codes	No studies reported nationally representative data. Twenty-two studies reported proportions of ICU admissions among RSV hospitalized infants (range: 6.3%–71.4%) Higher ICU admissions were observed in younger vs. older infants (up to 64.3% in those younger than six months vs. 54.5% in those six months and older; 2013–2016), preterm vs. full-term infants (52.2% vs. 33.3%; 1992–2017) From 2003 to 2007, 21.8% of infants with CHD and 13.3% of infants with CLD hospitalized for RSV had ICU admissions

Table 2: Summary of included studies on the burden of disease of respiratory syncytial virus in infants and young children (*continued*)

Author, year (reference), country	Study design	Study period	Population	Outcome definition	Results
RSV respiratory tract infection with death					
Schanzer *et al.*, 2018 (20) Canada (except QC)	Retrospective population-based study	September 2003 to August 2014 (nine influenza seasons, excluding the 2008/2009 and 2009/2010 seasons)	All patients admitted to an acute care hospital for a respiratory condition	Hospitalization with an ICD-10 code for RSV (J12.1, J20.5, J21.0, B97.4)	RSV-attributed inpatient death rate: 0.6 (95% CI: −0.1–1.3) per 100,000 population (not limited to paediatric)
Buchan *et al.*, 2023 (13) Canada (ON)	Population-based birth cohort study	First hospitalization in children born 2009/05–2019/06	Children born May 2009 to June 2015 (n=826,140)	RSV hospitalizations were identified using a validated algorithm based on ICD-10 codes and/or laboratory-confirmed outcomes	12,573 (1.4%) incident cases of RSV hospitalization A small proportion of those (0.2%) died within 30 days of discharge
Reichert *et al.*, 2022 (21) US	Population-based birth cohort study	1999–2018	All infants born to residents of the US and those who died at younger than one year of age with RSV, bronchiolitis or influenza as the cause of death (n=80,764,705 live births, 510,502 total infant deaths from all causes)	RSV was defined by at least one ICD-10 cause of death codes: B97.4 (RSV), J12.1 (RSV, influenza), J20.5 (acute bronchitis due to RSV) and J21.0 (acute bronchiolitis due to RSV)	The overall infant mortality rates from 1999 to 2018: • RSV: 6.9 (95% CI: 6.4–7.5) per 1,000,000 live births (n=561) • Bronchiolitis: 19.8 (95% CI: 18.9–20.8) per 1,000,000 live births (n=1,603) • Influenza: 6.2 (95% CI: 5.7–6.8) per 1,000,000 live births (n=504) Infant RSV mortality rates by birth year from 2008 to 2018 ranged from 8.1 (95% CI: 5.5–11.4) to 3.4 (95% CI: 1.9–5.7) per 1,000,000 live births Infant RSV mortality rates among younger than 29 wGA infants was 103.5 (95% CI: 81.8–129.1) RSV mortality burden was greatest in full-term (53.7%) infants
Li *et al.*, 2022 (8) World Bank income regions (data reported for high income)	Systematic review of studies published 2017/01/01–2020/12/31	2019 or before (i.e., before the onset of the COVID-19 pandemic)	Children 0–60 months of age	RSV-associated acute lower respiratory infection was defined as acute lower respiratory infection with lab-confirmed RSV infection RSV-attributable acute lower respiratory infection was defined as acute lower respiratory infection that could be causally attributable to lab-confirmed RSV-infection	Case fatality rate of in-hospital deaths in high-income countries for children 0–12 months with RSV-associated acute lower respiratory infection: 0.1% (95% CI: 0.1–0.3) (n=29 studies)

Abbreviations: ARI, acute respiratory infection; CHD, congenital heart disease; CI, confidence interval; CLD, chronic lung disease; COVID-19, coronavirus disease 2019; DNA, deoxyribonucleic acid; ED, emergency department; hMPV, human metapneumovirus; ICD, International Classification of Diseases; ICU, intensive care unit; NVSN, New Vaccine Surveillance Network; OECD, Organisation for Economic Co-operation and Development; ON, Ontario; PCR, polymerase chain reaction; PICU, paediatric intensive care unit; POCT, point-of-care testing; QC, Québec; RR, risk ratio; RSV, respiratory syncytial virus; RSVH, respiratory syncytial virus hospitalization; RT-PCR, reverse transcriptase polymerase chain reaction; RT-qPCR, quantitative reverse transcription polymerase chain reaction; RTI, respiratory tract infection; UR, uncertainty range; US, United States; wGA, weeks gestational age

[a] Including cardiovascular, respiratory, renal, gastrointestinal, haematological, neurological, endocrine, immunological, musculoskeletal, oncological, or congenital disorders

In summary, RSV-related hospitalization rates vary by age and risk factors, with consistent trends of decreasing rates with increasing age. Despite vulnerability in high-risk groups, the majority of hospitalized children have no underlying medical conditions and RSV tends to lead to more hospitalizations compared to influenza.

Intensive care unit admission associated with RSV respiratory tract infection: Canadian studies indicate that approximately 5% of RSV-hospitalized children required ICU admission.

Papenburg *et al.* found that 5.2% needed ICU care (10), while Pisesky *et al.* reported 5.6% ICU admission among RSV-hospitalized children younger than three years (12). Buchan *et al.* reported 5% ICU admission for healthy children younger than five years, increasing to 10% with comorbidities (18). In their 2023 study, ICU admission reached 8.1% among RSV-hospitalized children under five, with higher rates for premature births (13). In one Canadian study, ICU admission was more common with RSV compared to influenza (19).

International data align with this rate. A European birth cohort study in healthy term infants found 5.5% of RSV-associated hospitalizations led to ICU admissions (7). An SR of RSV disease in the US identified ICU admission proportions ranging from 6.3% to 71.4% and linked risk factors to younger age, prematurity, congenital heart disease and chronic lung disease (16). In summary, Canadian research suggests approximately 5% of RSV-hospitalized children required ICU admission, with higher rates among those with risk factors. In comparison to influenza, there is some evidence that RSV leads to more ICU admissions.

Death associated with RSV respiratory tract infection: Existing literature suggests a low risk of RSV-related mortality in both Canada and the US. An overall mortality rate of 0.6 per 100,000 population was reported by Schanzer *et al.*'s 2018 Canadian model of all patients in Canada admitted to hospital with a respiratory condition (from infancy to older than 65 years) (20). Buchan *et al.*'s 2023 Ontario cohort found a 0.2% mortality rate within 30 days of discharge from RSV hospitalization (13). In the US, an infant cohort followed from 1999 to 2018 showed an RSV mortality rate of 6.9 (95% CI: 6.4–7.5) per one million live births, with preterm infants at the highest risk (21); however, the majority of deaths occurred in full-term infants (53.7%), primarily those between one and four months of age (63.8%). Globally, a systematic analysis reported a 0.1% (95% CI: 0.1–0.3) case fatality rate for in-hospital RSV deaths in children 0–12 months of age (8).

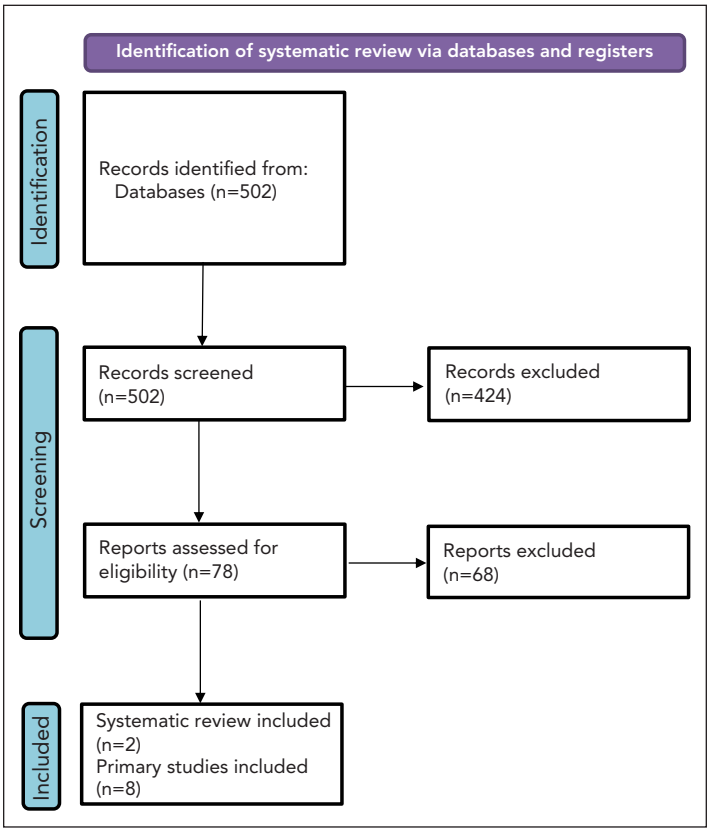
Pregnant women and people

Study selection: After removing duplications, 474 primary evidence studies and 28 systematic reviews underwent screening (**Figure 2**). In total, two SRs and eight studies were included in the narrative synthesis of RSV burden in pregnant women and people (**Table 3**). No data on RSV-related mortality was identified in pregnant women and people.

Medically attended RSV respiratory tract infection: Two US cross-sectional studies by Hause *et al.* investigated RSV infection rates in pregnant women and people in their second or third trimester during the 2015–2016 RSV season. In one study, with combined PCR and serological data, the RSV attack rate among ambulatory pregnant women and people receiving routine prenatal care was estimated at 10%–13% (22). In the second study, approximately 10% of acute lower respiratory tract illness cases in pregnant women and people were confirmed as RSV (23).

Hospitalization associated with RSV respiratory tract infection: The literature on RSV-associated hospitalizations presents a broad range of rates. A retrospective study within the Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) 2010–2016 found a 2.5% RSV-positive rate, contrasting with a 51% influenza-positive rate (24). A US population-based study from 2015 to 2018 revealed higher hospitalization rates among pregnant women and people compared to non-pregnant adults

Figure 2: Study selection PRISMA flow diagram in pregnant women and people



(average rate of 620 vs. 320 per 100,000) (25). Additionally, one retrospective case series documented adverse pregnancy outcomes in ten pregnant individuals hospitalized with RSV, including pneumonia, respiratory failure and sepsis, with six experiencing obstetrical complications during hospitalization, including preterm contractions, coinfections and preeclampsia (26). In summary, the literature suggests a wide range of possible RSV hospitalization rates among pregnant women and people, with one study indicating a higher burden compared to non-pregnant adults.

Intensive care unit admission associated with RSV respiratory tract infection: Evidence on RSV-related ICU admissions is limited. In a retrospective case series focusing on adverse pregnancy outcomes, one of 10 pregnant women and people required ICU admission and mechanical ventilation (26). Another case series of three pregnant women and people with RSV found that two required ICU admission and mechanical ventilation, while the third was monitored as an outpatient (27). A case report describes a pregnant person admitted with RSV pneumonitis and sepsis, requiring ICU admission, mechanical ventilation and emergency C-section (28). However, data regarding the risk of ICU admission among pregnant women and people remain scarce.

Table 3: Summary of included studies on the burden of disease of respiratory syncytial virus in pregnant people

Author, year (reference), country	Study design	Study period	Population	Outcome definition	Results
Medically attended RSV respiratory tract infection					
Hause *et al.*, 2019 (22) US	Cross-sectional study	2015/11/03–2016/05/10	Pregnant women and people in their 2nd or 3rd trimester enrolled prospectively during their regular prenatal visits (n=155)	Lab-confirmed acute respiratory illness	Seven of 65 (11%) pregnant women and people with ARI at their initial enrollment and eight of 77 (10%) pregnant women and people with ARI during the study period (initial or re-enrollment) had PCR-confirmed RSV infection Four (50%) PCR-confirmed RSV ARI cases reported symptoms of a LRTI, one was hospitalized RSV had an attack rate of 10%–13% among ambulatory pregnant women and people receiving routine prenatal care during the respiratory virus season
Hause *et al.*, 2018 (23) US	Cross-sectional study	2015/10/01–2016/05/10	Pregnant women and people in their 2nd or 3rd trimester enrolled prospectively during their regular prenatal visits (n=155)	RSV infection was determined by PCR or serology	Of the 81 ARI cases, 52 (64%) respiratory pathogens were detected: The most frequently detected viruses were rhinovirus (n=22; 27%), coronavirus (n=14; 17%) and RSV (n=8; 10%) 12 patients had fever; 17 had symptoms of LRTI Of the seven cases with fever in the ALRTI group, three were RSV-positive (one had HRV coinfection) Of those patients with LRTI, two reported decreased fetal heart rate and one RSV-positive case was hospitalized for respiratory illness
RSV respiratory tract infection with hospitalization					
Regan *et al.*, 2018 (24) Australia, Canada (ON), Israel and the US	Retrospective database study	2010–2016	Pregnant women and people aged 18–50 years who were admitted to hospital with an ARFI (n=1,604,206 pregnant women and people)	An RSV-positive ARFI hospitalization was defined as a positive RT-PCR test result within three days of hospital admission	13,694 hospitalized acute respiratory tract/febrile illness; 846 tested for RSV and influenza 2.5% (n=21) tested positive for RSV 51% (n=430) tested positive for influenza Fewer than 1% tested positive for both influenza and RSV
Nowalk *et al.*, 2022 (25) US	Population-based retrospective aggregate cohort study	2015/09/01–2018/08/31	Adults ages 18–64 years, 65 years and older and including pregnant women and people (n=13,174 pregnant women and people)	Aggregate data used to determine population-based RSV hospital burden	RSV burden of hospitalization ranged from 0 to 808 per 100,000 pregnant women and people: • 2015–2016: no hospitalized cases of RSV among pregnant women and people • 2016–2017: 431 per 100,000 • 2017–2018: 808 per 100,000 Average burden from 2015 to 2018 of 620/100,000 in pregnant women and people which was higher than the burden for non-pregnant adults 18 years and older (n=320/100,000)
Hause *et al.*, 2021 (26) US	Retrospective case series	2010/08/01–2017/04/30	Pregnant women and people aged 14–49 years who tested positive for RSV and were hospitalized for RSV infection during pregnancy (n=10)	Variable	275,349 pregnant women and people; 1,057 tested for RSV; 25 (2%) tested positive; 10 hospitalized during pregnancy and tested positive within two weeks prior to or during hospitalization Diagnoses: pneumonia/atelectasis (n=5), upper respiratory tract infection (n=2), asthma exacerbation (n=2), respiratory failure (n=2), sepsis (n=2) Six had obstetrical complications (one exacerbation of pre-existing short cervix with preterm labour, three preterm contractions (two of which had co-infections), one induction for preeclampsia); one preterm birth; one ICU admission/ mechanical ventilation
RSV respiratory tract infection with intensive care unit admissions					
Hause *et al.*, 2021 (26) US	Retrospective case series	2010/08/01–2017/04/30	Pregnant women and people whose pregnancy ended in live birth (n=10)	Hospitalization during pregnancy and positive RSV test by culture or PCR	275,349 pregnant women and people; 1,057 tested for RSV; 25 (2%) tested positive; 10 hospitalized during pregnancy and tested positive within two weeks prior to or during hospitalization One of 10 (10%) required ICU admission and mechanical ventilation

Table 3: Summary of included studies on the burden of disease of respiratory syncytial virus in pregnant people (*continued*)

Author, year (reference), country	Study design	Study period	Population	Outcome definition	Results
RSV respiratory tract infection with intensive care unit admissions (*continued*)					
Wheeler *et al.*, 2015 (27) US	Case series	Winter 2014	Antepartum RSV infection treated at single tertiary care facility (n=3)	N/A	Two of three cases required ICU admission and mechanical ventilation; all three cases complicated by pre-existing lung conditions (asthma, comorbid influenza, group A streptococcus infection)
Deshmukh *et al.*, 2014 (28) UK	Case report	Not stated	40-year-old pregnant person (n=1)	N/A	Pregnant person admitted to hospital in UK requiring ICU admission, mechanical ventilation, and emergency C-section at 33 weeks for maternal reasons (RSV pneumonitis and sepsis)
Preterm labour/birth with RSV infection					
Regan *et al.*, 2018 (24) Australia, Canada (ON), Israel and the US	Retrospective database study	2010–2016	Pregnant women and people 18–50 years of age who were admitted to hospital with an ARFI (n=1,604,206 pregnant women and people)	An RSV-positive ARFI hospitalization was defined as a positive RT-PCR test result within three days of hospital admission	13,694 hospitalized acute respiratory tract/febrile illness; 846 tested for RSV; 2.5% (n=21) tested positive by RT-PCR No difference in preterm, small-for-gestational age and low birth weight births between RSV-positive and RSV-negative participants Association observed between RSV positivity and subsequent preterm birth (p=0.034): • RSV-positive participants, 29% • RSV-negative participants, 15%
Chu *et al.*, 2016 (29) Nepal	Prospective randomized trial	April 2011 to May 2014	Pregnant women and people in the 2nd trimester of pregnancy and followed until six months postpartum (n=3,693; 14 RSV illness episodes over 3,554 person-year surveillance)	RSV-positive tests were determined by rt-PCR	Seven (50%) pregnant participants sought care for RSV illness; none died Of the seven (50%) illness episodes during pregnancy, all had live births with two (29%) preterm births and a median birth weight of 3,060 grams. This compares to 469 (13%) preterm births and a median birth weight of 2,790 grams in persons without RSV during pregnancy
Hause *et al.*, 2021 (26) US	Retrospective case series	2010/08/01–2017/04/30	Pregnant women and people whose pregnancy ended in live birth (n=10)	Hospitalization during pregnancy and positive RSV test by culture or PCR	275,349 pregnant women and people; 1,057 tested for RSV; 25 (2%) tested positive; 10 hospitalized during pregnancy and tested positive within two weeks prior to or during hospitalization One of 10 (10%) participants had pneumonia and preeclampsia and was induced between 36 and 37 weeks

Abbreviations: ALRTI, acute lower respiratory tract infection; ARFI, acute respiratory infection or febrile illness; ARI, acute respiratory infection; HRV, human rhinovirus; ICU, intensive care unit; LRTI, lower respiratory tract infection; N/A, not applicable; ON, Ontario; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; rt-PCR, real-time polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; UK, United Kingdom; US, United States

Outcome for both infants and pregnant women and people—preterm labour/birth: Three studies reported data on the risk of preterm labour/birth associated with RSV infection. In the Pregnancy Influenza Vaccine Effectiveness Network study, no difference was observed in preterm, small for gestational age, and low birth weight births between RSV-positive and RSV-negative pregnant women and people (24). However, among ARI admissions without delivery during the hospital admission, RSV positivity was associated with subsequent preterm birth (29% vs. 15%). A study from Nepal showed a higher rate of preterm birth with RSV illness episodes during pregnancy (29% vs. 13%) (29). In a case series of ten pregnant women and people hospitalized with RSV, one had preterm birth (10%) (26). In summary, available evidence is insufficient to assess the risk of preterm labour/birth due to RSV infection during pregnancy.

Discussion

This rapid review offers insight into RSV burden in predominantly high-income countries, with a focus on Canada, the US and Europe. More robust evidence was available for infants and young children, with Canadian studies contributing significantly, while evidence for pregnant women and people primarily stemmed from small observational studies outside Canada. In infants and young children, medically attended RSV was common, and RSV hospitalization rates varied but generally decreased with age. Most hospitalized children had no underlying medical conditions. Approximately 5% of RSV-hospitalized children in Canada required ICU admission, and the risk of death was low. Respiratory syncytial virus caused a higher burden of disease than influenza in this population.

Novel and previously unpublished data from the Yukon support the conclusions of this literature review, noting a higher burden of RSV than influenza and the highest burden in younger age groups. For pregnant women and people, RSV severity appeared to be similar to non-pregnant women and people, with an attack rate of 10%–13% during the respiratory virus season. One study reported higher RSV hospitalization rates than those for non-pregnant women and people. Data on ICU admission, death and preterm birth related to RSV in pregnancy were limited, although two studies suggested an association with preterm birth.

This rapid review highlights limitations in characterizing RSV burden in Canada. Studies often focused on RSV-associated hospitalization and ICU admission, which are critical outcomes for assessing severe clinical consequences. However, it is also essential to grasp the significance of other outcomes in the Canadian context, in particular medically attended RSV and death related to RSV infection. Currently, Canada has limited enhanced national RSV surveillance data. Recent research initiatives have leveraged existing healthcare administrative databases to characterize RSV burden; however, those data are expected to underestimate RSV disease especially in the community and outpatient setting due to undertesting in routine clinical care, the lack of generalizability to the Canadian population and healthcare coding systems that do not capture all possible contributors to RSV-related complications (30).

Limitations

This rapid review has limitations. It primarily focused on short-term outcomes and did not consider potential long-term effects such as asthma, which may be associated with early-life RSV infection (31,32). Detection of RSV infection was not limited to laboratory confirmation; some studies relied on clinical diagnostic codes, potentially inflating RSV incidence. Estimates were imprecise. Robust data on severe RSV outcomes in pregnant women and people were lacking; however, historically, pregnant women and people have not been known to specifically be at higher risk of RSV infection. Although the goal of forthcoming RSV immunization products is to reduce complications of RSV in infants, it is essential to also consider the potential benefits of an RSV vaccine for pregnant people, given their increased susceptibility to certain respiratory pathogens such as influenza resulting from pregnancy-related changes in anatomy and the immune and cardiovascular systems. This review did not specifically focus on RSV burden during the coronavirus disease 2019 (COVID-19) pandemic. The public health measures in place during the early phase of the pandemic led to a significant reduction of seasonal respiratory virus circulation (33). In recent seasons, there has been a substantial increase in RSV cases, with changes in age distribution and atypical seasonality patterns compared to prior to the COVID-19 pandemic, attributed to larger populations of RSV-naive children (34,35). For example, a recent publication from 13 paediatric centres in Canada noted a significant burden of RSV hospitalizations, with a significant increase in hospitalizations in 2021–2022 compared to pre-pandemic (36). Despite these limitations, the data presented here provide a foundation for understanding the typical RSV burden in infants and young children.

Conclusion

A high incidence of medically attended RSV is observed in infants and young children, with hospitalization rates decreasing with age. Approximately 5% of hospitalized infants and young children with RSV required ICU admission. The risk of death appears to have been low. Pregnant and non-pregnant women and people showed similar RSV severity, although data were limited for pregnant individuals. With the introduction of interventions, RSV's disease burden is expected to change; robust surveillance systems at the provincial, territorial and national levels will be crucial for evaluating the public health impact of RSV immunization programs. This review contributes to the literature, aiding in characterizing RSV's burden in Canada and guiding RSV immunization strategies for infant protection.

Authors' statement

EMA — Conceptualization, data analysis, data interpretation, writing–original draft
PDP — Conceptualization, data analysis, data interpretation, writing–original draft
PD — Data analysis, data interpretation, writing–reviewing
NB —Writing–reviewing
AI — Writing–reviewing
WS — Conceptualization, writing–reviewing
AK — Conceptualization, writing–reviewing

Competing interests

None.

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Supplemental material

These documents can be accessed on the Supplemental material file.

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Canadian vaccine safety surveillance reports following immunization with seasonal influenza vaccines, 2021–2022

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Abstract

Background: Seasonal influenza vaccines (SIV) authorized for use in Canada have all undergone rigorous regulatory assessments for safety and effectiveness. Serious adverse events following immunization (AEFI) can occur, though they are rare. Continuous safety surveillance of vaccines during the post-marketing phase is a critical component of vaccination programs. This enables the detection of rare, late onset, or unexpected adverse events. An updated safety summary following the introduction of any new vaccines and/or formulations to immunization programs is necessary for refining the risk-benefit profile of a specific vaccine and maintaining public confidence. Here we provide an updated safety summary for SIVs distributed during the 2021/2022 influenza season from AEFI reports submitted to the Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) and the Canadian Vigilance Database (CVD).

Methods: We searched CAEFISS and CVD for individuals who were vaccinated with a SIV between October 1, 2021, and March 31, 2022. Descriptive statistics were calculated, including median age of vaccinated individuals, vaccines co-administered with SIV, and the most frequently reported AEFIs. Crude AEFI reporting rates were calculated by severity of the AEFI report, and SIV-type using doses distributed data. Medical reviews were conducted for reports including death, serious events (or outcomes) after SIV were administered alone, and selected adverse events (i.e., anaphylaxis, Guillain-Barré syndrome, febrile seizures, oculo-respiratory syndrome). Disproportionality analysis was used to identify potential safety signals among SIV and AEFI pairs.

Results: There were 448 AEFI reports, with most AEFI classified as non-serious events (84.2%). The majority of reports described vaccination in adults at least 65 years of age (38.6%). The most frequently reported AEFIs were vaccination site pain, urticaria, pyrexia and rash. Medical review of AEFI reports did not find any evidence that reported deaths were related to vaccination with SIV. Among serious reports, nervous system disorders were the most commonly reported medical conditions. A higher number of events related to vaccination errors were also identified using disproportionality analysis.

Conclusion: Findings from our analysis of reports to CAEFISS and CVD following vaccination with SIV are consistent with the known safety profile of SIVs distributed during the 2021/2022 influenza season. The majority of reports were non-serious with the most common AEFI symptoms occurring at the vaccination site or systemic symptoms that were self-limiting. The majority of vaccination error reports involved the administration of the vaccine at an inappropriate site, although no serious AEFIs were reported.

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Keywords: influenza, vaccine adverse event, pharmacovigilance, vaccine safety, adverse event following immunization, AEFI

Introduction

Annual vaccination with seasonal influenza vaccine (SIV) remains the most effective strategy to decrease morbidity and mortality of influenza virus infection (1). In Canada, annual influenza vaccination is recommended for anyone six months of age and older, with a focus on targeted groups at highest risk of influenza-related complications (1). Several influenza vaccines are currently authorized for use in Canada; during the 2021/2022 influenza season, five types of SIVs were distributed in Canada, including standard dose (IIV4-SD) and high-dose (IIV4-HD) egg-based quadrivalent inactivated influenza vaccine, standard-dose cell culture-based quadrivalent inactivated influenza vaccine (IIV4-cc), quadrivalent live attenuated influenza vaccine (LAIV4), and adjuvanted egg-based inactivated influenza vaccine (IIV3-Adj) (1). Among these SIVs, the most frequently reported non-serious adverse events following immunization (AEFI)s in both children and adults were vaccination site reactions (e.g., pain, redness, swelling) and self-limiting systemic symptoms (e.g., fever, headache, nausea) (1).

All influenza vaccines authorized in Canada are considered to be safe (1); nevertheless, routine safety monitoring of AEFIs following SIV remains an essential component of annual influenza immunization programs. Notable AEFIs of concern include immediate hypersensitivity reactions such as anaphylaxis, Guillain-Barré syndrome (GBS), oculo-respiratory syndrome (ORS) and febrile seizures (1). Anaphylaxis reactions may be due to either an active component or additive in the vaccine; however, true anaphylaxis reactions are rare and occur at a rate of one per million doses for many vaccines (2). A proven association between use of the pandemic swine flu vaccine and GBS was identified in 1976 in the United States, which paused this particular vaccination campaign (3). Since 1976–1977, GBS has not been consistently associated with influenza vaccines; however, there is a need to monitor for GBS occurrence during mass vaccination campaigns, particularly following the use of pandemic influenza vaccines (4). Minor unexpected AEFIs have also been reported in Canada, including reports of ORS following receipt of past influenza vaccines (5). There is a small increased risk for febrile seizures when an inactivated influenza vaccine is administered during the same visit with PCV13 (pneumococcal) vaccine or the diphtheria, tetanus and pertussis (DTaP) vaccine (6). However, the risk of febrile seizures with any combination of these vaccines is small (up to 30 febrile seizures per 100,000 children vaccinated) and should be interpreted in the context of preventing pneumococcal and influenza infections among children (6).

Although rare, serious and unexpected AEFIs can occur following SIV. Post-marketing vaccine safety surveillance to identify late onset, rare or unexpected AEFIs is critical to any immunization program to enable effective public health action and to maintain vaccine confidence and public trust. The Public Health Agency of Canada (PHAC) and Health Canada share the monitoring of the quality, safety and effectiveness of vaccines marketed in Canada. At the national-level, AEFI reports are received in two safety surveillance systems: Canadian Adverse Event Following Immunization Surveillance System (CAEFISS) (7) (managed by PHAC); and Canada Vigilance Database (CVD) (8) (coordinated by Health Canada). The objective of this report is to summarize influenza AEFI reports received in both CAEFISS and CVD to assess the general safety profile of SIVs distributed during the 2021/2022 influenza season and to compare SIV safety trends over time.

Methods

Data sources

The CAEFISS is managed by PHAC and involves both passive and active surveillance monitoring systems that are designed to detect rare, late onset or unexpected events for any authorized vaccine in Canada (7). The CAEFISS receives spontaneous (passive) AEFI reports from federal, provincial and territorial public health authorities. Active surveillance is conducted through the Canadian Immunization Monitoring Program, ACTive (IMPACT) by nurse monitors under the supervision of paediatric and/or infectious disease medical specialists (9). The AEFI reports submitted to CAEFISS do not imply a causal relationship between the vaccine and AEFI, but that reported events are temporally associated with the vaccine (i.e., occur after vaccination within a biologically plausible timeframe) and have no other clear cause at the time of reporting. The AEFI form (10) submitted to CAEFISS collects information on sex, age, vaccines administered, doses and lot number, medical history and AEFIs experienced. AEFIs, including signs, symptoms and diagnoses, are assigned preferred terms (PT) by trained personnel using the Medical Dictionary for Regulatory Activities version current at the time of data collection (11). A systematic medical case review is conducted by trained health professionals who classify cases for reporting using standardized case definitions as applicable (12). A serious AEFI report is identified based on the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (13), as an event that results in death, is life-threatening, requires inpatient

hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or results in congenital anomalies/birth defects. Any medical event that may not be immediately life-threatening but requires intervention to prevent one of the outcomes listed above may also be considered serious.

Health Canada coordinates CVD, which contains information about suspected adverse reactions to health products (including vaccines) that are submitted voluntarily by consumers and healthcare professionals. In addition, market authorization holders (manufacturers and distributors) are required to report serious AEFIs involving their marketed health products to CVD when they become aware of them. Specific reporting requirements for market authorization holders are described in the Food and Drug Regulations (14). The adverse reaction form collects information on reporter's profession, age and sex of the vaccine recipient, vaccine(s) administered, the adverse reaction experienced and the level of care obtained. Signs and symptoms are coded using Medical Dictionary for Regulatory Activities (11) and reports are considered serious based on the definitions included in the Food and Drug Regulations (14) and the International Council on Harmonisation serious definition (13).

Data analysis

We searched CAEFISS and CVD for AEFI reports among persons of any age who were vaccinated with SIV between October 1, 2021, and March 31, 2022 (analytic period). Our search included any report where SIV was administered alone or concomitantly with at least one other vaccine on the same day. Since healthcare providers and consumers can voluntarily submit AEFI reports to their federal, provincial and territorial public health authority (reports are sent to CAEFISS) and to CVD, there is the potential for duplicate reports between surveillance systems. To minimize duplicate reporting, initial groupings of CAEFISS and CVD reports were performed based on primary case information such as sex, age of the vaccinee, date the vaccine(s) was administered, vaccine trade name(s) and AEFIs to consolidate duplicate reports.

Descriptive statistics

We described all reports submitted to CAEFISS and CVD for persons of any age who were vaccinated with SIV during the analytic period. Descriptive statistics were calculated, including median age and sex of the vaccine recipient, time-to-onset (the date from vaccination to onset of first symptoms), concomitant vaccine administrations with SIV, and the most frequently reported preferred terms. All data analyses were performed in R, the programming language for statistical computing (R version 4.1.3) (15).

Crude AEFI reporting rates were calculated for all reports and serious reports and by SIV-type (i.e., IIV3-Adj, IIV4-SD, IIV4-HD, IIV4-cc, LAIV-4) by dividing the number of AEFI reports received during the analytic period by the total number of SIV doses distributed in Canada during the 2021/2022 influenza season.

Medical review of reports

All reports that described death following vaccination with SIV and all reports of serious AEFIs were medically reviewed (where medical records were available). For each report, we identified the primary AEFI that initiated the report and the respective System Organ Class (SOC) and preferred term(s) for the primary AEFI. In addition, we reviewed reports and accompanying medical information, where available, for selected AEFI conditions, which include reports of anaphylaxis, GBS, febrile seizures and ORS. Where applicable, Brighton Collaboration Case Definitions (BCCD) were applied to assess the level of case certainty (16–18).

Disproportionality analysis

Using CAEFISS reports only, we calculated the information component (IC) statistic to identify AEFI and SIV pairings that were disproportionately reported during the 2021/2022 influenza season compared to the expected reporting in prior influenza seasons (2010/2011 through 2020/2021). Values greater than zero for the lower credibility interval endpoint of the IC ($IC_{0.25}$) were considered statistically significant and were subject to medical review unless they were previously included in our list of selected AEFI conditions (see Methods, Medical review of reports). Significant values do not imply causality of an AEFI and vaccine pair but can suggest potential vaccine safety adverse events that require further medical investigation.

Results

Our search identified 448 AEFI reports in CAEFISS and CVD following receipt of SIV during the surveillance period and are summarized in **Table 1**. Of these, 377 reports (84.2%) were considered non-serious AEFIs, while 71 (15.8.%), which included 13 reports of death, met the definition for serious case. The median age of vaccinees was 52 years (range: 5 months–104 years) and most reports described receipt of SIV in persons aged 65 years and older (38.8%), followed by children aged 5–17 years (21.9%). The median time-to-onset was one day (range: 0–15 days). The majority of reports were among females (65.2%) compared to males (34.4%). Of the 286 reports with SIV given alone, 31 (10.8%) were classified as serious.

There were 162 reports (36.1%) that listed at least one additional vaccine administered on the same day as the SIV. The most commonly co-administered vaccines varied in accordance with age-based recommendations in the immunization schedule. Among children aged 0–4 years, the measles, mumps and rubella vaccine was the most frequently reported vaccine co-administered with SIV (60.5%), followed by diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b vaccine

Table 1: Characteristics of serious adverse events following immunization reports following seasonal influenza vaccine received in CAEFISS and CVD, October 1, 2021–March 31, 2022, N=448

Characteristic	N	%
Surveillance system		
CAEFISS	414	92.4
CVD	34	7.6
Seriousness		
Non-serious	377	84.2
Serious	71	15.8
Sex		
Female	292	65.2
Male	154	34.4
Not specified	2	0.4
Time-to-onset in days[a], median (range)	1.0	0.0–15.0
Age (years), median (range)	52.0	0.5–104
Age groups (years)		
0–4	61	13.6
5–17	98	21.9
18–49	40	8.9
50–64	71	15.8
65 and older	173	38.6
Unknown/not specified	5	1.1
Co-administrations		
1 (seasonal influenza vaccine given alone)	286	63.8
2	116	25.9
3 or more	46	10.3
Reporter profession		
Consumer/non-health professional	28	6.3
Health professional (MOH/MHO, MD, RN, Pharmacist)	214	47.8
IMPACT	9	2.0
Unknown/Not specified	197	43.9

Abbreviations: CAEFISS, Canadian Adverse Event Following Immunization Surveillance System; CVD, Canadian Vigilance Database; IMPACT, Canadian Immunization Monitoring Program, ACTive; MD, doctor of medicine; MOH/MHO, medical officer of health; RN, registered nurse; SIV, seasonal influenza vaccine
[a] Based on reports where time-to-onset was available

(DTaP-IPV-Hib, 36.8%) and meningococcal conjugate C vaccine (Men-C-C, 36.8%). Among adults aged 65 years and older, coronavirus disease 2019 (COVID-19) vaccines (67.1%) and pneumococcal polysaccharide 23 vaccines (Pneu-P-23, 31.6 %) were the most frequently co-administered with SIV. Reports describing co-administration are not mutually exclusive, as vaccine recipients can receive more than one co-administered vaccine on the same day. The 10 most frequently reported AEFIs are shown in **Table 2** and included vaccination site pain (17.4%), urticaria (11.6%), rash (10.7%) and pyrexia (10.7%).

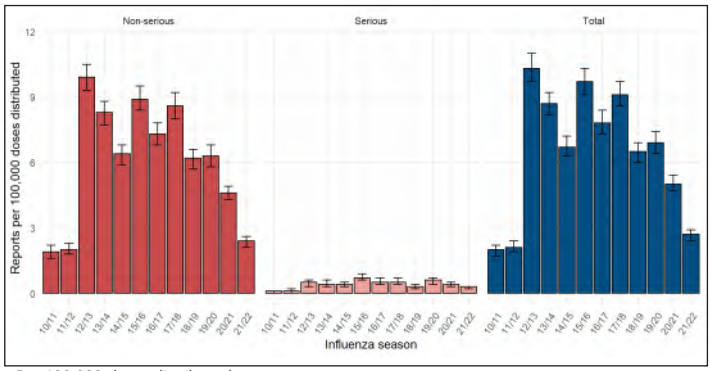
Table 2: Most frequently reported Medical Dictionary for Regulatory Activities preferred terms following administration with seasonal influenza vaccines, by seriousness, October 1, 2021–March 31, 2022

MedDRA preferred term	N	%[a]
Vaccination site pain	78	17.4
Urticaria	52	11.6
Pyrexia	48	10.7
Rash	48	10.7
Vaccination site erythema	43	9.6
Vaccination site swelling	43	9.6
Pruritus	39	8.7
Erythema	37	8.3
Vomiting	36	8.0
Dyspnea	33	7.4

Abbreviation: MedDRA, Medical Dictionary for Regulatory Activities
[a] Percentage calculated as a proportion of total reports for each MedDRA term

During the 2021/2022 influenza season, 15,605,176 SIV doses were distributed in Canada. Based on only the 414 CAEFISS reports per Table 1 (as historical information from CVD was not available), the overall crude reporting rate in 2021/2022 was 2.7 reports per 100,000 doses distributed. Similarly for serious reports, with 41 serious reports from CAEFISS, the crude reporting rate was 0.3 per 100,000 doses distributed. Since the 2019/2020 influenza season, there has been a consistent downward trend in reporting rates among total and serious reports, with non-overlapping confidence intervals (**Figure 1**).

Figure 1: Crude adverse event following immunization reporting rate[a] following receipt of seasonal influenza vaccine by seriousness, 2010/2011 to 2021/2022 influenza seasons[b]



[a] Per 100,000 doses distributed
[b] Canadian Adverse Event Following Immunization Surveillance System reports only

Based on SIV-type, crude reporting rates were highest among IIV4-HD vaccine (4.2 reports per 100,000 doses distributed), followed by IIV3-SD vaccines (2.2 reports per 100,000 doses distributed), while among other SIV-types, fewer than 10 reports were reported (**Table 3**). Across all SIV-types, the reporting rate for serious events remained low, with one or fewer report per 100,000 doses distributed.

Table 3: Description of adverse event reports following receipt of seasonal influenza vaccine-type, N=389[a]

Report descriptor	Influenza vaccine type				
	IIV3-Adj	IIV4-SD	IIV4-HD	IIV4-cc	LAIV-4
Total reports	Fewer than 10	296	79	Fewer than 10	Fewer than 10
Non-serious	SDC	262	67	SDC	SDC
Serious	SDC	34	12	SDC	SDC
Proportion serious	SDC	11.5%	15.2%	SDC	SDC
Total doses distributed	69,587	13,456,161	1,876,475	34,533	168,420
Reporting rate (95% CI)[b]	SDC	2.2 (2.0–2.5)	4.2 (3.3–5.2)	SDC	SDC
Serious rate (95% CI)	SDC	0.3 (0.2–0.4)	0.6 (0.3–1.1)	SDC	SDC

Abbreviations: CI, confidence interval; IIV3-Adj, adjuvanted egg-based trivalent inactivated influenza vaccine; IIV4-cc, standard-dose cell culture-based quadrivalent inactivated influenza vaccine; IIV4-HD, high-dose egg-based quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose egg based quadrivalent inactivated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine; SDC, statistical disclosure control (suppression of small cell counts)

[a] Fifty-seven reports with missing influenza vaccine name and type, and two reports with vaccines distributed in previous season were excluded

[b] Rates were calculated per 100,000 doses distributed

Deaths

There were 13 reports of death following vaccination with SIV. Medical information (e.g., patient medical history, clinical information leading up to events, pre-existing and concurrent comorbidities) was available for 10 of these reports. Of these, neurocognitive disorders were the most cited cause of death (n=4/10, 40%). Six reports did not provide cause of death or results of further investigations (at the time of reporting), but all six reports described pre-existing medical conditions including chronic obstructive pulmonary disease, coronary artery disease, diabetes, hypertension and a genetic disorder. The majority of deaths (n=9/13, 69%) occurred among adults aged 65 years and older, and the median age was 84 years (range: 12 months–98 years). The remaining three reports had insufficient information on cause of death, patient medical history or clinical information leading up to events. Of those with sufficient information for causality assessment, none were deemed to be consistent with a causal association with vaccination.

Serious reports

There were 31 reports classified as serious following vaccination with SIV only. The most common SOC was nervous system disorders, including diagnosis of GBS (two reports), seizure (one report), syncope (one report) and petit mal epilepsy (one report). There was one AEFI report identified for the following SOCs: gastrointestinal disorders (one report of abdominal pain); general disorders and administration site conditions (one report of chest pain); immune system disorder (one report of event managed anaphylaxis); investigations (one cerebrospinal fluid test abnormal); respiratory, thoracic and mediastinal disorders (one report of dyspnea); and skin and subcutaneous tissue disorders (one report of urticaria). The remaining 20 reports did not identify the primary event that prompted the report; therefore, the respective SOC and preferred term for the primary event could not be determined.

Selected adverse events

Our search did not find any reported cases of ORS following receipt of a SIV distributed during the 2021/2022 influenza season. Twenty-nine possible reports of select AEFIs (i.e., anaphylaxis, GBS, febrile seizures) were identified from our search and are further described below.

Anaphylaxis: There were 16 reports that had at least one PT suggestive of anaphylaxis, most of which (n=12/16, 75%) described anaphylaxis following receipt of SIV alone. In 14 of the 16 (87.5%) reports, IIV4-SD was the SIV-type received. Only six reports met the BCCD criteria. One report was classified as level 1 (highest level of diagnostic certainty) and five reports were classified as level 2. The remaining 10 reports did not contain sufficient information to either assign a certainty between BCCD levels 1–3 or rule out anaphylaxis (i.e., BCCD level 5). Further, there was no information within these reports to confirm whether the reactions experienced (at time of reporting) were immunoglobulin E (IgE)-mediated. Among the six confirmed reports, the median time-to-onset was 43 minutes (range: 4–230 minutes) and most reports (n=12/16, 75%) described anaphylaxis following receipt of SIV alone.

Guillain-Barré syndrome: Four reports of possible GBS were identified following receipt of a SIV. After applying the BCCD, one report was classified as level 3; the remaining three reports could not be classified according to BCCD, mainly due to incomplete medical information within the AEFI report. The time-to-onset was nine days, and the single report described GBS after receipt of more than one vaccine.

Febrile seizures: There were nine possible reports suggestive of a febrile seizure. Four reports were considered serious: following medical review, all four reports were classified as BCCD level 1 and all four reports occurred among children two years of age and younger and a median age of one year (range: 1–1.5 years). Among these reports, the time to onset for all reports was one day. All four reports listed SIV concomitantly administered with

more than one childhood vaccine, including measles, mumps and rubella, pneumococcal conjugate 13 (Pneu-C-13), varicella, DTaP-IPV-Hib and Hepatitis B (HB) vaccines.

Disproportionality analysis

When compared to previous influenza seasons, two preferred terms were reported more frequently this season than expected in the CAEFISS database: "vaccination error" and "lymphadenopathy". There were 15 reports of vaccine error, where the frequency of observed reports was 2.7 times ($IC/IC_{0.25}$: 1.45/0.57) the proportion of reports received in prior influenza seasons in CAEFISS. The most common reason for vaccine error was vaccine administration at an inappropriate site (n=13/15, 86.7%), while the remaining report indicated the vaccine was given outside the recommended age indication. Further review of vaccine error reports identified AEFI conditions consistent with shoulder injury related to vaccine administration (SIRVA; i.e., joint range of motion decreased, shoulder injury, joint movement impairment); however, all reports were considered non-serious.

There were 13 reports of lymphadenopathy, where the frequency of observed reports was 2.1 times higher ($IC/IC_{0.25}$: 1.10/0.16) than the proportion of lymphadenopathy reports in CAEFISS observed in prior influenza seasons. Given that the majority of AEFIs reports were non-serious, and lymphadenopathy has been reported as an AEFI during clinical trials (19) and during post-approval use among SIV (20), no further medical review was conducted.

Discussion

This article describes reports to CAEFISS and CVD following receipt of SIV between October 2021 and March 2022. Most reports were for adults aged 65 years and older (38.6%), the group for which SIV is routinely recommended due to increased risks for complications from influenza, including hospitalizations and death (1). Overall, AEFIs reported were consistent with the known safety profile of SIV, characterized by pre-licensure studies and post-marketing surveillance, and included vaccination site reactions (i.e., pain, swelling, erythema) and systemic reactions (i.e., fever, nausea, vomiting). The overall and non-serious reporting rates were significantly lower than those observed during previous influenza seasons. Given that the annual SIV campaign is not new, vaccine recipients and providers may be less likely to report milder and less serious AEFIs with vaccines they are familiar with, an epidemiological phenomenon referred to as the Weber effect (21). There is some evidence of an observed reduction in non-serious spontaneous reporting due to the COVID-19 pandemic, which may be driven primarily by changes in reporting practices by healthcare professionals or vaccine recipients. Our data supports this observation as the reduction is mainly seen in non-serious reports, while serious reporting rates remain within historic ranges (22). The data are also comparable to other studies looking into the safety of SIVs in other countries (1,23–25).

Based on the medical information available, most reports of death following receipt of SIV were due to neurocognitive disorders. There were six reports (out of the 13 reports with an outcome of death) that indicated a broad range of pre-existing medical conditions that may have contributed to increased risk of severe clinical outcomes of influenza infection, including death. Among these reports, we did not identify any patterns or further evidence to suggest a causal relationship between vaccination and death. Because reports received in CAEFISS and CVD do not always contain complete medical information on the patient, we were unable to assess for potential confounders (i.e., pre-existing medical conditions, medications) or for causality for some of these reports.

Among reports classified as serious, the most commonly reported AEFIs following vaccination of SIV alone were classified as nervous system disorders and are mentioned in the associated SIV product monographs as having been reported after vaccination but for which causal association is unknown (19,26). Reassuringly, their occurrence remained rare, though providers are expected to communicate risk-benefit information to vaccine recipients and caregivers along with advice for what to do if such an event occurs (1).

There was disproportionate reporting of vaccine error terms, with the majority of reports describing symptoms consistent with SIRVA. Shoulder injury related to vaccine administration typically occurs moments to days after the vaccine is injected and can result in prolonged and even permanent shoulder dysfunction. While the incidence of SIRVA is not well known, it is assumed to be uncommon (27).

Limitations

It is important to consider the limitations of CAEFISS and CVD that are inherent to passive surveillance systems. These can include under-reporting, reporting bias, varied report quality and completeness, and appropriate denominator data for contextualizing the number of AEFI reports received. Currently, there is no mechanism for tracking the number of SIV doses administered nationally. In the absence of such data, doses of SIV distributed served as a proxy for doses of SIV administered; therefore, crude reporting rates should be interpreted with caution. Further, absence of an unvaccinated control group makes it difficult to examine the association between an AEFI and the vaccine(s). It is rarely possible to determine causality based on reports submitted to national passive surveillance systems alone. When a signal is detected, further investigation is always warranted at the individual and population level to determine causality (28). Nonetheless, these surveillance systems provide a means for identifying statistical safety signals for rare and unexpected AEFIs and can be used to make general conclusions of the safety of vaccines administered in Canada.

Conclusion

The overall goal of post-marketing safety surveillance is to detect rare or unusual safety concerns that may signal previously unknown associations between a given vaccine and AEFIs, or changes in expected safety profiles in terms of frequency or severity of selected AEFIs. Based on this updated summary, we did not observe any trends or patterns of concern following receipt of a SIV in Canada during the 2021/2022 influenza season. Our findings are consistent with data from pre-licensure clinical trials and post-licensure safety assessments and support that SIV exhibit a favourable safety profile (1,23,29).

Authors' statement

EG — Formal analysis, validating, data visualization, writing–original draft, writing–review and editing
YX — Writing–review and editing
TN — Formal analysis
AW — Writing–review and editing
AS — Writing–review and editing
MB — Writing–review and editing
BS — Writing–review and editing
SOC — Supervision, writing–review and editing

Competing interests

None.

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SCOPING REVIEW

Disease burden attributable to respiratory syncytial virus outbreaks in long-term care

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Abstract

Background: Respiratory syncytial virus (RSV) disease burden is significant among children; however, RSV can also cause excess morbidity and mortality among older adults. Populations in long-term care homes (LTCHs) may be at greater risk of exposure and increased infection severity. The objectives of this article are to identify evidence regarding disease burden and outcome severity attributable to RSV outbreaks among residents and staff in LTCHs; and to highlight reported population and outbreak characteristics.

Methods: All types of evidence were eligible for inclusion. Data utilized by included studies was between the end of the 2010 H1N1 influenza pandemic and the beginning of the coronavirus disease 2019 (COVID-19) pandemic. Evidence from the following countries was considered: G7, the European Union, Australia and New Zealand. A total of 167 articles were identified; 58 full texts were analyzed and four sources of evidence were eligible for inclusion. Data related to population characteristics, outbreak type and resident and staff outcomes were manually charted.

Results: There is a paucity of evidence sources pertaining to RSV outbreak burden among residents and staff in LTCHs. Outbreak duration ranged from 13 to 21 days. For each outbreak, 4–7 residents had confirmed RSV infection. Attack rates ranged from 12% to 38%. A spectrum of disease attributable to RSV outbreaks in LTCHs was identified, ranging from mild cold-like symptoms to death.

Conclusion: Integration of RSV into existing respiratory pathogen surveillance programs is important to characterize susceptibility, transmissibility and virulence of RSV in at-risk populations. There is a need for public health organizations to publish the findings from outbreak investigations to provide evidence to inform RSV outbreak prevention and response in LTCH settings.

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Introduction

Respiratory syncytial virus (RSV) is a pathogen responsible for a significant proportion of lower respiratory tract illnesses worldwide (1–3). It is mostly associated with causing disease burden among infants and young children; however, a significant burden can be placed on older and at-risk adults by RSV, as it is considered one of the most significant causes of excess morbidity and mortality among older adults (4–8). Respiratory syncytial virus may lead to complications and severe outcomes like those caused by seasonal influenza infection among older adults (9–11).

Long-term care (LTC) residents and staff spend significant time in congregated indoors settings where respiratory outbreaks are commonplace (12). Long-term care residents, who tend to be 80 years old on average, may be at increased risk of heightened respiratory infection severity—including severe symptoms, hospitalization, or mortality (13–15). Considering the growing proportion of older adults and projected increased demand for LTC services and staff, LTC populations might require additional attention to prevent and mitigate the consequences of LTC outbreaks of RSV (16–18).

Disease burden due to RSV outbreaks among LTC populations can be mitigated; however, for prevention and response to be population specific and most effective, these interventions need to be evidence-informed. Understanding the extent of currently available evidence and current knowledge gaps could help to inform subsequent research and public health activities with the goal of minimizing the burden in long-term care homes (LTCHs) from RSV outbreaks. Currently, little evidence synthesis on RSV outbreak burden among residents and staff in LTC settings is available, which makes current gaps in the literature challenging to identify. Some recently published reviews on RSV outbreaks and disease burden among older adults and in LTC exist (4,15,19); however, these reviews are not specific to both LTC populations and RSV outbreaks. This is the first scoping review to synthesize available evidence related to RSV outbreak burden among residents and staff in LTCHs using more recently published literature from 2010 to 2020. The objectives of this review are a) to understand the extent of the evidence regarding disease burden attributable to RSV outbreaks in LTCHs, among both residents and staff; b) to highlight reported population and outbreak characteristics; and c) to highlight RSV outcome severity among residents and staff members.

Methods

Eligibility criteria

Eligibility criteria were determined before screening and review of identified sources (**Table 1**). Studies were eligible for inclusion if they were published in English or French and utilized data collected between the end of the H1N1 pandemic (2010) and the start of the coronavirus disease 2019 (COVID-19) pandemic (2020). The identification of a viral pathogen that is etiologically responsible for respiratory illness became more common around the time of the H1N1 pandemic, with the inclusion of other viral pathogens, including RSV, on routine multiplex polymerase chain reaction (PCR) tests. Therefore, this date range was chosen to include existing studies from the period where viral identification became more widespread, as well as to identify relevant literature that reflects more recent RSV dynamics in LTCHs. Sources were included if they discussed outbreaks of RSV in LTCHs in any G7 country (Canada, France, Germany, Italy, Japan, the United Kingdom, the United States, and the European Union—which is a non-enumerated member of the G7), Australia or New Zealand. These locations were chosen because their seasonal patterns of RSV outbreaks and culture of health care use and access are like Canada's. Sources were included if the reported outbreaks occurred in LTC settings, which were defined as residential institutions in which primarily older adults receive care. Mixed outbreaks were included in the review if at least one case of RSV was detected in the outbreak. Studies were not excluded based on the type of diagnostic or confirmatory testing that was used. Outbreaks involving only residents, only staff or both residents and staff were considered for inclusion.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
I*1: Studies published and used data that were collected between April 2010 and March 2020.	E*1: Excluded studies that were published in 2010–2020 but using data collected during the H1N1 influenza and/or COVID-19 pandemics.
I*2: Published in English or French.	E*2: Excluded review studies that did not provide discussion regarding RSV disease burden in any of the identified populations as these studies will not provide relevant information to answer the research questions.
I*3: Study included or assessed data from G7 countries, Australia or New Zealand.	-
I*4: Population under study includes: older adults in LTC and adults working in LTC.	-
I*5: Studies that assessed the epidemiology (incidence, severity, mortality) of RSV outbreaks.	-
I*6: Studies that assessed the clinical epidemiology (presentation, course, dynamics, and severity) of RSV. In scope: clinical severity outcomes are hospitalization, ICU admission, death, duration of outbreak(s), severe symptoms.	-
I*7: Studies that assessed RSV disease burden at a population/ outbreak level.	-

Abbreviations: COVID-19, coronavirus disease 2019, ICU, intensive care unit; LTC, long-term care; RSV, respiratory syncytial virus; -, there were no items to list in the cell

Search strategy

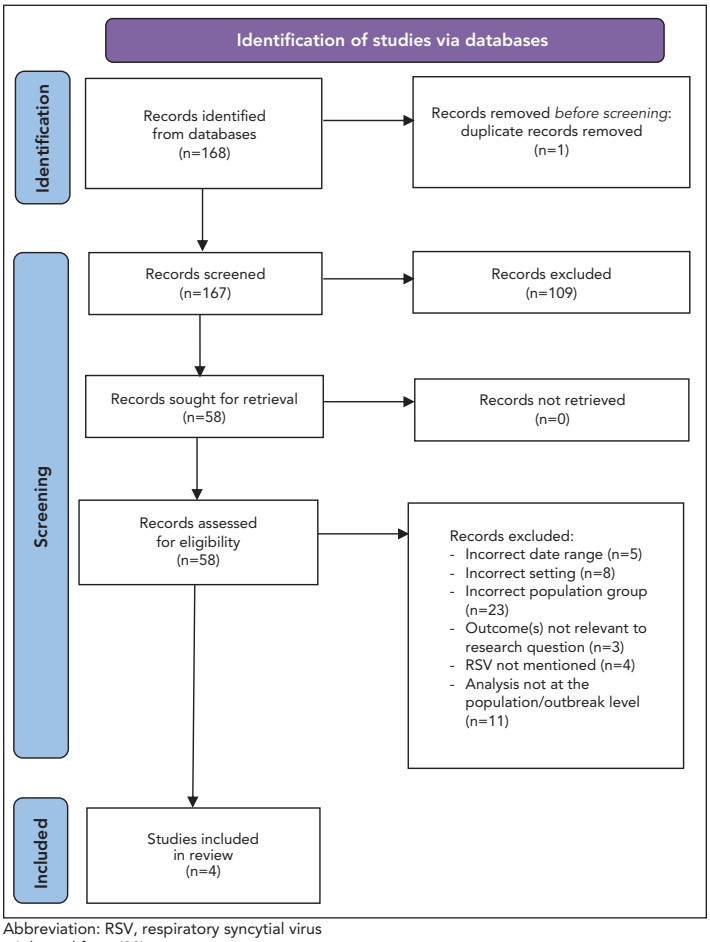
Four databases were searched to identify potentially relevant evidence sources: MEDLINE, Embase, Global Health, and Scopus. The search strategy was developed with input from all authors. The literature search was conducted by the Health Canada Library. Keywords used for the literature search identified the setting, population, and outcomes of interest, including "LTC outbreak", "respiratory syncytial virus", "nursing home", "older adult*", "hospital*", "mortalit*" and "respiratory infection". A sample search of one database is presented in **Appendix** (**Table A1**). Due to time constraints, a grey literature search was not conducted as part of this review.

Selection of evidence sources

After removal of duplicates, 167 articles were considered for inclusion. References were imported into Zotero, a reference management system. Covidence, a screening and data extraction tool, was used during the screening process. Due to time constraints for the completion of this study, screening was conducted by a single reviewer. The first stage involved screening the titles and abstracts of all 167 articles. Inclusion and exclusion criteria were applied to determine whether the

article would move onto the second round of screening. The second round involved the full-text review of 58 articles. Inclusion and exclusion criteria were used to determine if the source was eligible for inclusion in the review (Table 1). After full-text review, four articles met inclusion criteria, and were included in this review (**Figure 1**).

Figure 1: Selection process for included studies based on literature searches[a]



Abbreviation: RSV, respiratory syncytial virus
[a] Adapted from (20)

Data charting was conducted by a single reviewer using an online form developed using Covidence; however, data charting criteria were developed with input from all authors.

Synthesis of results and quality assessment

Population characteristics (age, gender, type and number of LTC settings affected per outbreak) and outbreak characteristics (pathogens involved, outbreak duration, symptom and outcome severity, attack rates and number of residents and staff cases) were extracted, grouped and analyzed. Individual characteristics of each article (data collection dates, study population and location) were also extracted, grouped and analyzed.

Results

The four articles included in the scoping review were published and used data collected between 2013 and 2017. **Table 2** describes the characteristics of each included article (n=4) for which data were charted. The studies were conducted in four different countries: Japan; Slovenia; the Netherlands; and the United States. Three articles are case series and one is a prospective study. The sample sizes across all included articles ranged from 10 to 99 residents, and zero to 42 staff members. All were primary sources of evidence.

Synthesis of results

The average age of the resident study population was reported in three articles (81.5, 85.5 and 84 years) (8,21,22). Average age of RSV positive residents was reported in one article (84 years) (22). The age range for residents was provided in three articles, with the overall age ranging from 68 to 90 years (8,21,22). One article provided the average age of staff members at the affected LTCH (average of 38 years; range: 35–46 years) (8). Gender proportion for residents who tested positive for RSV was provided in one article, where (50% (n=2/4) of RSV positive cases were male and 50% (n=2/4) were female (22). Gender proportion for staff was discussed in one article, where 97.6% of the LTCH staff identified as female (8). All outbreaks took place in LTCHs, with residents affected in each outbreak (n=4/4). All four articles discussed single-facility outbreaks of RSV. Discussion of staff was presented briefly in one article, in which no staff cases were reported during this RSV outbreak (8).

Comorbidities among residents were discussed in all four articles. In two articles, various forms of dementia were identified as a common comorbidity among the overall resident study population; however, identification of RSV-positive cases with attributable comorbidities was not available (8,23). In one study, no comorbidities were identified among RSV-positive cases who developed pneumonia, and comorbidities for the remaining study population were not discussed (21). Comorbidities reported among those who were RSV positive included respiratory allergy, hypertension, diabetes mellitus, kidney dysfunction, heart failure and frailty (22).

Resident vaccine status was discussed in one article, where a large proportion of residents at the LTCH were vaccinated against influenza; however, no resident vaccination rate was provided (23). No article discussed staff vaccine status.

Exposure source was not confirmed in any article. One article identified the possibility of pathogen introduction to the facility via infected visitors or the childcare centre/intergenerational program that operates within the facility (22). Presenteeism, which occurs when an employee attends work despite the presence of an illness that might prevent them from functioning fully while at work (24), might have been associated with RSV exposure among residents in two outbreaks (22,23).

Table 2: Characteristics of included sources of evidence (n=4)

Author, citation	Study title	Journal	Publication type	Publication date	Study location (country)	Sample size	Study purpose	Study outcome(s)
Doi *et al.*, (21)	An outbreak of acute respiratory infections due to human respiratory syncytial virus in a nursing home for the elderly in Ibaraki, Japan, 2014	*Japan Journal Infectious Diseases*	Case series	2014	Japan	99 residents	To report the molecular epidemiological analysis of an outbreak of RSV in a nursing home.	Genetic sequences showed RSV-B outbreak in nursing home with 24 infected and 5 of 24 residents received a pneumonia diagnosis.
Meijer *et al.*, (22)	Outbreak of respiratory syncytial virus infections in a nursing home and possible sources of introduction: The Netherlands, winter 2012/2013	*The American Geriatric Society*	Case series	2013	The Netherlands	10 residents	To describe an outbreak of RSV in a nursing home and to identify possible sources of introduction.	Four RSV positive cases among residents detected during the outbreak, all experienced mild symptoms and recovered within 2 weeks of illness onset.
Spires *et al.*, (23)	Paramyxovirus Outbreak in a Long-Term Care Facility: The Challenges of Implementing Infection Control Practices in a Congregate Setting	*Infection Control and Hospital Epidemiology*	Case series	2017	United States	41 residents	To describe an outbreak of viral respiratory illness caused by RSV and hMPV in an LTCF among residents with a high rate of influenza vaccination. To highlight infection prevention challenges in an LTCF.	Among residents, 6 cases of RSV, 7 cases of hMPV and 1 case of influenza detected in the outbreak.
Uršič *et al.*, (8)	Viral respiratory infections in a nursing home: a six-month prospective study	*BMC Infectious Diseases*	Prospective study	2016	Slovenia	90 residents, 42 staff	To assess and compare the incidence of acute respiratory illness in nursing home residents and staff, to identify viruses involved in acute respiratory infection, and to correlate viral etiology with clinical manifestations of acute respiratory infection.	Five RSV cases detected among residents leading to 5 lower respiratory tract infections due to RSV. Zero RSV cases were detected among staff.

Abbreviations: hMPV, human metapneumovirus; LTCF, long-term care facility; RSV, respiratory syncytial virus

Outbreak duration was discussed in three articles, with an average of 17 days and a range of 13 to approximately 21 days (8,22,23). None of the articles discussed the criteria that were used by the LTCH to determine when an outbreak was declared over.

One article reported an outbreak definition that was used by either researchers or the LTCH during their respective outbreak investigations, which required at least two cases of acute respiratory infection with identification within five days in the same unit and with laboratory confirmation of infection with the same virus (8). One article provided a case definition that was based on clinical manifestations of symptoms of respiratory pathogen infection; however, these identified cases also underwent testing to identify the infectious agent (23).

Respiratory syncytial virus cases were identified in each outbreak and ranged from four to seven resident cases per outbreak. The attack rate, defined as the proportion of a population exposed to RSV who then developed symptoms of RSV infection and tested positive for RSV, ranged from 12% to 38% for residents. In three articles, insufficient information was provided about the number of staff members at risk of infection with RSV. One article identified the number of respiratory infections during a mixed outbreak that were not due to RSV, where eight of 14 infections (57%) were due to a pathogen other than RSV, specifically human metapneumovirus (hMPV) or influenza (23). In three studies, all cases identified in the RSV-attributable outbreaks were due to RSV infection among residents, and no other pathogens were detected in the associated outbreaks (8,21,22).

Respiratory syncytial virus subtype was reported in three articles in which RSV-B was identified (21–23). One article did not discuss the subtype of RSV detected in the outbreak (8).

Information regarding co-infection was provided by two articles. One article identified one co-infection in a resident who tested positive for both RSV and hMPV (23). In contrast, another included article did not identify any co-infections during the RSV outbreak (8). Co-infections among residents infected with RSV were not discussed in two articles (21,22).

Symptom severity ranged from mild cold-like symptoms to more severe manifestations, including pneumonia and lower respiratory tract infection (LRTI) attributable to RSV infection. Clinical severity for cases of RSV was reported in three articles (8,21,22). Of these outbreaks and among those who tested positive for RSV, pneumonia was reported in two articles (8,21). One article reported four RSV-positive cases (n=4/4; 100%) who developed acute respiratory infection with mild cold-like symptoms (22). One article reported the development of pneumonia in 10 residents; however, symptoms of RSV-positive cases were not distinguishable from symptoms experienced by those who tested positive for hMPV or influenza (23). Clinical symptom severity for RSV cases could not be distinguished from symptoms of non-RSV infections in one article (23). Symptom severity among staff was excluded from three articles and was not applicable in one study because no staff cases were detected (8).

No hospitalizations due to RSV were reported in two articles (21,22). Information regarding resident hospitalization was not provided in two articles (8,23). Staff hospitalizations were not discussed in three articles (21–23) and one article reported no RSV cases amongst staff (8).

Information about resident deaths due to RSV was reported in three articles (8,21,22). In one article, one out of five resident RSV cases confirmed by diagnostic testing died (case fatality rate: 20%) (8), whereas in two articles, no case fatalities were reported and all affected residents recovered (21,22). Staff mortality information due to RSV was not provided in three articles (21,23). In one article, information regarding staff mortality was not relevant since zero staff RSV cases were detected (8).

Two articles discussed outbreak mitigation measures in affected LTCHs (**Table 3**) (22,23). In both outbreaks, cohorting of infected residents occurred, which is an effective outbreak mitigation method of separating infected and uninfected individuals during an outbreak (25). One facility struggled to cohort staff members and infected residents due to the large number of sick and absent staff (23). One facility reported the LTCH's architectural layout enabled cohorting (22). One LTCH implemented infection prevention and control measures outlined in The Netherland's infection prevention working group guidelines (22), though it is unknown which of these measures were implemented within the affected LTCH.

Discussion

Summary of evidence

This review highlights the lack of available evidence pertaining to RSV outbreak burden during the study period and a large knowledge gap pertaining to the burden of RSV outbreaks among LTCH staff. Symptom severity ranged from mild cold-like symptoms to pneumonia, LRTI and death. The range and severity of symptoms among residents align with what has been previously reported. Severe respiratory symptoms in older adults in LTCH may be more likely to occur due to age-associated immunity impairments, presence of comorbid conditions, such as diabetes mellitus and chronic obstructive pulmonary disease, living conditions within LTCHs, and existing prevalence of pneumonia and LRTI among older adults (14,19,26,27). Older adults in LTC, particularly those prone to frailty, may be at even greater risk of severe complications due to RSV infection (19,28). Additionally, a large proportion of residents developed LRTI attributable to RSV, which aligns with existing literature as RSV is a major cause of LRTI (29).

Table 3: Main findings of each included study

Author, citation	Outbreak setting	Outbreak type	Pathogen(s) detected	Pathogen detection method	Outbreak duration (days)	Residents with confirmed RSV infection (n)	Staff infected and confirmed by testing (n)	Attack rate	Co-infection(s)	Hospitalization(s) due to RSV	Death(s) due to RSV	Symptom severity	RSV subtype detected	Outbreak mitigation measures implemented	Hypothesized exposure source
Doi *et al.*, (21)	1 LTCH; most infections contained to 2nd floor	RSV	RSV	RT-PCR testing	Unknown	7	Unknown	24	Unknown	0	0	5 residents with pneumonia; 4 of 7 that tested positive for RSV presented with pneumonia and acute wheezing	RSV-B	Unknown	Unknown
Meijer *et al.*, (22)	1 LTCH; limited to mostly 1 unit	RSV	RSV	Unknown	21[a]	4	Unknown	38	Unknown	0	0	4 diagnosed with acute respirator infection and common cold; mild symptoms	RSV-B	Followed nursing home-specific guidelines for infection prevention and control; outbreak spread mitigated due to cohorting and isolation of infected and directly exposed residents	Actual exposure source unknown; hypothesized exposure from presenteeism, sick visitors, intergenerational geriatric remotivation
Spires *et al.*, (23)	1 LTCH; spread across 2 locked units	Mixed	RSV, hMPV, influenza	RT-PCR testing	16	6	Reported sick staff members, pathogen involved not specified	15	1	Unknown	Unknown	15 residents transferred to acute care; 10 diagnosed with pneumonia and 5 deaths[b]	RSV-B	Cohorting of infected residents into private rooms or shared rooms with another case; placement of case residents into droplet; contact precautions (e.g., limitations on travel outside patient room and use of personal protective equipment); messaging to staff to avoid presenteeism; emphasis on staff hand hygiene and proper respiratory etiquette; daily leadership meetings; cessation of unit-based group activities; visitor restrictions; closure of unit to new admissions	Actual exposure source unknown; presenteeism discussed as potential source
Uršič *et al.*, (8)	1 LTCH	RSV	RSV	PCR testing	13	5	0	12	0	Unknown	1	All developed lower respiratory tract infection; pneumonia also reported	Unknown	Unknown	Unknown

Abbreviations: hMPV, human metapneumovirus; LTCH, long-term care home; PCR, polymerase chain reaction; RSV, human respiratory syncytial virus; RT-PCR, reverse transcription polymerase chain reaction

[a] This outbreak was reported to have a duration of approximately three weeks; duration was converted to approximately 21 days to keep the unit (days) for this outcome consistent across evidence sources

[b] Could not distinguish which outcomes were due to RSV, hMPV or influenza

Considering the lack of available vaccination information for both staff and residents, data on routine vaccinations in older adults could be improved. Improved collection of routine vaccination data for multiple respiratory pathogens, including influenza, severe acute respiratory syndrome coronavirus 2 and pneumococcal infections could improve mitigation and allow for intervention research on new vaccines in LTCH and at-risk populations.

Some possible exposure sources included presenteeism, the presence of intergenerational programs within the LTCH and the introduction of RSV into the facility by visitors or volunteers (22–24). Further research to understand the relative impact of the introduction of RSV into LTCHs and the identification of common exposure sources or transmission routes associated with RSV outbreaks in LTCHs may be useful to inform more effective outbreak management (30–32). Cohorting staff and residents in affected LTCH units as part of outbreak management was an identified challenge. Additional research pertaining to the effectiveness of cohorting methods and other outbreak mitigation measures may benefit an LTCH's ability to strategically prepare outbreak management plans.

This scoping review meets the objective to understand the current state of evidence regarding RSV outbreak burden data among residents and staff in LTCHs. Currently, the evidence base is scarce, so the integration of RSV surveillance and the publication of these data are important to better characterize the epidemiology of RSV outbreaks in LTCHs and to inform public health interventions to prevent and respond to RSV outbreaks among LTC populations. However, although sparse, the evidence in this review shows that RSV outbreaks have occurred in LTCHs and required enhanced measures to control—often over many days (13–21 days). Respiratory syncytial virus outbreaks in LTC can cause morbidity and mortality among residents. In some cases, symptoms are mild and self-limiting, while in others, attack rates and severe outcomes including hospitalization, pneumonia and death are documented.

Strengths and limitations

This review highlights gaps in the knowledge base rather than generating novel ideas, which is a critical part of the exploratory research process. The application of broad inclusion criteria enabled a sensitive literature search, so it is likely that this article provides an accurate picture of currently available published evidence. Article screening and abstraction were conducted by a single reviewer, which could increase the risk of introducing errors and biases. Lastly, a grey literature search was not conducted due to time constraints, which might have excluded some relevant data sources since surveillance reports are often not published in peer-reviewed journals.

Conclusion

This scoping review highlights a lack of published, peer-reviewed evidence pertaining to RSV outbreak burden in LTC settings. There is a paucity of available evidence that describes RSV outbreak burden among residents and particularly among staff members. This evidence could help to inform future research and population-specific public health measures to reduce the burden of RSV outbreaks in LTCHs.

Consideration of qualitative factors, like RSV outbreaks' impact on physical symptomatology, mental health and financial impacts or factors that might influence the risk of presenteeism might provide important evidence to inform outbreak management and response in LTCHs. Population-wide studies to describe the epidemiology of RSV outbreaks in LTCHs could also provide valuable data for public health interventions. Overall, the implementation of RSV outbreak surveillance, and its integration with surveillance of other respiratory pathogens in LTC, could enable better characterization of the susceptibility, transmissibility and virulence of RSV and other respiratory pathogens in LTCHs. The results of this scoping review also highlight the need for public health organizations to publish findings from outbreak investigations, so this evidence can be used to inform public health policy, practice and decision making to prevent and respond to RSV outbreaks in LTC.

Authors' statement

CF — Conceptualization, project administration, formal analysis, investigation, writing–review and editing
CB — Conceptualization, project administration, writing–review and editing, supervision
NA — Conceptualization, project administration, writing–review and editing, supervision

Competing interests

None.

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Appendix

Table A1: Sample search strategy utilized by the Health Canada Library Database(s), Ovid MEDLINE(R) ALL 1946 to February 14, 2023

#	Searches	Results
1	Respiratory Syncytial Virus Infections/	8,468
2	(respiratory syncytial vir* or respiratory syncytial pneumov* or RSV or hrsv).tw,kf,kw.	20,982
3	1 or 2 [RSV]	21,627
4	exp *Aged/ or *Geriatrics/	53,958
5	(((old* or aging) adj (adult* or woman or women or man or men or people? or person? or resident?)) or elder? or geriatric* or aging or ageing or senior? or retiree* or retired or pensioner* or "over 65" or "over 80" or baby boomer? or babyboomer? or silent generation or septuagenarian? or octogenarian? or nonagenarian? or centenarian? or geronol* or (("65" or "66" or "67" or "68" or "69" or 7# or 8# or 9# or "100") adj year*)).ti,kf. or (((older or aging) adj (adult* or woman or women or man or men or people? or person? or resident?)) or elder? or geriatric* or aging or ageing or senior? or retiree* or retired or pensioner* or "over 65" or "over 80" or baby boomer? or babyboomer? or silent generation or septuagenarian? or octogenarian? or nonagenarian? or centenarian? or geronol* or (("65" or "66" or "67" or "68" or "69" or 7# or 8# or 9# or "100") adj year*)).ab. /freq=2	461,347
6	4 or 5 [Older Adults]	481,298
7	long-term care/ or exp nursing homes/	66,904
8	((long term or extend* or continu* or advance* or chronic* or aged) adj3 care).tw,kf.	91,739
9	(((nursing or retirement* or care) adj2 (home* or communit* or facilit*)) or assisted living* or hopsice*).tw,kf.	122,066
10	or/7-9 [Long Term Care Homes]	218,119
11	exp "quality of life"/ or exp morbidity/ or exp mortality/ or hospitalization/ or exp critical care/ or "severity of illness index"/ or "length of stay"/ or "cost of illness"/ or Respiratory Tract Infections/ or exp bronchitis/ or Healthcare-Associated Pneumonia/ or Multiple Organ Failure/ or Sepsis/	1,840,212
12	(mortalit* or morbidit* or death? or die or died).tw,kw,kf.	2,126,484
13	("quality of life" or "quality adjusted life year*" or qaly or "disability adjusted life year*" or daly).tw,kw,kf.	371,153
14	((health* or wellness or disease* or disorder* or illness* or condition*) adj3 burden*).tw,kf.	74,734
15	(Burden* or Proportion or Case fatality rate* or case fatality ratio* or CFR or Attack rate* or Hospitalization* or Intensive care unit* or ICU or incidence* or duration* or span or timespan or period of time or length or Respirator* failure* or respiratory tract infection* or URTI or LRTI or Bronchi* or Pneumonia or Multi* organ failure* or Sepsis or septic* or Fever* or outbreak*).tw,kw,kf.	3,845,127
16	or/11-15	6,297,775
17	exp australia/ or austria/ or exp baltic states/ or exp belgium/ or exp canada/ or chile/ or czech republic/ or exp "scandinavian and nordic countries"/ or exp france/ or exp germany/ or greece/ or hungary/ or exp ireland/ or israel/ or exp italy/ or exp japan/ or exp republic of korea/ or luxembourg/ or mexico/ or exp netherlands/ or exp new zealand/ or poland/ or exp portugal/ or slovakia/ or slovenia/ or exp spain/ or exp switzerland/ or turkey/ or exp united kingdom/ or exp united states/ or (australia* or new south wales or queensland or tasmania or victoria or sydney or melbourne or brisbane or austria* or vienna or viennese* or belgium* or belgian* or brussels or flemish* or canad* or ottawa* or british columbia* or colombie britannique* or vancouver* or alberta* or edmonton* or calgar* or saskatchewan* or regina* or saskatoon* or manitoba* or winnipeg* or ontari* or toronto* or quebec* or montreal* or new brunswick* or nouveau brunswick* or fredericton* or nova scotia* or nouvelle ecosse* or halifax* or haligonian* or prince edward island* or ile du prince edouard* or pei or charlottetown* or newfoundland* or terre neuve* or labrador* or nfld or yukon* or whitehorse* or northwest territor* or territoires du nord ouest* or nwt or yellowknife* or nunavut* or iqaluit* or chile* or santiago or czech* or prague or denmark* or danish or dane* or faroe* or copenhagen or estonia* or tallinn or finland* or finnish* or helsinki* or france* or french* or paris* or marseille or lyon or lille or nice or toulouse or bordeaux or german* or deutschland* or berlin* or hamburg or munich or cologne or frankfurt or stuttgart or dusseldorf or greece* or hellenic* or greek* or athens or macedonia* or hungary* or hungarian* or budapest or iceland* or reykjavik or ireland* or irish* or dublin* or israel* or jerusalem or tel aviv or italy or italian* or rome or milan or naples or turin or sicily or japan* or tokyo or yokohama or osaka or nagoya or sapporo or kobe or kyoto or korea* or seoul or busan or daegu or daejeon or gwangju or incheon or ulsan or latvia* or riga or lithuania* or vilnius or luxembourg* or netherland* or holland* or dutch* or amsterdam or rotterdam or hague or new zealand* or aotearoa or wellington or auckland or maori or mexic* or norway* or norwegian* or oslo or poland* or polish or warsaw or krakow or wroclaw or lodz or portug* or lisbon or slovak* or bratislava or slovenia* or slovene* or ljubljana or spain* or spanish* or spaniard* or madrid or barcelona or catalonia* or valencia* or seville or zaragoza or malaga or basque or scandinavia* or sweden or swedish or swede* or stockholm or switzerland* or swiss* or zurich or geneva or bern or turkey or turkish or istanbul or constantinople or britain* or british* or united kingdom* or scotland* or scottish or wales* or welsh or england* or belfast or london or manchester or glasgow or birmingham or leeds or bradford or liverpool or alabama* or alaska* or arizona* or arkansas* or california* or colorado* or connecticut* or delaware* or florida* or georgia* or hawaii* or idaho* or illinois* or indiana* or iowa* or kansas* or kentucky* or louisiana* or maine* or maryland* or massachusetts* or michigan* or minnesota* or mississippi* or missouri* or montana* or nebraska* or nevada* or new hampshire* or new jersey* or new mexico* or new york* or north carolina* or north dakota* or ohio* or oklahoma* or oregon* or pennsylvania* or rhode island* or south carolina* or south dakota* or tennessee* or texas* or utah* or vermont* or virginia* or washington* or west virginia* or wisconsin* or wyoming* or montgomery* or juneau* or anchorage* or phoenix* or little rock* or sacramento* or los angeles* or san diego* or san francisco* or denver* or hartford* or dover* or tallahassee* or miami* or orlando* or atlanta* or honolulu* or boise* or springfield* or chicago* or des moines* or topeka* or frankfort* or baton rouge* or new orleans* or augusta* or annapolis* or boston* or lansing* or detroit* or st?paul* or jackson* or jefferson city* or helena* or lincoln* or carson city* or reno* or las vegas* or concord* or trenton* or santa fe* or albany* or raleigh* or bismarck* or columbus* or oklahoma city* or salem* or harrisburg* or providence* or columbia* or peirre* or nashville* or austin* or dallas* or salt lake city* or montpelier* or richmond* or olympia* or seattle* or charleston* or madison* or cheyenne* or district of columbia* or usa or united states or europ* or north america*).tw,kf.	5,302,035
18	3 and (6 or 10) and 16 and 17	152
19	limit 18 to yr=2010-2020	55
20	limit 19 to english	55
21	limit 19 to french	1
22	20 or 21	55

COMMENTARY

PCV13, PCV15 or PCV20: Which vaccine is best for children in terms of immunogenicity?

Philippe De Wals[1,2,3]*

Abstract

Background: The new 15 and 20-valent pneumococcal conjugate vaccines (PCV15 and PCV20) have been marketed on the basis of immunogenicity criteria, one of them being a non-inferior response as compared with the 13-valent vaccine (PCV13). In the past, PCV13 was also authorized on the basis of the same criteria, using the 7-valent vaccine (PCV7) as a reference.

Methods: Our aim was to compare the immunogenicity of these three vaccines in toddlers. Functional opsonophagocytotic activity (OPA) titre ratios measured in the same and different randomized trials were computed to assess the respective immunogenicity of these four products.

Results: Results suggest that both PCV15 and PCV20 are less immunogenic than PCV13 for most common serotypes and that the two new vaccines induce a broadly similar response. The PCV7 vaccine was already slightly more immunogenic than PCV13 meaning that PCV15 and PCV20 compare poorly with PCV7. Results also point towards a reduced immunogenicity of the 2+1 dose schedule compared to the 3+1 dose schedule for PCV13, PCV15 and PCV20.

Conclusion: Post-marketing studies will have to be conducted to assess the effectiveness of PCV15 and PCV20 and their real-life benefit over PCV13.

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Keywords: pneumococcal conjugate vaccine, immunogenicity, randomized trial, opsonophagocytotic activity

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Introduction

The first pneumococcal conjugate vaccine containing seven serotypes (PCV7) was authorized in 2000, according to a 3+1 doses schedule in infants. The authorization was based on a Phase 3 randomized clinical trial (RCT) demonstrating a protective efficacy of 97.4% (95% CI: 82.7%–99.9%) against invasive pneumococcal disease caused by vaccine serotypes in the intent-to-treat analysis (1). For ethical and feasibility reasons, the 13-valent vaccine (PCV13) containing the same carrier protein as PCV7 (CRM_{197}) was authorized in 2010 on the basis of immunogenicity criteria rather than the demonstration of clinical protection (2). In 2005, a first set of immunogenicity criteria was proposed by the World Health Organization (WHO) for the licensure of new pneumococcal conjugate vaccines and used for marketing the new 15-valent (PCV15) and 20-valent (PCV20) conjugate vaccines in 2022–2023 (3). One of these criteria is the demonstration of a non-inferior immune response when compared to a registered vaccine. The non-inferiority requirement applies to serotype-specific proportions of responders, Immunoglobulin G (IgG), and functional antibody levels. For antibody levels, non-inferiority is declared if the lower limit of the two-sided 95% CI of the new/old geometric mean ratio is above 0.5 (3). However, non-inferiority does not mean equivalence, and the sequential use of PCV7, followed by PCV13, as references for the authorization of newer vaccines may have cumulative negative consequences on the level of protection and its duration. In this commentary, functional opsonophagocytotic activity (OPA) titre ratios measured in RCTs pertaining to PCV7, PCV13, PCV15 and PCV20 were compared to assess the respective performance of these four products in terms of immunogenicity, which is associated with clinical effectiveness.

Analysis

The comparison of mean OPA titres one month after the toddler dose in three PCV trials using a 3+1 doses schedule (2, 4, 6 and 12–15 months) is presented in **Table 1**. The first comparison comes from the pivotal United States (US) study on the safety, tolerability, and immunogenicity of PCV13 with PCV7 as a reference, the two vaccines having been administered with routine paediatric vaccinations, according to the US-recommended infant vaccination schedule at that time (4). Post-booster means OPA titres were lower with PCV13 than with PCV7 for six of the seven common serotypes (19F was the exception), with an average PCV13/PCV7 OPA ratio of 0.77. The second comparison comes from a Phase 3, multicentre trial aiming to evaluate the safety, tolerability, and immunogenicity of a four-dose regimen of PCV15 using PCV13 as a comparator (5). With the exception of serotype 14, all PCV15/PCV13 OPA ratios were below one, with an average value of 0.75. The third trial was a Phase 2 study on the safety and immunogenicity of PCV20 using PCV13 as a comparator in healthy infants in the US (6). Overall, OPA titres with PCV20 were lower than those observed with PCV13, with an average PCV20/PCV13 ratio of 0.72 for the common serotypes. Using the results of the two latest trials, it is possible to compare PCV15 with PCV20 for the 13 serotypes included in PCV13. As seen in Table 1, most PCV15/PCV20 ratios were close to one, with the exception of serotype 14 (ratio=1.82). The average PCV15/PCV20 ratio was 1.04, suggesting that the two new vaccines have rather similar immunogenicity. When their immunogenicity was compared to that of PCV7 for the seven common antigens, however, a reduced immunogenicity was observed, with a mean PCV15/PCV7 ratio of 0.63 and a mean PCV20/PCV7 ratio of 0.54.

The 2+1 PCV13 schedule was authorized on the basis of a comparison with the 3+1 PCV13 schedule. A direct comparison between PCV13 and PCV7 for this schedule is not available. As seen in **Table 2**, both PCV15 and PCV20 generated lower OPA titres than PCV13 for a majority of the common serotypes in the two pivotal Phase 3 trials supporting their respective authorization in a 2+1 schedule (7,8). The mean PCV15/PCV13 ratio was 0.75, similar to the mean PCV20/PCV15 ratio of 0.76.

From results presented in Table 1 and Table 2, it is possible to compare the immunogenicity of the 3+1 and 2+1 schedules. For PCV13, the average 3+1/2+1 OPA ratio was 1.39 in the two trials conducted by Merck (5,7), and the mean ratio was 1.35 in the two trials conducted by Pfizer (6,8). For PCV15, the average 3+1/2+1 OPA ratio was 1.35 in the two trials conducted by Merck (5,7). For PCV20, the average 3+1/2+1 OPA ratio was 1.31 in the two trials conducted by Pfizer (6,8). These results point towards a reduced immunogenicity of the 2+1 dose schedule compared to the 3+1 dose schedule following the toddler booster dose.

Table 1: Comparison of mean geometric opsonophagocytotic activity, titres one month after the toddler dose in trials using a 3+1 doses schedule (2, 4, 6 and 12–15 months)

Reference	Yeh *et al.*, 2010			Lupinacci *et al.*, 2023			Senders *et al.*, 2021			Indirect comparisons		
Serotype	OPA PCV13	OPA PCV7	Ratio PCV13/ PCV7	OPA PCV15	OPA PCV13	Ratio PCV15/ PCV13	OPA PCV20	OPA PCV13	Ratio PCV20/ PCV13	Ratio PCV15/ PCV20	Ratio PCV15/ PCV7	Ratio PCV20/ PCV7
	A	B	C=A/B	D	E	F=D/E	G	H	I=G/H	J=F/I	K=FxC	L=IxC
1	N/A	N/A	N/A	138.5	228.6	0.61	50.4	92.9	0.54	1.12	N/A	N/A
3	N/A	N/A	N/A	389.1	455.9	0.85	93.0	109.3	0.85	1.00	N/A	N/A
4	1,180	1,492	0.79	2,558.3	3,492.6	0.73	490.3	662.5	0.74	0.99	0.58	0.59
5	N/A	N/A	N/A	1,062.9	1,538.8	0.69	78.7	112.8	0.70	0.99	N/A	N/A
6A	N/A	N/A	N/A	5,553.5	7,784.6	0.71	1,671.4	2,155.8	0.78	0.92	N/A	N/A
6B	3,100	4,066	0.76	4,641.8	5,897.0	0.79	1,354.9	1,808.1	0.75	1.05	0.60	0.57
7F	N/A	N/A	N/A	10,098.6	12,301.9	0.82	2,590.7	3,280.7	0.79	1.04	N/A	N/A
9V	11,856	18,032	0.66	1,714.5	4,237.1	0.40	1,280.2	2,030.0	0.63	0.64	0.27	0.41
14	2,002	2,366	0.85	4,558.1	3,010.5	1.51	938.8	1,127.9	0.83	1.82	1.28	0.70
18C	993	1,722	0.58	2,471.0	3,319.6	0.74	2,016.2	2,703.3	0.75	1.00	0.43	0.43
19A	N/A	N/A	N/A	3,370.4	5,584.6	0.60	651.3	874.8	0.74	0.81	N/A	N/A
19F	200	167	1.20	2,286.4	2,626.7	0.87	500.5	751.0	0.67	1.31	1.04	0.80
23F	2,723	4,982	0.55	6,098.6	13,677.9	0.45	693.1	1,253.9	0.55	0.81	0.24	0.30
Mean of ratios	N/A	N/A	**0.77**	N/A	N/A	**0.75**	N/A	N/A	**0.72**	**1.04**	**0.63**	**0.54**
Median of ratios	N/A	N/A	**0.76**	N/A	N/A	**0.73**	N/A	N/A	**0.74**	**1.00**	**0.58**	**0.57**

Abbreviations: N/A, not applicable; OPA, opsonophagocytotic activity; PCV7, 7-valent vaccine; PCV13, 13-valent vaccine; PCV15, 15-valent vaccine; PCV20, 20-valent vaccine

Table 2: Comparison of mean geometric opsonopgagocytotic activity, titres one month after the toddler dose in trials using a 2+1 doses schedule (2, 4, and 11–15 months)

Reference	Martinon-Torres *et al.*, 2023			Pfizer, NCT04546425 results, 2023			Ratio PCV15/ PCV20
Serotype	OPA PCV15	OPA PCV13	Ratio PCV15/ PCV13	OPA PCV20	OPA PCV13	Ratio PCV20/ PCV13	
	A	B	C=A/B	D	E	F=D/A	G=C/F
1	136.8	164.6	0.83	54	101	0.53	1.55
3	321.5	303.0	1.06	99	129	0.77	1.38
4	2,231.7	3,206.4	0.70	904	992	0.91	0.76
5	791.6	947.9	0.84	60	82	0.73	1.14
6A	3,274.9	5,387.2	0.61	1,101	1,304	0.84	0.72
6B	2,439.9	3,182.4	0.77	537	864	0.62	1.23
7F	6,300.9	10,071.7	0.63	1,811	2,197	0.82	0.76
9V	1,904.4	2,616.6	0.73	3,254	4,544	0.72	1.02
14	2,638.8	2,682.1	0.98	738	920	0.80	1.23
18C	1,968.6	2,091.8	0.94	1,296	1,870	0.69	1.36
19A	2,995.6	4,254.3	0.70	754	707	1.07	0.66
19F	1,793.9	4,254.3	0.42	183	258	0.71	0.59
23F	4,517.8	7,987.6	0.57	697	975	0.71	0.79
Mean of ratios	N/A	N/A	**0.75**	N/A	N/A	**0.76**	**1.02**
Median of ratios	N/A	N/A	**0.73**	N/A	N/A	**0.73**	**1.02**

Abbreviations: N/A, not applicable; OPA, opsonophagocytotic activity; PCV13, 13-valent vaccine; PCV15, 15-valent vaccine; PCV20, 20-valent vaccine

Discussion

Studies based on a face-to-face comparison of the two new PCV15 and PCV20 in infants are unavailable. Results presented here from indirect comparison with PCV13 as a common reference do suggest that both PCV15 and PCV20 are less immunogenic than PCV13 for most common serotypes and that the two new vaccines induce a broadly similar response. The first PCV7 conjugate product was already slightly more immunogenic than PCV13 for their common antigen, meaning that PCV15 and PCV20 compare poorly with PCV7. Several biological mechanisms have been proposed to explain the negative interference resulting from an increase in the number of bacterial polysaccharides included in conjugate vaccines, including a "carrier-induced-epitopic suppression" that may occur when the response to the polysaccharide is diminished in a competition with the anti-peptide-carrier response, a problem that may be aggravated by prior exposure to the carrier from another vaccination (9,10). A reduced immune response may negatively affect the short-term protection provided by a particular vaccine schedule, the duration of protection, and the herd immunity at population levels, especially for pneumococcal serotypes that are less sensitive to vaccine-induced antibodies such as ST3, ST7F, ST19A and ST19F (11). Following a recent National Advisory Committee on Immunization (NACI) statement published in March 2023, discussions are underway in all Canadian jurisdictions as to which PCV to select for children (12). Besides economic considerations and serotype coverage that will certainly be dominant arguments in the vaccine selection, the strength of the immunologic response must also be looked at, although the exact clinical meaning of observed differences is difficult to predict.

Another interesting observation is the lower immunogenicity of the 2+1 immunization schedule compared with the 3+1 schedule, as shown for PCV13, PCV15 and PCV20. In a case-control study performed during a period of shortage of PCV7 in the US, many children received less than the recommended four doses. There was a minimal difference in the effectiveness of two doses given before eight months of age with a booster dose given at 12–16 months (98%; 95% CI: 75%–100%) and three doses given before eight months of age with a booster dose given at 12–16 months (100%; 95% CI: 94%–100%) (13). For economic considerations and to decrease the total number of vaccines administered to children, a 2+1 PCV schedule is now accepted as a standard of care for healthy children by the WHO (14). In January 2020, a 1+1 immunization PCV13 schedule (3 and 12 months of age) was introduced in the United Kingdom, replacing the 2+1 schedule, on the basis of an immunogenicity trial and the effect on nasopharyngeal carriage (15). The effectiveness of this reduced schedule remains to be seen.

The approach selected here to compare immune responses in different trials have also been used in a recently published paper comparing OPA responses following one PCV15 dose or one PCV20 dose in adults, although a more sophisticated statistical analysis was performed in the comparison (16). The OPA measurement is recognized as a better predictor of the clinical

effectiveness of PCVs than anti-capsular polysaccharide antibody levels determined by the enzyme-linked immunosorbent assay (ELISA), although the latter method has the advantage of being standardized for inter-laboratory comparisons (17,18). Mean geometric OPA titres cannot be compared between different laboratories and between different serotypes in a same laboratory. However, the use of serotype-specific ratios of titres generated by different vaccines measured in a same laboratory, at the same time, overcomes these difficulties.

One limitation of this short commentary is that confidence intervals of ratios are not presented. In Phases 2/3 immunogenicity trials aiming to demonstrate a non-inferior immune response of an investigational vaccine compared to a registered product, several hundred participants are typically recruited. The number of participants in each arm of the trials reported in Table 1 and Table 2 ranged from a minimum of 230 to a maximum of 860 (5,6). The calculation of ratios of means from independent samples generates much larger confidence intervals than those obtained for mean estimates in each of the samples, and this problem is even more important when ratios of ratios are computed (19). Also, multiple comparisons as reported in Table 1 (n=60) and in Table 2 (n=26), mean that more stringent *p*-values would have to be applied to declare a statistically significant result, less than 0.0008 and 0.002, respectively, with the Bonferroni correction (20). The interpretation of results in this analysis has thus to therefore been made on trends rather than on individual estimates.

Conclusion

Results suggest that both PCV15 and PCV20 are less immunogenic than PCV13 and especially PCV7 for most common serotypes, and that the two new vaccines induce a broadly similar response. The increasing number of pneumococcal polysaccharides included in conjugate vaccines is associated with a trend towards reduced immunogenicity. Means to circumvent this problem include an increase in the polysaccharide dose, as made for an investigational 21-valent CRM_{197} PCV targeting serotypes found in adults (21), or the use of another protein-carrier and novel conjugation technique, as made for another investigational 24-valent pneumococcal vaccine (22). Several years will be needed before a possible marketing of extended newer-generation PCVs for children. In the meantime, Phase 4 post-marketing studies will have to be conducted to assess the effectiveness of PCV15 and PCV20 and their real-life benefit over PCV13.

Author's statement

PDW — Conceptualization, data collection, data analysis, data interpretation, writing manuscript

The content and view expressed in this article are those of the author and do not necessarily reflect those of the Government of Canada.

Competing interests

None to report.

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COVID-19 outcome trends by vaccination status in Canada, December 2020–January 2022

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic in Canada has evolved rapidly. Since late 2020, COVID-19 vaccines have been relied on to protect against severe outcomes in the presence of circulating variants of concern (VOC).

Objective: This surveillance report provides a retrospective descriptive analysis of national trends in COVID-19 cases and severe outcomes by vaccination status, contextualizing trends against case demographics and circulating VOCs, from December 2020 to January 2022.

Methods: Case and vaccination coverage surveillance data were obtained from the National COVID-19 Case Dataset and the Canadian COVID-19 Vaccination Coverage Surveillance System for 12 of 13 provinces and territories. Descriptive analyses were produced to describe trends over time among individuals aged 12 years and older by COVID-19 outcome, vaccination status, and demographics. Age-standardized and age-stratified incidence rates and incidence rate ratios were computed for cases, hospitalizations, and deaths.

Results: From mid to late-2021, incidence rates for cases and severe outcomes were consistently lowest among those with a completed primary series and highest among those who were unvaccinated. Unvaccinated individuals were much more likely to be hospitalized or to die compared to those with a completed primary series in all variant periods. Age-specific rates of severe outcomes were consistently highest among those aged 80 years and older across all vaccination statuses.

Conclusion: Vaccination remains one of the most important public health interventions, particularly among older adults, to protect against COVID-19 severe outcomes as the pandemic evolves. Routine monitoring of COVID-19 outcomes by vaccination status can identify changes in COVID-19 epidemiology and inform public health action and policy.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been one of the most significant public health crises in the last century, resulting in increased morbidity, mortality, and social and economic disruption in Canada and worldwide (1,2). Until vaccines were first authorized in Canada on December 9, 2020, broad and stringent public health measures (PHMs) were heavily relied on to slow transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and mitigate its impacts on health and society (1,3).

From December 2020 to January 2022, the COVID-19 pandemic in Canada evolved rapidly. Variants of the SARS-CoV-2 wild-type virus, including Alpha, Beta, Gamma, Delta, and Omicron, emerged, with differential impacts on COVID-19 outcomes (3). In Canada, public health falls under provincial/territorial jurisdiction and PHMs (e.g., travel restrictions, work/school closures, and personal protective measures, such as masking, and physical distancing) (3), testing strategies, and vaccine policies varied across provinces and territories (hereafter referred to as

jurisdictions). Confirmatory COVID-19 testing was made broadly available across jurisdictions (4). Canadian COVID-19 vaccination campaigns began on December 14, 2020, initially prioritizing vulnerable and at-risk populations (3,5). Between March and November 2021, jurisdictions expanded vaccination eligibility from older adults to children older than five years, following changes to the availability of vaccines and recommendations from the National Advisory Committee on Immunization (NACI) (5,6). From September to December 2021, NACI recommended a booster dose of an authorized mRNA COVID-19 vaccine for key populations to address waning immunity and suboptimal primary series vaccine effectiveness (7–9). By January 1, 2022, 88% of people aged 12 years or older had received a primary COVID-19 vaccine series, and 19% had received a primary series with one additional dose (10).

This report provides a retrospective, descriptive analysis of national trends in COVID-19 outcomes by vaccination status among individuals aged 12 years and older, contextualized by variant and case demographic characteristics, from December 2020 to January 2022.

Methods

Data sources

Data were obtained from the National COVID-19 Case Dataset, a case-based surveillance system that collects data on demographics, clinical status and outcomes, risk factors, vaccination, and variant lineages of COVID-19 cases in Canada. Jurisdictions report case data electronically to the Public Health Agency of Canada (PHAC) at varying frequencies. Data are subsequently mapped and stored in a Postgres (PostgreSQL) database maintained by PHAC (Metabase).

Data on vaccination coverage (VC) estimates were obtained from provincial and territorial immunization repositories through the Canadian COVID-19 Vaccination Coverage Surveillance System (CCVCSS). The numbers of people vaccinated were aggregated by jurisdiction, week, age group (i.e., 12–17, 18–39, 40–59, 60–79, and 80+ years) and vaccination status. Yearly population estimates were obtained from Statistics Canada and supplemented by the Northwest Territories and Yukon governments. The unvaccinated population was calculated by subtracting the number of people with at least one dose of a COVID-19 vaccine from the population estimate. For the weeks when population estimates were lower than the population with at least one dose, the latter was used as the population estimate for each jurisdiction.

This analysis covers the period of December 14, 2020, the start of the Canadian COVID-19 vaccination campaign, to January 1, 2022. By January 1, 2022, most jurisdictions had reduced the scope of their testing strategies to prioritize individuals at higher risk of experiencing severe outcomes. For incidence rate analyses, the period of June 19, 2021, to January 1, 2022, was used due to VC data availability. Data were extracted on April 28, 2023, from the National COVID-19 Dataset and on April 23, 2023, from CCVCSS.

Definitions

This analysis includes COVID-19 cases that met the national confirmed case definition (11). Vaccination statuses (defined in **Table 1**) were assigned using information about the number of doses received, time interval between vaccination and episode date, and vaccine product as per Health Canada authorization (4). Vaccination statuses were derived from VC definitions and include time to build immunity (12).

Data analysis

Descriptive statistics were computed to explore demographic and clinical characteristics of COVID-19 cases by vaccination status. To visualize changes in VC in Canada, the proportion of the population with a completed primary series was plotted over time by age group and a 14-day lag was applied to coverage counts to account for time to build immunity (12,15).

To contextualize changes in severity and transmissibility due to circulating variants, six variant periods were defined: wild-type, mixed variant of concern (VOC) emergence, mixed VOC predominance, Delta emergence, Delta predominance, and Omicron emergence in Canada. The start and end of a variant predominance period occurred when the specified variant first and last accounted for 75% of sequenced cases, hospitalizations, ICU admissions, and deaths. When cases, hospitalizations, ICU admissions, or deaths predominance dates were different, the latest start date was used to capture the most specific cut point for all indicators. Emergence periods were defined as the day following the end of a predominance period until the next variant reached predominance. The mixed VOC period includes the Alpha, Beta, and Gamma variants, as no single VOC represented over 75% of sequenced cases.

Incidence rates were calculated using VC data as denominators. Denominator data were not available during this analysis period for cases with a complete primary series and one additional dose; these cases were grouped with those with a complete primary series for incidence rate calculations. Population estimates were used to calculate population fractions by age group for computing weekly age-standardized incidence rates for cases, hospitalizations, and deaths. To compare trends between variant periods, the average weekly incidence rate and incidence rate ratios (IRR) of these averages were computed by vaccination status for each variant period, similar to previously published methodologies using COVID-19 surveillance data (16,17). Case data were cleaned using SQL in Metabase and were analyzed using R Statistical Software version 4.0.4.

Table 1: Summary of vaccination status categories and definitions

Vaccination status	Definition
Unvaccinated	Cases with no recorded vaccine doses at time of the episode date.
Not yet protected	Cases whose episode date occurred less than 21 days after their first dose of the vaccine, as per NACI dose interval recommendations (2).
Partially vaccinated	Only applies to two-dose series vaccines. Cases whose episode date was 21 days or more after receipt of first vaccine dose or less than 14 days after receipt of second vaccine dose of a Health Canada authorized vaccine.
Primary series completed	Cases whose episode date was 14 days or more after receipt of a second dose in two-dose series, 14 days or more after receipt of one dose of a one-dose vaccine, or 0 to <14 days after receipt of a first additional dose (e.g., third or booster) of a Health Canada authorized COVID-19 vaccine.
Primary series completed with one additional dose[a]	Cases whose episode date was 14 days or more following the receipt of one additional dose of a Health Canada authorized vaccine, after completing a primary series. Individuals who received one additional dose prior to September 28, 2021 (e.g., as part of a three-dose primary series or for travel purposes), were categorized as primary series completed.
Unknown status	• Cases with missing or "unknown" value in the vaccinated variable (yes/no). • Cases with missing or "unknown" vaccine product names. • Cases with approved vaccine but the respective vaccination date is missing. • Cases with vaccine products not authorized by Health Canada. • Cases with vaccination dates before December 14, 2020. • Cases with a second dose of primary series administered less than 21 days after the receipt of a first dose. • Cases with vaccination dates for booster doses less than 14 days after the previous vaccine dose. • Cases with the Medicago Covifenz vaccine product. Approval for this product was given in 2022 and later discontinued by Health Canada as of April 17, 2023 (13). • Cases with vaccine product of COVISHIELD received after Health Canada authorization had expired on September 16, 2021 (14).

Abbreviations: COVID-19, coronavirus disease 2019; NACI, National Advisory Committee on Immunization
[a] Based on NACI recommendations for additional doses (8), this vaccination status group was incorporated into analyses as of September 28, 2021

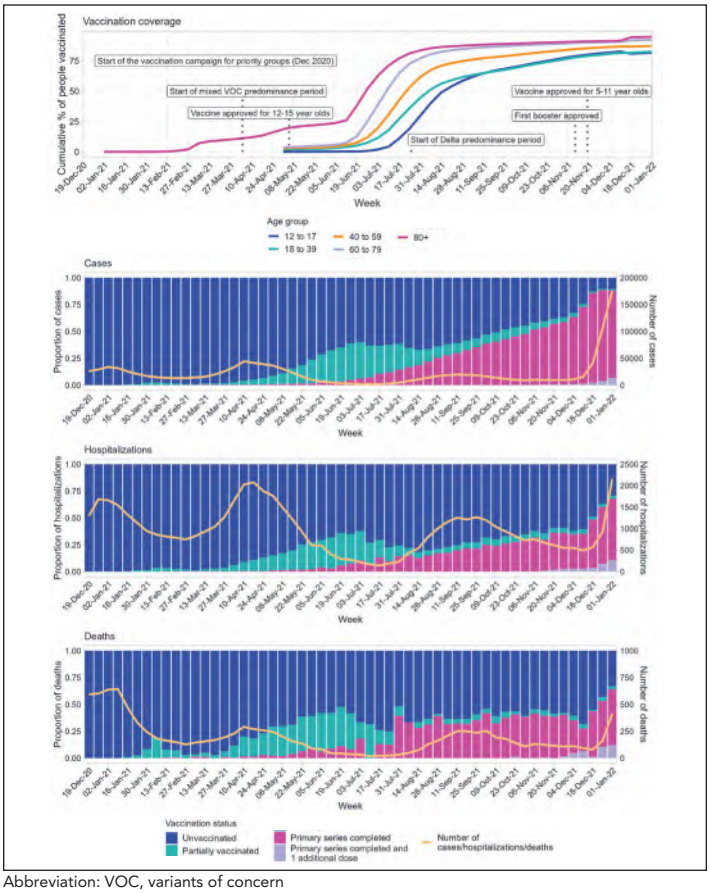
Data quality, missing data, and reporting delays

Vaccination data were available for 12 of 13 jurisdictions (all except Québec), representing 78% of the Canadian population (18). Cases less than 12 years old were excluded since they were not eligible for vaccination until November 19, 2021 (6). Cases with missing information on vaccination status or age were excluded. Cases categorized as "not yet protected," "primary series completed and two additional doses," and "unknown status" were excluded. Vaccination coverage was consistently reported by jurisdictions beginning June 5, 2021; as such, incidence rates were calculated for cases with episode dates of June 19, 2021, onward (accounting for two weeks to build immunity) (19).

Results

Vaccination coverage gradually increased in Canada from December 2020 as vaccination eligibility expanded, with the proportion of individuals aged 12 years and older with a completed primary series reaching over 80% by the end of 2021 (**Figure 1**). From late-2020 to mid-2021, unvaccinated individuals accounted for the highest proportion of cases; however, this proportion decreased as more vaccinated individuals became cases in late 2021, aligning with the gradual increase in VC. A larger increase in the proportion of vaccinated cases was noted in December 2021, following the emergence of the Omicron variant (20).

Figure 1: Vaccination coverage of the Canadian population[a], December 14, 2020, to January 1, 2022



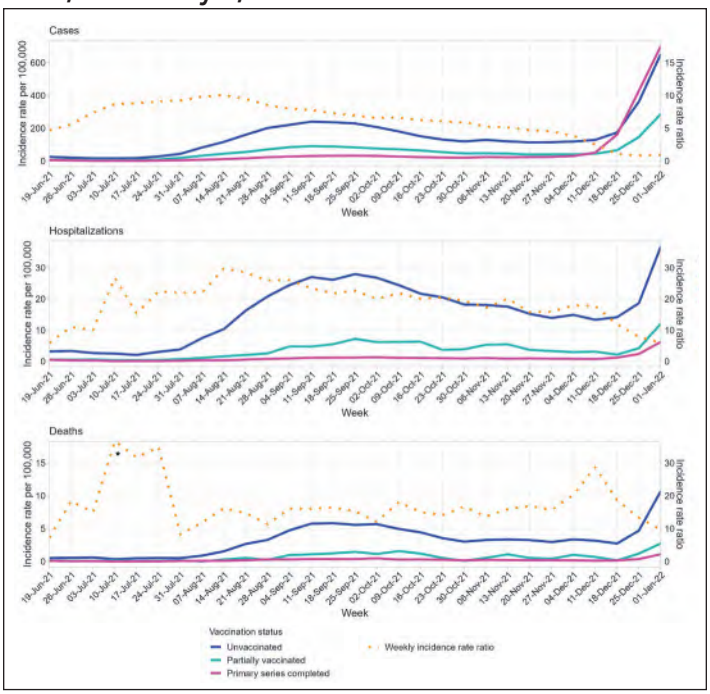
Abbreviation: VOC, variants of concern
[a] With a primary series completed (December 14, 2020, onward) and vaccine rollout timeline and variant predominance periods, and proportion and number of cases, hospitalizations, and deaths by vaccination status

From December 14, 2020, to January 1, 2022, a total of 1,194,694 COVID-19 cases with complete case-level vaccination history (73.6% of all cases) over the age of 12 years were reported to PHAC (**Table 2**). The majority of these cases were unvaccinated, and the lowest proportion of cases was among those with a completed primary series and one additional dose. The proportion of cases was higher among females than males. Unvaccinated cases were generally younger than vaccinated cases. The highest proportions of hospitalized cases and deaths were reported among those who were unvaccinated, followed by those who completed a primary series.

During the Delta emergence period, age-standardized incidence rates for all COVID-19 outcomes remained low for all vaccination statuses (**Figure 2** and **Table 3**). During the Delta predominance period, incidence rates increased for cases in August; severe outcomes peaked in mid-September, remaining elevated until mid-December. The increase was more pronounced among unvaccinated cases. Incidence rates for cases, hospitalizations, and deaths were consistently highest in the unvaccinated and lowest in those with a completed primary series from mid to late-2021. However, in mid-December 2021, overall cases and severe outcomes rapidly increased, and the case incidence rate among those who completed a primary series surpassed that of the unvaccinated.

Incidence rate ratios (IRR) for unvaccinated cases, hospitalizations, and deaths compared to those with a completed primary series remained high for most of the year (Figure 2). During the Delta emergence period, unvaccinated people were 11.4 and 17.5 times as likely to be hospitalized or to die due to COVID-19, respectively, compared to people who completed a primary series (Table 3). During the Delta predominance period, the IRR of the unvaccinated compared to those with a completed primary series increased for hospitalizations and decreased for deaths, compared to the Delta emergence period. During the Omicron emergence period, there was a decrease in IRR for cases, hospitalizations, and deaths, when compared to the Delta predominance period, though the IRR for cases had a more pronounced decrease. Following the emergence of the Omicron variant in mid-November, the weekly IRR decreased as more vaccinated people became infected (**Figure 3**).

Figure 2: Weekly age-standardized incidence rate of COVID-19 cases, hospitalizations, and deaths per 100,000 population by vaccination status, June 19, 2021, to January 1, 2022[a,b]



[a] Weekly incidence rate ratios compare those unvaccinated to those with a completed primary series
[b] Incidence rate for primary series completed was zero during the week of July 10, 2021, as no deaths were reported

Table 2: Descriptive statistics of cases by vaccination status and demographics and outcomes, December 14, 2020, to January 1, 2022

Demographic characteristic or outcome	Unvaccinated (N=748,456)	Partially vaccinated (N=57,995)	Primary series completed (N=370,574)	Primary series completed and one additional dose (N=17,669)	Overall[a] (N=1,194,694)
Female	364,036 (48.8%)	30,460 (52.6%)	198,372 (53.7%)	11,232 (63.7%)	604,100 (50.7%)
Male	382,161 (51.2%)	27,457 (47.4%)	170,969 (46.3%)	6,390 (36.3%)	586,977 (49.3%)
12–17 years	66,535 (8.9%)	2,824 (4.9%)	22,598 (6.1%)	36 (0.2%)	91,993 (7.7%)
18–39 years	366,261 (48.9%)	23,340 (40.2%)	178,406 (48.1%)	5,142 (29.1%)	573,149 (48.0%)
40–59 years	217,499 (29.1%)	16,262 (28.0%)	117,101 (31.6%)	6,139 (34.7%)	357,001 (29.9%)
60–79 years	80,988 (10.8%)	11,895 (20.5%)	43,190 (11.7%)	4,752 (26.9%)	140,825 (11.8%)
80+ years	17,173 (2.3%)	3,674 (6.3%)	9,279 (2.5%)	1,600 (9.1%)	31,726 (2.7%)
Cases hospitalized	42,708 (80.9%)	3,592 (6.8%)	6,116 (11.6%)	394 (0.7%)	52,810 (100.0%)
Cases deceased	8,309 (78.3%)	767 (7.2%)	1,450 (13.7%)	84 (0.8%)	10,610 (100.0%)

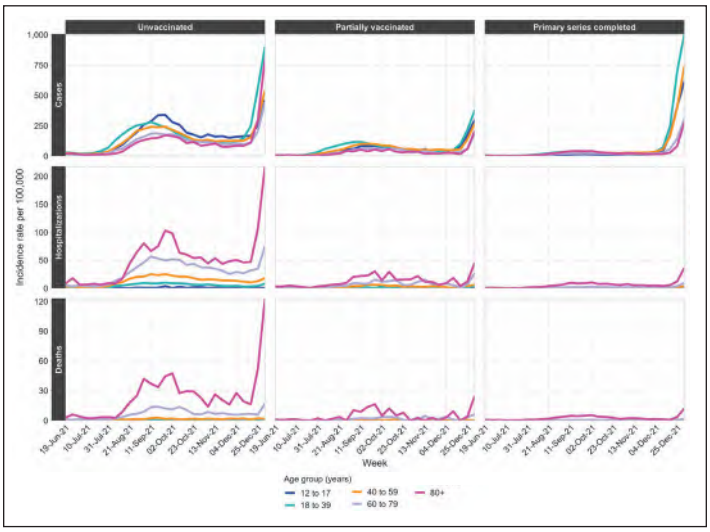
[a] Cases with vaccination status of "Not yet protected" were excluded from this analysis

Table 3: Average of the weekly incidence rates and incidence rate ratios for cases, hospitalizations, and deaths by vaccination status and variant period, June 19, 2021[a] to January 1, 2022

Variant period (date range)	Cases and severe outcomes	Average weekly incident rates (per 100,000 population)			Average weekly incidence rate ratio
		Unvaccinated	Partially vaccinated	Primary series completed	Unvaccinated/primary series completed
Delta emergence (May 31, 2021[a]–July 24, 2021)	Cases	21.4	6.7	3.1	6.8
	Hospitalizations	2.8	0.5	0.2	11.4
	Deaths	0.5	0.08	0.03	17.5
Delta predominance (July 25, 2021–December 5, 2021)	Cases	152.6	57.3	24.7	6.2
	Hospitalizations	18.4	4.0	0.8	21.0
	Deaths	3.6	0.7	0.2	15.4
Omicron emergence (December 6, 2021–January 1, 2022)	Cases	396.5	166.7	430.2	0.9
	Hospitalizations	23.2	6.1	3.3	7.1
	Deaths	6.0	1.4	0.5	11.3

[a] Although the Delta emergence period began on May 31, 2021, vaccination coverage denominator data for incidence rate calculations were not available until June 19, 2021

Figure 3: Weekly age-stratified incidence rate of COVID-19 cases, hospitalizations, and deaths per 100,000 population by 20-year age group and vaccination status, June 19, 2021, to January 1, 2022



Age-specific rates of severe outcomes were consistently highest among those aged 80 years and older, followed by those aged 60 to 79 years, for all vaccination statuses (Figure 3). Case incidence rates were highest among individuals aged 18 to 39 years, followed by those aged 40 to 59 years, from mid-2021 to late August 2021. The incidence rate of cases in these two age groups declined following VC increases until the Omicron emergence period.

Discussion

Summary of key results

From December 14, 2020, to January 1, 2022, a total of 1,194,694 cases of COVID-19 over 12 years of age and with complete case-level vaccination history were reported to PHAC. From mid to late-2021, incidence rates for cases, hospitalizations, and deaths were consistently highest among unvaccinated people and lowest among those with a completed primary series. In December 2021, following the emergence of the Omicron variant, the case incidence rate among those who completed a primary series surpassed that of the unvaccinated; however, rates of severe outcomes remained lower among those who completed a primary series.

Key results and comparison

Vaccination coverage and case incidence

Vaccination coverage steadily increased in Canada as eligibility expanded, varying by age groups (3,12). Like in the United Kingdom, case incidence in 2021 was consistently highest in unvaccinated individuals, with younger age groups having the highest incidence rates (17,21). Starting in spring 2021, there was an increase in vaccine breakthrough cases, consistent with studies showing that, although completion of a primary vaccination series was highly effective in preventing infection against the wild-type virus and Alpha variant, it was slightly less effective against the Beta, Gamma, and Delta variants (22).

Severe outcomes

Incidence rate ratio analyses showed that people who were unvaccinated were much more likely to be hospitalized and to die from COVID-19 than those who completed a primary series during the Delta emergence, Delta predominance, and Omicron emergence periods. Although IRRs for hospitalization and death

decreased during the Omicron emergence period, protective effects against severe outcomes were still observed in those who completed a primary series. These trends are similar to those reported in the United States during the same period (17). Incidence rates for severe outcomes were highest in individuals aged 80 years and older, in agreement with studies showing that advanced age increased the risk of COVID-19 death (16,23). Among individuals aged 80 years and older, severe outcomes were lowest in those who completed their primary series, followed by those who were partially vaccinated, consistent with studies illustrating that a primary vaccine series was highly protective against severe outcomes from the Alpha, Beta, Gamma, Delta, and Omicron variants (16,17,21), and that partial vaccination was also effective at preventing hospitalizations and deaths (15,24).

Waning immunity during Delta period

When the more severe and transmissible Delta variant was predominant (25), there was an increase in the incidence of cases among individuals who completed a primary series, similar to trends observed in other countries (17,26–28). This shift could be due to potential waning of vaccine-induced immunity against symptomatic infection (29,30), a longer time since vaccination (26,27), and reduced effectiveness of available vaccines at preventing infection against the Delta variant (22). Although case IRRs decreased during the Delta predominance period, IRRs for hospitalizations and deaths remained high, suggesting that a primary series was still protective against severe outcomes, consistent with the literature (17,26). Age-stratified incidence rates for hospitalizations and deaths in fall 2021 were substantially higher among cases aged 80 years and older across all vaccination statuses. This age group was prioritized for vaccination and completed their primary series earlier in the year, further raising concerns about waning immunity (26). Routine monitoring of severe outcomes following vaccination helped inform NACI booster dose recommendations, which recommended earlier booster shots for individuals at higher risk of severe illness (8).

Emergence of the Omicron variant

The introduction of the immuno-evasive Omicron variant (20) in mid-November 2021 was followed by a resurgence in cases and severe outcomes, corresponding to when over 85% of the population over the age of 12 years had completed their primary series. Although there was a substantial increase in case incidence among individuals who completed a primary series, the increases in the incidence of hospitalizations and deaths were proportionally lower than that of cases. Moreover, even with the increase in case incidence following this case resurgence, severe outcomes remained lowest among those who were vaccinated. Primary vaccination series still conferred good protection against severe outcomes from the Omicron variant, despite reduced protection against infection (17,22). Studies showed that a booster dose offered additional protection against infection and severe outcomes with the Omicron variant (23,31–33).

Strengths and limitations

Of 13 jurisdictions in Canada, 12 and 13 regularly reported case-level vaccination history data and VC data to PHAC, respectively. Strong participation and collaboration between federal and jurisdictional entities in Canada, alongside widespread community testing, enabled monitoring of highly representative national trends in COVID-19 outcomes following vaccination during this period. As such, the differential impacts of vaccination on COVID-19 outcomes by demographics and SARS-CoV-2 variants were effectively captured as vaccines became more widely available and administered in Canada.

Vaccination rollout timelines and uptake, testing strategies, PHMs, and VOC emergence differed across and within jurisdictions; therefore, national trends should be interpreted with caution. Denominator data were not available before June 2021 as VC data was not consistently reported from jurisdictions, precluding analysis of more stable incidence rate trends during this period. Public health testing in many jurisdictions prioritized high-risk individuals and healthcare workers during this period, which may have introduced bias into earlier descriptive trends. Additionally, distribution of rapid antigen tests to the population could lead to an underestimate of PCR-confirmed cases in late 2021. The overlap of variant periods with circulating VOCs could have introduced bias in the results. The analysis period ends shortly after the emergence of the Omicron variant and does not fully capture waning of vaccine-induced immunity. Analyses could not account for reinfection and natural or hybrid immunity, as these data were not available. This analysis does not include cases aged younger than 12 years, as they were not eligible for vaccination for most of the analysis period. Demographic data were limited to age and gender, as data on race/ethnicity and socioeconomic status were not available. Lastly, cases that were excluded from the analysis due to missing or unknown data (e.g., vaccination status) may differ from those that were included by characteristics for which data were not available (e.g., health conditions).

Conclusion

In Canada, hospitalizations and deaths due to COVID-19 were highest in older age groups; however, vaccination reduced the incidence of severe outcomes by a notable margin across all age groups. Routine monitoring of COVID-19 outcomes by vaccination status is an important pillar in Canadian COVID-19 epidemiology and surveillance to understand the impact of vaccines across Canada. It has informed Canadians about the COVID-19 epidemiologic situation in Canada and provided evidence to support policies, directives, and recommendations on vaccination and public health interventions from NACI, the PHAC Office of the Chief Public Health Officer, and jurisdictions. Though the landscape of COVID-19 is ever-changing, vaccination remains one of the most important public health interventions to protect against COVID-19 severe outcomes.

Author's statement

DD — Conceptualization, methodology, software, formal analysis, writing–original draft, writing–review and editing, visualization
SM — Conceptualization, supervision, methodology, writing–original draft, writing–review and editing
MC — Conceptualization, methodology, software, writing–review and editing
CC — Conceptualization, methodology, writing–review and editing
BHMF — Writing–review and editing
FB — Writing–review and editing
JR — Writing–review and editing
SD — Conceptualization, supervision, writing–review and editing

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National safety monitoring of vaccines from the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), 2018–2019

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Abstract

Background: The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is a comprehensive vaccine safety surveillance system that includes both passive and active surveillance of vaccines administered in Canada. This work presents a summary of adverse events following immunization (AEFI) nationally for 2018 and 2019.

Methods: Data extracted from CAEFISS included all AEFI reports received by the Public Health Agency of Canada by April 30, 2022, for vaccines marketed in Canada and administered between January 1, 2018, and December 31, 2019. Descriptive statistics were conducted on AEFI reports by type of surveillance program (i.e., active vs. passive), AEFIs, demographics, healthcare utilization, outcome, seriousness of adverse events and type of vaccine.

Results: Between 2018 and 2019, 5,875 AEFI reports were received from across Canada. The average annual AEFI reporting rate was 10.9/100,000 doses distributed in Canada for vaccines administered during 2018–2019 and was found to be inversely proportional to age. The majority of reports (91%) were non-serious events, involving vaccination site reactions, rash and allergic events. Overall, there were 511 serious adverse event reports during 2018–2019. Of the serious adverse event reports, the most common primary AEFIs were anaphylaxis followed by seizure. There were no unexpected vaccine safety issues identified or increases in frequency or severity of adverse events.

Conclusion: Canada's continuous monitoring of the safety of marketed vaccines during 2018–2019 did not identify any increase in the frequency or severity of AEFIs, previously unknown AEFIs, or areas that required further investigation or research.

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Keywords: vaccine safety, pharmacovigilance, adverse events following immunization

Introduction

Vaccine safety surveillance is essential to detect any emerging issues or changes in the frequency of adverse events following immunization (AEFI). The Public Health Agency of Canada (PHAC) and Health Canada share the monitoring of the safety of vaccines in Canada.

The Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) is a federal, provincial, and territorial (FPT) public health post-market vaccine safety surveillance system (1). The CAEFISS is managed by PHAC and is unique in that it includes both passive (spontaneous reports from

FPTs) and active surveillance. The primary objectives of CAEFISS 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 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 (1).

In Canada, healthcare providers, manufacturers and the public each have a role to play in vaccine pharmacovigilance (2). Federal, provincial and territorial public health officials monitor vaccine safety through the Vaccine Vigilance Working Group (VVWG) of the Canadian Immunization Committee (CIC). The VVWG includes representatives from all FPT immunization programs across the country as well as Health Canada regulators and the Canadian Immunization Monitoring Program ACTive (IMPACT) surveillance system.

For more information about CAEFISS, IMPACT and VVWG, please refer to the **Technical Annex**, **Supplemental material**, for annual vaccine safety reports. In addition, a more comprehensive description of the roles and responsibilities for post-market pharmacovigilance can be found in the Canadian Immunization Guide and on the CAEFISS webpage (1,2). Details on provincial and territorial vaccination schedules can be found on the PHAC website (3). National reports on vaccine safety surveillance data have been published periodically using CAEFISS data (4–15).

The objectives of this report are to provide 1) a descriptive analysis of AEFI reports submitted to CAEFISS for vaccines administered in Canada in 2018–2019, 2) a descriptive review of healthcare utilization and outcome following an AEFI and 3) an analysis of serious adverse events (SAEs).

Methods

Definitions

An AEFI is defined as any untoward medical occurrence that follows immunization but that does not necessarily have a causal relationship with the administration of the vaccine. The adverse event may be a sign, symptom or defined illness (15).

A serious AEFI in CAEFISS is identified based on International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use as an event that results in death, is life-threatening, and requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or results in a congenital anomaly/birth defect. Any medical event which may not be immediately life-threatening but requires intervention to prevent one of the outcomes listed above may also be considered as serious (16).

Data sources

The CAEFISS combines reports from passive and active surveillance. Active surveillance is conducted by IMPACT, a network of 12 tertiary care paediatric hospitals across Canada that screens hospital admissions for specific AEFIs. Passive surveillance is initiated at the local public health level and relies on reporting of AEFIs by healthcare providers, vaccine recipients or their caregivers.

We searched CAEFISS for all AEFI reports received by April 30, 2022, with a date of vaccine administration between January 1, 2018, and December 31, 2019. The AEFI report forms used in Canada collect information on sex, age, vaccine administered, medical history, concomitant medications and adverse events experienced. In addition, historic AEFI reports with a date of vaccine administration between 2008 and 2017 were extracted from CAEFISS to assess trends over time. It should be noted that for one province/territory, not all AEFI reports were included due to technical issues with uploading the information onto the CAEFISS platform. The reports that were not included from this province/territory were of a small enough volume that this issue did not impact our confidence in the results.

Data analysis

Descriptive analyses were conducted for AEFI reports by year, type of surveillance (active vs. passive), primary reason for reporting, seriousness, healthcare utilization and outcome. Rates of AEFI were calculated using dose distributed data where possible. Sex and age-specific AEFI rates were calculated using population estimates as the denominator. Missing data were excluded from the calculations. All reports were medically reviewed and only reports with an outcome of death underwent causality assessment for this report. All analyses were conducted using SAS EG 7.1 and Microsoft Excel 2016.

Technical annex

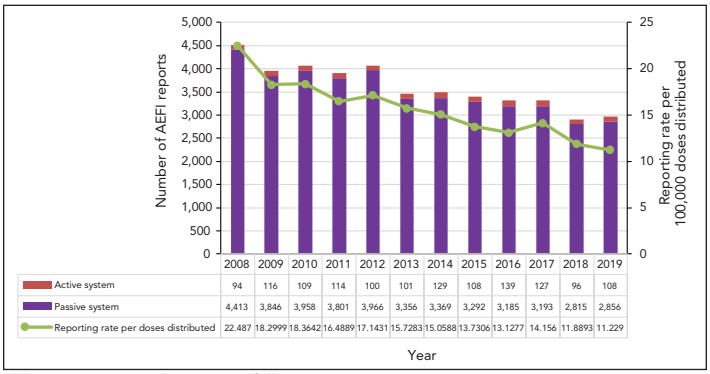
The Technical Annex contains detailed methodological descriptions of the AEFI reporting process as well as the data extraction and analysis of the surveillance data. In addition, the annex includes information on AEFI surveillance definitions (i.e., primary AEFI, active and passive surveillance), how rates are reported, limitations of CAEFISS, information regarding vaccine abbreviations and marketed product/trade names, medical case review AEFI categories/subcategories and information on the severity classification for primary AEFIs in the medical case review.

Results

Our search identified a total of 5,875 AEFI reports between 2018 and 2019 in CAEFISS from 12 provinces and territories: 2,911 AEFI reports from 2018 and 2,964 AEFI reports from 2019. During this period, over 50 million vaccine doses were distributed. This represented an AEFI reporting rate of 11.5 per

100,000 doses distributed in 2018 and 2019. Over the preceding 11 years, the AEFI reporting rate decreased from 22.5 in 2008 to 11.2 per 100,000 doses distributed in 2019 ($p<0.01$) (**Figure 1**). The reduction in reporting occurred from the passive surveillance source, while the annual number of reports from active surveillance remained generally stable over time.

Figure 1: Total number of adverse events following immunization reports and reporting rate by reporting source, 2008–2019 (N=5,875)[a]



Abbreviation: AEFI, adverse event following immunization
[a] Does not include the influenza A(H1N1) 2009 pandemic influenza AEFI reports

Distribution of adverse events following immunization by age group

The median age of all cases reported in 2018–2019 at time of vaccination was 12 years (range: newborn to 100 years). The majority (55%) of AEFI reports were for children and adolescents under 18 years of age. Age-specific reporting rates were higher for younger age groups and lower for older age groups. Rates were highest for children younger than one year of age (123.9 per 100,000 population), followed by children one to younger than two years of age (123.6 per 100,000 population) (**Figure 2**). Among other age groups, the reporting rates were lower than 50 per 100,000 population.

Overall, between 2008 and 2019, decreases in AEFI reporting rates were seen in all age groups. The largest decrease (−62%) was seen in the 1 to <2 years age group, followed by the 2 to <7 years age group (−50%). The rate in the latter age group had slightly increased from 2018 to 2019 (+40%).

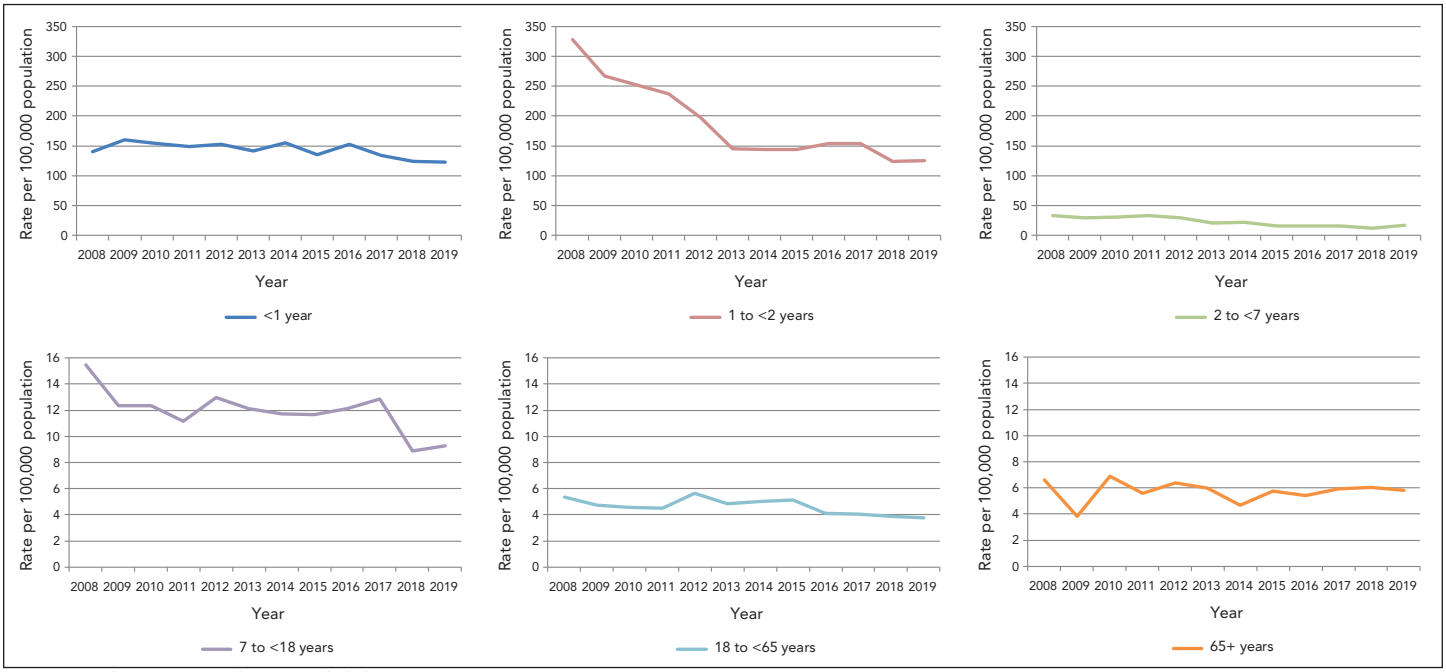
Distribution of adverse events following immunization by sex

Of the 5,875 reports, 60.5% were for females. As shown in **Figure 3**, there appears to be a slight male predominance of adverse events observed for children younger than seven years of age. Most age groups had relatively similar rates for males and females; however, within the age groups 18–64 years and 65 years and older the rate was higher for females.

Primary reason for reporting adverse events following immunization

Table 1 provides a breakdown of reasons for submitting an AEFI report. The percentage of serious reports for each AEFI subcategory and the overall category is shown in the table. Vaccination site reactions were the most common primary AEFI reported (n=2,283, 40%) followed by allergic or allergic-like

Figure 2: Annual rate of adverse events following immunization by age group, 2008–2019 (N=5,814)[a]



[a] 61 reports with missing age and sex are excluded

Table 1: Frequency of reports and percent that is serious for each primary adverse event following immunization subcategory, 2018–2019 (N=5,726)

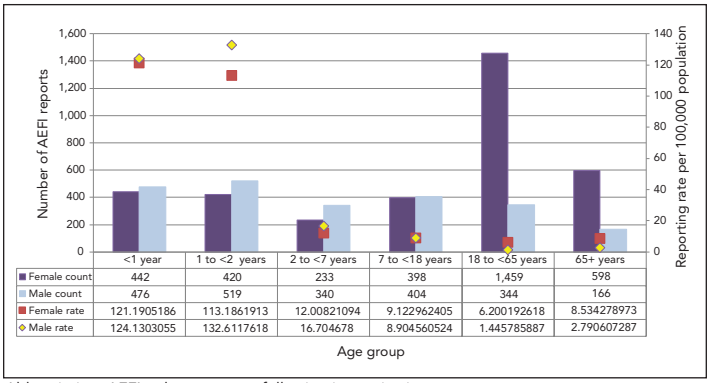
Main reason for reporting	Detailed reason for reporting[a]	Number of reports	Serious reports (%)
Allergic or allergic-like events	Events managed as anaphylaxis	101	100
	Oculo-respiratory syndrome	61	0
	Other allergic events[b]	753	1
	Total	915	12
Infection/ syndrome/ systemic symptoms[c]	Fever only	22	9
	Influenza-like illness	13	0
	Infection	79	27
	Rash with fever and/or other illness	115	4
	Syndromes	39	82
	Systemic	75	12
	Total	343	20
Immunization anxiety	Other anxiety-related[d]	9	0
	Presyncope	12	8
	Syncope	37	3
	Total	58	3
Neurologic events	Aseptic meningitis	5	100
	Ataxia/cerebellitis[e]	3	67
	Bell's palsy	14	14
	Encephalitis/acute disseminated encephalomyelitis/ myelitis	14	100
	Guillain-Barré syndrome	13	92
	Other neurologic event[f]	64	30
	Seizure	223	43
	Total	336	44
Other	Arthralgia	34	6
	Arthritis	20	10
	Gastrointestinal event	452	7
	Hypotonic-hyporesponsive episode	48	31
	Intussusception	16	75
	Other events[g]	427	9
	Paraesthesia/ anaesthesia	61	2
	Parotitis	8	0
	Persistent crying	37	0
	Sudden unexpected/ unexplained death syndrome	2	100
	Thrombocytopenia	30	90
	Vaccination failure	1	100
	Total	1,136	11
Rash alone	Extent unknown	36	0
	Generalized	530	0
	Localized	87	0
	Total	653	0
Vaccination error	Total	1	0
Vaccination site reactions	Abscess	21	19
	Cellulitis	649	4
	Extensive limb swelling[h]	187	2
	Other local reaction[i]	1,291	1
	Limb pain more than 7 days	135	1
	Total	2,283	2

[a] 149 reports with missing primary adverse events following immunization (AEFI) category
[b] Other includes, but is not limited to, hypersensitivity and urticarial
[c] Infection/syndrome/systemic symptoms are primarily events involving many body systems often accompanied by fever. They include 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). They also include symptoms occurring in one or more body parts
[d] Other includes, but is not limited to, dizziness and dyspnoea
[e] Cerebellar ataxia is defined as sudden onset of truncal ataxia and gait disturbances (17). 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 (18)
[f] Other includes, but is not limited to, seizure-like phenomena and migraine
[g] Other includes, but is not limited to, lymphadenopathy and arthralgia
[h] Extensive limb swelling of an entire proximal and/or distal limb segment with segment defined as extending from one joint to the next (19)
[i] Other includes, but is not limited to, vaccination site pain and vaccination site swelling

events (n=915, 16%) and rashes (n=653, 11%). These three categories combined represent 67% of all adverse event reports and 14% of all SAE reports submitted in 2018–2019. **Figure 4** shows that the proportion of serious events was highest for the neurological event category (44%), followed by infection/ syndrome/systemic symptoms (20%). Of note, only one report included vaccination errors, which was not a serious event. All AEFI reports were medically reviewed.

Figure 5 shows the distribution of AEFI by primary reason for reporting by age group. Vaccination site reactions represented the greatest number of AEFIs for all age groups except for children younger than one year of age. For children under the age of one, excluding the "other" event category, the most commonly reported AEFI was rash, followed by allergic event.

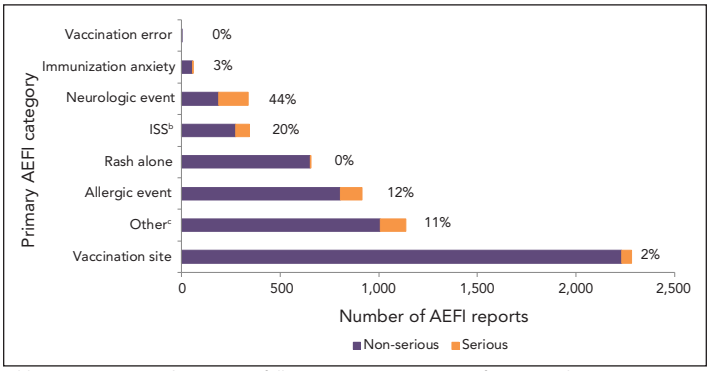
Figure 3: Number and reporting rate of adverse events following immunization reports by age group and sex, 2018–2019 (N=5,814)[a]



	<1 year	1 to <2 years	2 to <7 years	7 to <18 years	18 to <65 years	65+ years
Female count	442	420	233	398	1,459	598
Male count	476	519	340	404	344	166
Female rate	121.1905186	113.1861913	12.00821094	9.122962405	6.200192618	8.534278973
Male rate	124.1303055	132.6117618	16.704678	8.904560524	1.445785887	2.790607287

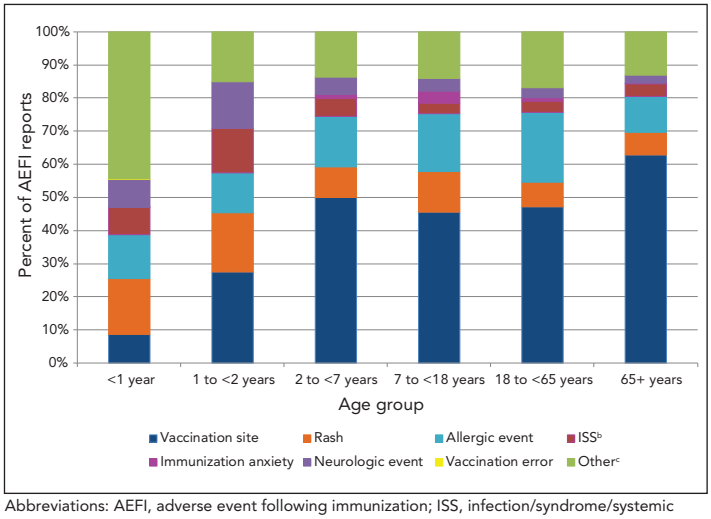
Abbreviation: AEFI, adverse events following immunization
[a] 61 reports with missing age and sex were excluded

Figure 4: Primary adverse events following immunization category by seriousness, 2018–2019 (N=5,726)[a,b,c]



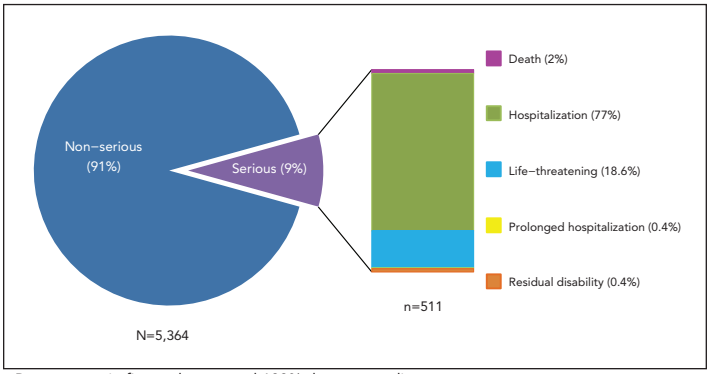
Abbreviations: AEFI, adverse event following immunization; ISS, infection/syndrome/systemic symptoms
[a] 149 reports with missing primary AEFI are excluded
[b] Infection/syndrome/systemic symptoms are primarily events involving many body systems often accompanied by fever. They include sub-categories such as recognized syndromes (e.g., Kawasaki syndrome, fibromyalgia, etc.), fever alone, influenza-like illness, and systemic events (such as fatigue, malaise and lethargy). They also include symptoms occurring in one or more body parts
[c] Other includes arthralgia, arthritis, hypotonic-hyporesponsive episode, intussusception, gastrointestinal disorder, parotitis, persistent crying, rash and thrombocytopenia

Figure 5: Distribution of primary adverse events following immunization reported by age group, 2018–2019 (N=5,726)[a,b,c]



Abbreviations: AEFI, adverse event following immunization; ISS, infection/syndrome/systemic symptoms
[a] 149 reports with missing age and three reports with missing primary AEFI are excluded
[b] ISS are primarily events involving many body systems often accompanied by fever. They include 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). They also include symptoms occurring in one or more body parts
[c] Other includes arthralgia, arthritis, hypotonic-hyporesponsive episode, intussusception, gastrointestinal diseases, parotitis, persistent crying, rash and thrombocytopenia

Figure 6: Classification of serious adverse event reports, 2018–2019[a]



[a] Percentages in figure do not total 100% due to rounding

Serious adverse event reports

There were 511 SAE reports out of over 50 million vaccine doses distributed during the reporting period. This represents a reporting rate of 0.7/100,000 doses distributed and 9% of all AEFI reports for the 2018–2019 period. **Figure 6** shows the distribution of SAE reports by reason for seriousness, with hospitalization (77%) and life-threatening events (19%) being the most common.

The most frequently cited reason for reporting was events managed as anaphylaxis (n=101, 20%), followed by seizure (n=95, 18.6%). The majority (n=364, 71%) of SAE reports had fully recovered at the time of reporting. For those patients who had not fully recovered at the time of reporting, these reports were revised if updated information was received by CAEFISS from the reporting federal, provincial or territorial health authority. Other outcomes for SAE reports included fatal outcome (n=10, 2%) and permanent disability/incapacity (n=2, 0.4%). The majority of SAE reports were for children and adolescents younger than 18 years of age (n=397, 78%), with three quarters (75%) of these reported for children younger than two years of age.

All 10 reports of death underwent careful medical review, and none was considered to be related to the vaccines administered. There were seven deaths in children younger than five years of age; three of the deaths were considered to be a result of pre-existing medical conditions and another three were due to infections unrelated to vaccination. The seventh case had insufficient information, with the cause of death reported as unknown. Three deaths were reported in adults older than 70 years of age and were as a result of pre-existing medical

conditions. There were two additional cases where outcome of persistent/significant disability were present at the time of reporting. No longer term outcome information was obtained on these cases.

Healthcare utilization

Table 2 shows the reported highest level of care sought following an AEFI. The most frequently reported was a non-urgent healthcare visit (43%). Most people with a reported AEFI (91%) did not require hospitalization. In 24% of the reports, no health care was sought, and these may have included self-reporting of milder AEFIs to public health units or healthcare providers.

Table 2: Highest level of health care sought for adverse events following immunization, 2018–2019 (N=5,489)

Highest level of care sought (N=5,489[a])	n	%[b]
Non-urgent visit	2,369	43
None	1,319	24
Emergency visit	1,119	20
Required hospitalization	405	7
Telephone advice from a health professional	195	4
Resulted in prolongation of existing hospitalization	1	0
Vaccination clinic	1	0
Unknown[c]	80	1

[a] The 386 reports with missing information on highest level of care sought were excluded. There is variation across provinces and territories with respect to data collection on levels of health care sought. Data is not collected at all levels by all provinces and territories
[b] Percentages in table do not total 100% due to rounding
[c] Unknown is selected only when the level of care sought is indicated as unknown in the report

Outcome

The outcome at time of reporting for all AEFI reports is shown in **Table 3**. Full recovery was indicated for 74% of the reports and 0.2% of reports reported death as an outcome.

Table 3: Outcome at time of reporting for all adverse events following immunization reports, 2018–2019 (N=5,753)[a]

Outcome	Number of reports	Proportion of reports%[b]
Fully recovered	4,244	74
Not yet recovered	1,222	21
Unknown[c]	275	5
Permanent disability/incapacity	2	0.0
Death	10	0.2

[a] 122 cases were missing information on outcome, therefore were excluded
[b] Percentages in table do not total 100% due to rounding
[c] Unknown is selected only when the outcome is indicated as unknown in the report

Discussion

In 2018–2019, the overall AEFI reporting rate was 11.5 per 100,000 doses distributed and represented a statistically significant decrease in reporting rates over the preceding 11 years. The decline in reporting rates over time may be due to increasing familiarity with expected side effects from vaccine over time (associated with reduced health care seeking for adverse events), under-reporting and changes in reporting requirements by jurisdictions over time. In comparison to the 2018 and 2019 Australian annual reporting rate of 16.9 and 14.9 per 100,000 population, respectively, the Canadian reporting rate is lower, which may in part be due to differences in case definitions used, immunization schedules, AEFI surveillance systems, reporting practices and population demographics (20,21). No vaccine safety issues or increases in frequency or severity of adverse events were identified by VWG during the reporting period.

The majority of AEFI reports involved vaccines given to infants and young children younger than two years of age. This was expected, given that this age group receives many vaccines, both at a single visit and spaced closer together, leading to more opportunities for adverse events to be temporally associated with immunization and reported to a healthcare provider. For all age groups, a significant decrease in AEFI reporting occurred over the preceding 11 years, with the greatest decrease seen in the one to younger than two years old age group. A greater proportion of reports involved females; similar to other findings where female adults were found to consistently report more adverse events (6,13,14,22,23). The reported sex differences in AEFI counts and rates by age may also be explained in part by higher vaccine coverage in female adults (24). This is similar to other studies of sex-specific differences in AEFI reporting rates (20–23,25).

The majority of reported adverse events from approximately 50 million doses of vaccine distributed in Canada were non-serious vaccination site reactions, such as pain and redness, and allergic events, such as hypersensitivity and rash. In 2018–2019, 9% of AEFIs reported were SAEs. Comparing this to other countries that use the same definition for a SAE, this proportion is higher compared to that reported in New Zealand (3.5%) for the same time period (26) and is lower than that reported in Australia in 2018 and 2019 (16% and 12%) (20,21). It is also similar to previous years in Canada (8% and 9%) (6,14). The variations in proportions seen among different countries may be due in part to differences in methodology as stated previously.

The majority of reported SAEs occurred in children and adolescents, which may in part be explained by IMPACT, which actively searches for specific surveillance targets in children admitted to 12 paediatric tertiary care hospitals in Canada, resulting in a higher reporting rate in this age group (27–29). Immunization Monitoring Program ACTive contributed 6% of all AEFI reports and 50% of all serious reports in children under

the age of 18 years, which is similar to the results reported in the 2013–2016 and 2017 reports for this age group. In all age categories, the proportion of SAEs was highest for the neurological event category, for which IMPACT specifically searches. No discernable trends were identified for the number of specific serious adverse events reported over the 2008–2019 time period. Regarding the most frequently cited reason for reporting among SAE reports for all age groups combined, the number and rate of reports of seizures have decreased from 0.45 to 0.19 per 100,000 doses distributed since 2016 and is below the expected frequency (very rare: less than 1/10,000 doses distributed) identified by the World Health Organization (30). The number and rate of reports of events managed as anaphylaxis have remained relatively stable since 2016 with an annual reporting rate of 0.20 per 100,000 doses distributed (two per million doses distributed), which is within the expected range of one to 10 episodes per million doses of vaccines administered (31). For both seizure reports and reports for events managed as anaphylaxis, the reports were distributed across multiple ages and vaccines with no lot-specific clusters. It should be noted that case definitions for events managed as anaphylaxis vary slightly by province and territory. In general, the definition of anaphylaxis is intentionally very sensitive to ensure that all potential cases of anaphylaxis are captured. At the time of reporting, the majority of individuals with SAEs had fully recovered. Of the 10 deaths reported over the two-year period, none were found to be related to the vaccines administered.

Limitations

Passive surveillance for AEFIs is subject to limitations such as under-reporting, lack of certainty regarding the diagnostic validity of a reported event, missing information regarding other potential causes such as pre-existing medical conditions or concomitant medications and differing AEFI reporting practices by jurisdictions within Canada. Passive surveillance detects temporal events; however, from the AEFIs described in this paper, causal inferences cannot be made since causality assessment was only conducted for reports that stated an outcome of death. Despite these limitations, passive surveillance is an essential tool for detecting potential vaccine safety signals, especially new or unusual adverse events too rare to assess during clinical trials. Seasonality was not analyzed as a potential variable in this report.

There are also limitations associated with active surveillance. Immunization Monitoring Program ACTive uses predetermined AEFI targets (such as seizure), which may limit its ability to identify new adverse reactions to immunizations. In addition, while IMPACT covers 90% of Canada's tertiary care pediatric beds and hospital admissions, its focus is on admitted paediatric cases, which means only the most serious cases are detected (29,30).

The number of doses administered in the population is not available at the national level; therefore, the denominator used in rate calculations was either doses distributed or population statistics. The use of doses distributed as the denominator can underestimate rates, as they do not take unused doses or 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, and this may not be true in all cases.

Conclusion

There were no vaccine safety issues identified or increases in frequency or severity of expected adverse events in the CAEFISS data. The majority of reported AEFIs were expected and mild in nature and the overall proportion of serious adverse events were similar to previous years.

Authors' statement

MEJ — Conceptualization, methodology, investigation, software, formal analysis, validation, writing–original draft, writing–review and editing
KJ — Conceptualization, methodology, writing–original draft, writing–review and editing
YX — Conceptualization, writing–review and editing, supervision
CW — Writing–original draft, writing–review and editing, methodology, validation
HA — Investigation, writing–original draft, writing–review and editing
AW — Validation, writing–review and editing
AY — Writing–review and editing
AS — Writing–review and editing, supervision
SO — Writing–review and editing, supervision

Competing interests

None.

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Supplemental material

These documents can be accessed on the Supplemental material file.

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Wastewater surveillance for COVID-19 in shelters: A creative strategy for a complex setting

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Abstract

People experiencing homelessness experience disproportionate rates of morbidity and mortality from coronavirus disease 2019 (COVID-19) compared to the general population and shelters for people experiencing homelessness are a major contributing factor to these negative outcomes. As a result of their unique structure, population and physical space, these settings pose several challenges to the prevention of COVID-19 infection that are not adequately addressed by conventional non-pharmaceutical public health interventions. Wastewater surveillance for COVID-19 is a viable strategy for health protection in shelters due to its ability to meet these unique challenges. Its passive nature does not depend on individual health-seeking behaviours, and it can provide useful epidemiological information early on in an outbreak setting. In this commentary, the authors examine a recent application of wastewater surveillance of COVID-19 in a men's shelter in Toronto. Further applications of wastewater surveillance for other infectious diseases of concern in shelters are proposed, and the need for the development of ethical frameworks governing the use of this technology is discussed.

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Introduction

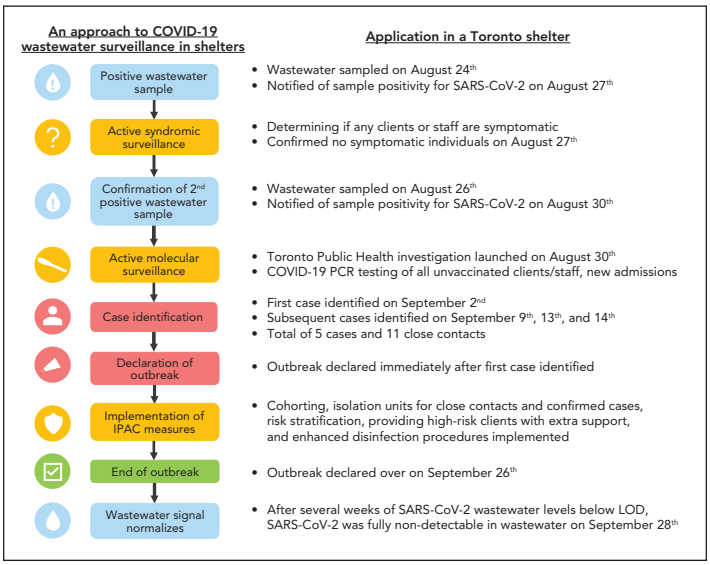
As of June 2023, Canada had reported over four million cases of coronavirus disease 2019 (COVID-19) and 40,000 COVID-19-related deaths (1). Although the impacts of COVID-19 were widespread, there were significant and sustained disparities in outcomes across Canada (2). People experiencing homelessness (PEH), a population estimated at 235,000 in Canada in a given year (3), were disproportionately harmed by COVID-19. People experiencing homelessness in Canada face a greater burden of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, as well as increased rates of hospitalizations, intensive care unit admissions and mortality from COVID-19 (4). People experiencing homelessness are affected by several inequities, collectively increasing their risk of COVID-19-related morbidity and mortality, including high rates of chronic illness and decreased access to healthcare services (5,6). Non-pharmaceutical interventions including physical distancing, screening for symptoms, testing and isolation are difficult to implement in a community burdened by mental health and substance use, and with existing distrust in healthcare institutions (7,8).

The physical context in which PEH live, interact and access resources can exacerbate many of these risks. Shelters for PEH feature high population density and rapid turnover, client marginalization and poverty, poor ventilation, lack of access to optimal hygiene, insufficient infection control and other regulatory protections, and limited staff training and resources, all of which increase the risk of transmission of COVID-19 and other respiratory diseases (9). Although guidelines for the control of COVID-19 in shelters have been developed and recommended by public health organizations during earlier phases of the pandemic (10), shelter service providers described feelings of uncertainty and powerlessness given limited resources in the support of PEH during the pandemic (11). These factors together contribute to the increased prevalence of COVID-19 in shelters relative to other settings (12). Shelters represent a specific setting, serving a unique population, requiring targeted strategies to prevent, identify and respond to COVID-19 and other communicable conditions.

Wastewater surveillance is a disease surveillance strategy in which sewage samples are routinely tested to identify the presence of, and quantify trends in, pathogens of interest. Wastewater surveillance has been used for the detection of poliovirus and human enteroviruses in communities (13,14). In recent years it has emerged as a tool to monitor SARS-CoV-2 and has been employed in high-risk settings such as correctional facilities and long-term care homes (15–17). Akingbola *et al.* described the successful implementation of a wastewater surveillance strategy in a men's shelter in Toronto, Ontario, where this approach facilitated the early detection of an outbreak and prompted measures to prevent further transmission in this setting (18). By testing for and monitoring communicable diseases at the community or facility level—rather than the individual case or patient level—wastewater surveillance combines elements of communicable disease and environmental health strategies. Like air or water quality surveillance systems, wastewater monitoring seeks to identify threats to public health and inform appropriate responses regardless of whether they have already elicited clinically identifiable morbidity. These kinds of strategies are needed to address and reduce the burden of communicable conditions in congregate settings such as shelters.

Monitoring wastewater for infectious diseases addresses some of the observed challenges in mitigating COVID-19 risks in shelters serving PEH. In many instances, positive signals in wastewater samples can be detected early in the disease course prior to symptom onset or in asymptomatic infections. This creates enhanced situational awareness and provides useful lead time for response, including earlier outbreak control. Wastewater monitoring can be part of a rapid response strategy in which a positive signal triggers immediate implementation of heightened infection protection and control measures, such as syndromic and molecular surveillance, enhanced cleaning procedures and support of at-risk clientele (18) (**Figure 1**).

Figure 1: Schematic of an approach to COVID-19 wastewater surveillance in shelters



Abbreviations: COVID-19, coronavirus disease 2019; IPAC, infection prevention and control; LOD, level of detection; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Wastewater surveillance is passive and does not rely on individual health-seeking behaviours (19), which is a benefit in a population that experiences decreased access to healthcare and may be reticent to disclose communicable symptoms in congregate settings. Similarly, as access to polymerase chain reaction testing continues to decrease, with rapid testing becoming more prevalent, wastewater surveillance provides an additional tool for ongoing facility- and community-level monitoring to track trends and inform action and policy (20). Wastewater surveillance for shelters has since been expanded to include other pathogens that PEH are at risk of contracting, including influenza and respiratory syncytial virus, similar to other community settings (21,22). Future applications in shelters can be used to monitor critical pathogens such as hepatitis A virus (23).

In the authors' experience of wastewater surveillance in Toronto, the marginal cost per sample was approximately CA$105, with additional costs incurred for additional testing sites, need for additional laboratory personnel and logistical factors. An economic analysis of wastewater surveillance in Japan favoured the use of wastewater surveillance over rapid antigen tests at single institutions, particularly at lower incidences of COVID-19 (24), although the generalizability of this study to a Canadian context is limited. An economic analysis of wastewater surveillance and rapid antigen testing in a Canadian context would be valuable.

Wastewater testing has prompted legitimate ethical discussions and the need for sound ethical frameworks to govern its use (25). In the case of small-scale, near-source testing, this strategy can be context specific to meet the needs and affirm the rights of the population being served. This proximity necessitates that shelter service providers and people with lived experience of

homelessness be engaged in guiding data collection, usage and responses in wastewater testing. Collaboration with partners in shelters, healthcare, public health, environmental services and ethical bodies can make shelter-based wastewater surveillance both effective and culturally appropriate.

Shelters are an essential resource and safety measure for PEH, but also challenge efforts to protect residents from health threats, including communicable diseases. Shelters, while necessary to provide accommodations and support for PEH, cannot replace accessible, affordable housing for all. Wastewater surveillance may serve to decrease unnecessary morbidity and mortality associated with homelessness alongside measures to end homelessness itself (8,26).

Conclusion

The COVID-19 pandemic has revealed that conventional approaches to communicable disease surveillance, case finding, outbreak response and health protection will continue to yield sustained inequities in exposure and access to preventive interventions. Innovative, community-responsive strategies like wastewater surveillance offer alternative and assertive approaches to redress these inequities. Leadership in this area by the Public Health Agency of Canada's National Wastewater Surveillance Program has fostered national support and collaboration for the use wastewater surveillance. Further support and meaningful intersectoral engagement from public health agencies, congregate settings and networks, water and sanitation systems, and academic centres will be necessary to steward the sustainable, effective implementation of this intervention. As communities transition into COVID-19 recovery, we face the threat that innovations developed in the context of crises might be cast aside as unwarranted or unworthy of sustained investments. At this juncture, we can and should invest in long-term programs including improved surveillance and service delivery to better address health risks faced by the most marginalized members of our community, or we can risk having learnt little from COVID-19.

Authors' statement

CR — Conceptualization, writing–original draft
SB — Conceptualization, writing–original draft
AMO — Conceptualization, writing–original draft
SES — Writing–reviewing & editing
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Competing interests

None.

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EPIDEMIOLOGIC STUDY

Evolution of illness severity in hospital admissions due to COVID-19, Québec, Canada, January to April 2022

Ernest Lo[1,2]*, Élise Fortin[1,3,4], Rodica Gilca[1,4,5], Pierre-Luc Trépanier[1], Hany Geagea[1], Zhou Zhou[1]

Abstract

Background: The coronavirus disease 2019 (COVID-19) severity is influenced by multiple factors, such as age, underlying medical conditions, individual immunity, infecting variant, and clinical practice. The highly transmissible Omicron variants resulted in decreased COVID-19 screening capacity, which limited disease severity surveillance.

Objective: To report on the temporal evolution of disease severity among patients admitted to Québec hospitals due to COVID-19 between January 2, 2022, and April 23, 2022, which corresponded to the peak period of hospitalizations due to Omicron.

Methods: Retrospective population-based cohort study of all hospital admissions due to COVID-19 in Québec, between January 2, 2022, and April 23, 2022. Study period was divided into four-week periods, corresponding roughly to January, February, March and April. Regression using Cox and Poisson generalized estimating equations (GEEs) was used to quantify temporal variations in length of stay and risk of complications (intensive care admission or in-hospital death) through time, using the Omicron peak (January 2022) as reference. Measures were adjusted for age, sex, vaccination status, presence of chronic diseases, and clustering by hospital.

Results: During the study period, 9,178 of all 18,272 (50.2%) patients hospitalized with a COVID-19 diagnosis were admitted due to COVID-19. Of these, 1,026 (11.2%) were admitted to intensive care and 1,523 (16.6%) died. Compared to January, the risk of intensive care admission was 25% and 31% lower in March and April respectively, while in-hospital fatality continuously decreased by 45% lower in April. The average length of stay was temporarily lower in March (9%).

Conclusion: Severity of admissions due to COVID-19 decreased in the first months of 2022, when predominant circulating variants were considered to be of similar severity. Monitoring hospital admissions due to COVID-19 can contribute to disease severity surveillance.

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Keywords: COVID-19, hospitalizations, severity, surveillance

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Introduction

When a new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant or sublineage appears, efforts are made to rapidly characterize its transmissibility and severity compared to previous variants. The Omicron BA.1 variant was first detected in Québec on December 8, 2021, during the Delta wave of the pandemic, and became predominant by December 12, 2021. Subsequently, the Omicron BA.2 variant appeared on January 1, 2022, and was predominant by March 27, 2022. A peak in hospital admissions due to SARS-CoV-2 (the coronavirus that causes COVID-19) was recorded on January 18, 2022 (1). Overall, the Omicron variant had higher transmissibility but lower severity compared to the Delta variant (2–6), while the Omicron BA.1

and BA.2 sublineages had comparable severity (5,7–9). Such information is essential for public health teams to help them anticipate the evolution of the epidemic, including the new variant's impact on healthcare resources. In Canada, where the number of hospital beds per inhabitant is low and the workforce has been affected by the COVID-19 pandemic, information on severity will help to determine whether or not public health measures should be applied or maintained (10,11).

Severity of COVID-19 cases depends on factors beyond the characteristics of the virus. In times of high incidence, more hospitalizations will occur and the threshold for hospital admission/discharge might change, regardless of virulence (12). Natural, vaccine-induced, and hybrid immunity have increased in the population since the beginning of the COVID-19 pandemic but will vary according to time since infection or vaccination (13–15). Clinical care has also evolved with increasing knowledge and experience in treatment, as well as with the arrival of antiviral treatments (16,17). Finally, with the explosion of cases following the emergence of Omicron variants and the availability of rapid tests, accurate estimates of the total number of cases and, consequently, the proportion of severe disease in the general population, were no longer possible. In contrast, all patients admitted to hospital in the province of Québec receive a PCR test for COVID-19, a practice that was consistent throughout the pandemic (18). Propensity of hospitalization given a certain level of severity in Québec also was not impacted by the adoption of rapid tests. Thus, tracking the evolution of the severity of cases among those admitted to hospital due to COVID-19 represents a potentially interesting alternative for disease severity monitoring.

We aimed to describe the severity of hospital admissions due to COVID-19 in Québec between January 2022 and April 2022, which corresponded to the Omicron BA.1 and BA.2 waves. We measured length of stay, risk of intensive care admission, and risk of in-hospital death, and quantified temporal variations of these measures.

Methods

Study design and population

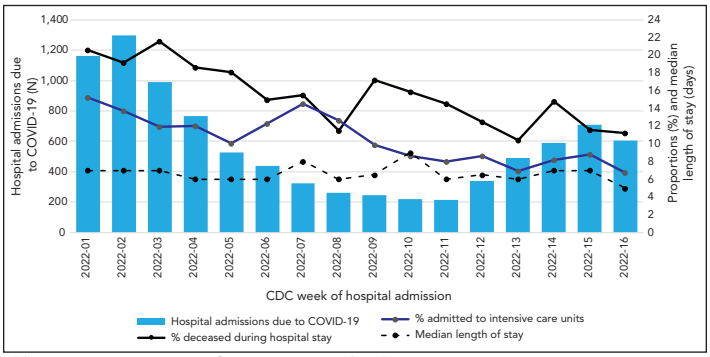
A retrospective population-based cohort was built using linked data to study all Québec hospitalizations for which COVID-19 led to hospital admission between January 2, 2022, and April 23, 2022 (Centers for Disease Control and Prevention, weeks 1–16). Patients were followed from admission until discharge, death, or final date of data extraction (May 25, 2022).

Data sources and variables

The COVID-19 hospitalizations were identified using the provincial hospital admissions database, which is a real-time version of the provincial hospital discharge database (MED-ECHO) routinely available before the pandemic. For this real-time database, hospital medical archivists reported any presence of COVID-19 during a hospital stay, regardless of other health conditions. Since December 30, 2021, archivists also provided admission diagnosis for all patients with a COVID-19 diagnosis during their hospital stay. Admission and hospital stay diagnoses are recorded according to the International Classification of Diseases 10th Revision (ICD-10). Among all patients with a COVID-19 diagnosis during their hospital stay, those with an admission code related to COVID-19 were identified as admissions due to COVID-19. The list of COVID-19-related diagnostic codes used in provincial surveillance is provided in **Appendix, Table A1**. In addition to admission diagnosis, admission and discharge dates, age, sex, intensive care admissions, and death while hospitalized are also recorded in this database. The study period was divided into four four-week periods that corresponded to the peak (January) and the tail (February) of the BA.1 wave, the transition towards BA.2 (March), and the beginning and peak of the BA.2 wave (April) (**Figure 1**). Using a unique identifier, the hospitalization database was linked to:

- The Québec Integrated Chronic Diseases Surveillance System to identify patients with at least one of 31 comorbidities (19)
- The provincial laboratory database to identify patients who had a positive SARS-CoV-2 test more than 90 days before the current admission (interpreted as a reinfection)
- The provincial immunization registry for information on COVID-19 vaccination status (individuals with at least two doses were considered adequately vaccinated)

Figure 1: Time trends in hospital admissions due to COVID-19, median length of stay and frequency of complications, Québec, January 2, 2022, and April 23, 2022



Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus disease 2019

Analyses

The proportion of admissions due to COVID-19 with an intensive care admission, as well as the proportion of patient deaths, were computed for each time period. The 25th, 50th and 75th percentiles of length of stay were additionally computed, once again for each time period. Although length of stay was censored after 28 days, the estimated percentiles were always less than 28 days and so were unaffected. These proportions and duration were also stratified by age group (0–45, 46–55, 56–65,

66–75 and over 75 years old), sex, vaccination status, history of COVID-19 infection, and presence or absence of comorbidities, respectively.

Regression analyses were used to quantify the association between both length of stay and risk of complications (intensive care admission or death) vs. time period, using the Omicron peak period (January 2022) as reference. Cox proportional hazards regression was used to analyze length of stay, using random effects to model the possible clustering effect of hospitals. General estimating equations using a Poisson distribution and exchangeable correlation matrix were used to analyze risk of intensive care admission and death, accounting for the possible clustering effect of hospitals. For the above regressions, unadjusted and fully adjusted associations with time period are presented. Fully adjusted models used age group, sex, vaccination status, and chronic disease as covariates; no adjustment was made for history of COVID-19 infection because patients hospitalized for a reinfection were too rare (less than 3% of patients hospitalized for COVID-19). To isolate changes in disease severity from patient immunity to the disease, additional models were produced only for patients who had no known history of COVID-19 infection and who were not vaccinated. In subgroup analyses, separate models were also produced for each age group. Finally, after learning that three hospitals had largely underestimated intensive care admissions in early 2022, the fully adjusted regression was done, excluding these three hospitals, in a *post hoc* sensitivity analysis. All analyses were done using R 4.0.2; mixed effects Cox regression was done using the coxme package (20), while Poisson GEE was done using the geepack package (21).

Results

Between January 2, 2022, and April 23, 2022, 9,178 (50.2%) of all 18,272 patients who were hospitalized with a COVID-19 diagnosis were admitted due to COVID-19. Of these, 1,026 (11.2%) were admitted to an intensive care unit and 1,523 (16.6%) died while hospitalized (these outcomes were not mutually exclusive). Slightly over half of patients admitted due to COVID-19 were male (52.8%), and a majority of patients were over 65 years old (72.2%), adequately vaccinated (72.1%), experiencing their first known SARS-CoV-2 infection (98.1%) and had at least one comorbidity (83.7%). These statistics are described per four-week period in **Table 1** (see **Table A2** and

Table 1: Description of hospital admissions due to COVID-19, by four-week periods, Québec, January 2, 2022, and April 23, 2022

Variable	January 2 to January 29, 2022		January 30 to February 26, 2022		February 27 to March 26, 2022		March 27 to April 23, 2022	
	n	%	n	%	n	%	n	%
Global	**4,216**	**100.0**	**1,550**	**100.0**	**1,015**	**100.0**	**2,397**	**100.0**
Admitted to ICU	565	13.4	187	12.1	89	8.8	185	7.7
In-hospital death	844	20.0	241	15.5	150	14.8	288	12.0
Age group (years)								
0–45	469	11.1	247	15.9	121	11.9	248	10.3
44–55	254	6.0	89	5.7	39	3.8	68	2.8
56–65	544	12.9	171	11.0	103	10.1	200	8.3
66–75	911	21.6	316	20.4	186	18.3	446	18.6
Over 75 years	2,038	48.3	727	46.9	566	55.8	1,435	59.9
Sex								
Male	2,252	53.4	809	52.2	538	53.0	1,243	51.9
Female	1,964	46.6	741	47.8	477	47.0	1,154	48.1
Vaccination								
Adequate	2,864	67.9	1,027	66.3	785	77.3	1,940	80.9
Inadequate	1,348	32.0	519	33.5	229	22.6	453	18.9
Missing information (or Unknown)	4	0.1	4	0.3	1	0.1	4	0.2
Prior infection according to laboratory tests								
No	4,151	98.5	1,520	98.1	993	97.8	2,338	97.5
Yes	65	1.5	30	1.9	22	2.2	59	2.5
Comorbidities								
None	521	12.4	219	14.1	122	12.0	236	9.8
At least one	3,526	83.6	1,247	80.5	846	83.3	2,066	86.2
Missing	169	4.0	84	5.4	47	4.6	95	4.0

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit

Table A3 for a description of intensive care unit admissions and deaths per four-week period). Patient characteristics were relatively stable over time, except for a higher proportion of older patients and a lower proportion of inadequately vaccinated patients in March and April. In any given group, patients still hospitalized after 28 days represented less than 10% of inpatients.

Globally, patients were more frequently admitted to intensive care units in January and February, while length of stay remained relatively stable over time (Figure 1). Patients also died more frequently during the January peak of hospital admissions, with a gradual decrease throughout the following weeks (Figure 1). These time trends were also observed in regression analyses, after adjusting for age, sex, vaccination status, and presence of at least one comorbidity (**Table 2**). The proportions of patients admitted to intensive care were 25% and 31% lower in March and April (peak of BA.2; Table 1), respectively, as compared with the Omicron peak (January); this trend towards a risk reduction in time was observed in all age groups except for those 0–45 years old (**Table 3**). Results were similar when excluding the three hospitals that underestimated intensive care admissions (adjusted risk ratios of 0.92, 0.76 and 0.70 for February, March and April, respectively). The proportion of in-hospital deaths decreased continuously and was 45% lower in April, compared to January (Table 2); this trend was driven by patients over 75 years old, as 78% of deaths occurred in this age group (Table A3). In non-vaccinated patients admitted for a first COVID-19 episode, adjusted time trends in risk of intensive care admission and in-hospital death were very similar to those observed in the entire cohort (Table 2). Finally, the probability of remaining in hospital after any given number of days was 9% lower in March (transition towards BA.2) compared to January (BA.1 peak), but this was a temporary decrease (Table 2). No statistically significant change in length of stay was observed for hospitalizations of non-vaccinated patients. Cox regressions stratified by age group had extremely high statistical variability, indicating both increasing or decreasing lengths of stay (Table 3).

Table 2: Evolution of length of stay[a], proportions of patients admitted to ICU[b] and in-hospital deaths[b] among hospital admissions due to COVID-19, Québec, January 2, 2022, and April 23, 2022

Population type by time period	Length of stay		Intensive care admissions		In-hospital deaths	
	Unadjusted hazard ratio (95% CI)	Fully adjusted[a] hazard ratio (95% CI)	Unadjusted proportion ratio (95% CI)	Fully adjusted[c] proportion ratio (95% CI)	Unadjusted proportion ratio (95% CI)	Fully adjusted[c] proportion ratio (95% CI)
Global						
January 2 to January 29, 2022	Reference	Reference	Reference	Reference	Reference	Reference
January 30 to February 26, 2022	1.01 (0.95–1.07)	1.01 (0.95–1.07)	0.90 (0.77–1.05)	0.91 (0.78–1.07)	0.78 (0.69–0.89)	0.81 (0.71–0.92)
February 27 to March 26, 2022	0.88 (0.82–0.94)	0.91 (0.84–0.97)	0.66 (0.53–0.82)	0.75 (0.61–0.93)	0.73 (0.63–0.86)	0.70 (0.60–0.82)
March 27 to April 23, 2022	0.99 (0.94–1.04)	1.03 (0.97–1.08)	0.57 (0.48–0.67)	0.69 (0.58–0.80)	0.60 (0.53–0.68)	0.55 (0.48–0.62)
Unvaccinated with no previous COVID-19 infection						
January 2 to January 29, 2022	Reference	Reference	Reference	Reference	Reference	Reference
January 30 to February 26, 2022	1.15 (1.01–1.31)	1.08 (0.95–1.22)	1.04 (0.82–1.32)	1.06 (0.83–1.34)	0.92 (0.69–1.21)	0.88 (0.68–1.15)
February 27 to March 26, 2022	1.03 (0.85–1.25)	0.96 (0.80–1.17)	0.74 (0.48–1.12)	0.73 (0.48–1.12)	0.66 (0.40–1.07)	0.74 (0.47–1.17)
March 27 to April 23, 2022	0.98 (0.85–1.13)	0.88 (0.76–1.01)	0.69 (0.51–0.95)	0.71 (0.52–0.97)	0.65 (0.46–0.92)	0.57 (0.41–0.81)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019
[a] Hazard ratios
[b] Proportion ratios
[c] Adjusted for age group, sex, vaccination status and presence or absence of comorbidities

Table 3: Evolution of length of stay[a], proportions of patients admitted to ICU[b] and in-hospital deaths[b] among hospital admissions due to COVID-19, by age group, Québec, January 2 and April 23, 2022

Age by time period	Length of stay	Intensive care admissions	In-hospital deaths
	Fully adjusted[c] hazard ratio (95% CI)	Fully adjusted[c] proportion ratio (95% CI)	Fully adjusted[c] proportion ratio (95% CI)
0–45 years			
January 2 to January 29, 2022	Reference	Reference	Reference
January 30 to February 26, 2022	1.3 (0.93–1.83)	0.65 (0.40–1.05)	1.17 (0.29–4.77)
February 27 to March 26, 2022	1.12 (0.72–1.73)	0.50 (0.25–1.02)	0.81 (0.09–7.06)
March 27 to April 23, 2022	1.2 (0.89–1.87)	0.77 (0.48–1.24)	2.20 (0.72–6.68)
46–55 years			
January 2 to January 29, 2022	Reference	Reference	Reference
January 30 to February 26, 2022	1.08 (0.85–1.37)	1.19 (0.73–1.93)	1.47 (0.50–4.31)
February 27 to March 26, 2022	1.62 (1.19–2.22)	0.93 (0.45–1.95)	1.44 (0.35–5.96)
March 27 to April 23, 2022	1.07 (0.83–1.38)	0.26 (0.08–0.83)	0
56–65 years			
January 2 to January 29, 2022	Reference	Reference	Reference
January 30 to February 26, 2022	0.97 (0.84–1.12)	0.81 (0.58–1.14)	0.88 (0.52–1.48)
February 27 to March 26, 2022	0.86 (0.71–1.04)	0.78 (0.50–1.22)	0.73 (0.36–1.47)
March 27 to April 23, 2022	1.13 (0.98–1.31)	0.61 (0.42–0.89)	0.63 (0.36–1.11)
66–75 years			
January 2 to January 29, 2022	Reference	Reference	Reference
January 30 to February 26, 2022	1.03 (0.9–1.17)	0.95 (0.73–1.24)	0.88 (0.66–1.18)
February 27 to March 26, 2022	0.86 (0.73–1.01)	0.84 (0.58–1.22)	0.85 (0.59–1.24)
March 27 to April 23, 2022	1.22 (1.08–1.38)	0.74 (0.56–0.97)	0.54 (0.39–0.75)
Over 75 years			
January 2 to January 29, 2022	Reference	Reference	Reference
January 30 to February 26, 2022	0.95 (0.87–1.04)	1.04 (0.77–1.40)	0.77 (0.67–0.90)
February 27 to March 26, 2022	0.85 (0.77–0.94)	0.76 (0.51–1.13)	0.67 (0.56–0.80)
March 27 to April 23, 2022	0.92 (0.86–0.99)	0.73 (0.55–0.96)	0.53 (0.46–0.61)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019
[a] Hazard ratios
[b] Proportion ratios
[c] Adjusted for sex, vaccination status and presence or absence of comorbidities

Discussion

This study showed a decreasing trend in the risks of intensive care admission and in-hospital death among patients admitted to hospital due to COVID-19 in Québec throughout the first 16 weeks of 2022. No clear trend emerged with respect to temporal variations in the length of hospital stay. Conclusions were similar in sensitivity analyses focusing on unvaccinated patients with no previous documented COVID-19 infection.

Many factors may have contributed to decreasing severity. Patient age, sex and comorbidities have been identified as risk factors for severe outcomes in the early stages of the pandemic (12,22–24), but analyses for these factors were adjusted and/or stratified, as well as controlled for vaccination status. Residual confounding may nevertheless remain. Xia *et al.* reported a positive association between in-hospital mortality (in all COVID-19-positive inpatients) and the proportion of available beds occupied by COVID-19-positive patients in Québec, during the first three waves of the pandemic (12). The arrival of the Omicron variant led to the highest number of patients hospitalized with a COVID-19 diagnosis since the beginning of the pandemic (1). This patient load may also have contributed to the trends observed in our study. However, the last four-week period included the peak of the BA.2 wave, and severity kept decreasing even though an increase would have been expected given the higher number of admissions. It is possible that this phenomenon may still have occurred but was not strong enough to reverse the overall trend. Clinical practices also keep evolving, with antiviral treatments becoming available at the beginning of the study period and with increasing accessibility over time (17,25). However, without access to patient load, healthcare worker absenteeism, or antiviral use data, these variables could not be accounted for. Finally, social determinants of health, which represent a well-known driver of inequalities in COVID-19 susceptibility and outcomes, were not accounted for in these analyses (26). However, the effect of social determinants is likely controlled for in the regression analyses, at least in part, through other covariates, such as comorbidities and vaccination status.

Variant composition also evolved during the study period and could have contributed to observed severity trends. Delta-infected patients were still being admitted to hospital in early January, which could explain a higher in-hospital mortality during the first four-week period, but not the decrease in severity observed for the last two periods (27). Estimates of the severity of the BA.1 and BA.2 sublineages have suggested a possible lower severity of BA.2 (5,7,8), though differences measured within each study were not statistically significant. Whole genome sequencing data were unavailable for hospitalized patients; therefore, an association between observed severity trends and variant composition could not be confirmed. Other possible factors are that patients from the more recent periods had shorter follow-up and thus less time to experience outcomes (discharge, intensive care unit admission or death), as not all

inpatients had been discharged by the end of the study period. However, all patients were followed for at least 28 days, which should be sufficient to capture the majority of outcomes. The practice of PCR testing of all the patients admitted to hospital in Québec (18) also rules out changes in testing practices as a factor in severity trends.

In the time preceding the study, PCR testing was done in the general population; nevertheless, not all cases, especially if mild or asymptomatic, were necessarily detected. Therefore, reinfection or the presence of previous COVID-19 infection could have gone undetected in some patients. However, this would only affect severity trends if the proportion of undetected reinfections varied over time. Overall, COVID-19 testing quality and coverage in Québec were high before December 2021 and the advent of Omicron. It is possible, however, that the proportion of hospital patients with unmeasured previous COVID infection acquired during or after December 2021 could have contributed to the observed decreasing severity for the month of April, since a previous infection is defined as one that occurs at least three months before the testing date. Finally, it is possible that the "adequate vaccination" criterion used in the regression analyses does not account for the effect of waning vaccine efficacy, which could result in misclassification of patients that were thought to be protected due to vaccine immunity. However, this effect is likely minimal, given that the majority (84%) of adequately vaccinated patients in this study received their last dose within seven months of hospital admission. This seven-month threshold is based on vaccine effectiveness studies (28). Sensitivity analyses (not shown), where patients receiving their last dose more than seven months after admission to hospital were classified as inadequately vaccinated, showed negligible difference in estimated severity trends.

When Omicron hit the province of Québec in December 2021, screening clinics and laboratories were quickly overloaded. January 2022 marked the end of two years of universal screening. At this time, a new screening strategy was adopted that targeted only certain subpopulations, mostly consisting of the elderly, especially in long-term care facilities, healthcare workers, and patients admitted to hospital (29). Surveillance of disease severity by following up on COVID-19 cases until hospital admission or death would therefore have been biased given the reasons behind the selection of these groups (e.g., increased vulnerability, higher exposure to disease and to vaccines, and the healthy worker effect). Monitoring severity among inpatients represented an alternative because all inpatients were still tested. Our previous work on disease severity comparing Omicron and Delta variants among inpatients suggested a lower severity of Omicron hospitalizations, concordant with other studies comparing these two variants with different methodologies (3–6,30). Wolter *et al.* reached convergent conclusions regarding the relative severity of BA.1 and BA.2 sublineages by measuring and comparing the difference in both risk of hospital admission among cases and risk of severe outcomes among inpatients (8).

The restriction of analyses only to patients admitted due to COVID-19 is an important strength of this study, as about half of all COVID-19-positive inpatients were admitted for other illnesses that can differ in severity from COVID-19. As well, healthcare-associated cases of COVID-19, which are more frequent in periods of high viral circulation, have been related to more severe outcomes (31,32). Unfortunately, admission diagnosis was only available from December 30, 2021, which prevented a comparison of Omicron waves with earlier waves. Before January 2022, all COVID-19-positive patients were analyzed, with the finding that median length of stay, proportion admitted to intensive care, and proportion of in-hospital deaths all varied in a similar manner over time, suggesting that length of stay could be used to inform disease severity (30). This correspondence was not observed in the present analysis, however. Length of stay may be influenced by patient load during peaks and its utility for surveillance of severity is therefore unclear. Also, the results of this study do not provide information on the effect of interventions that aim to prevent hospitalizations. For instance, compared to the general population, hospitalized cases over-represent individuals where vaccines and antivirals have not been successful. Finally, as was previously pointed out by Twohig *et al.*, this surveillance informs the evolution of severity with a delay, as admissions follow case onset by a few days and as a majority of patients have to be discharged before intensive care admissions, in-hospital deaths, and length of stay can be assessed (22).

Conclusion

Throughout the first months of 2022, the risks of in-hospital death or intensive care admission decreased in individuals admitted due to COVID-19. Many factors, including changing immunity, reinfection prevalence, antiviral usage, and patient load may have contributed to this trend, which occurred during a time when virulence of predominant circulating variants were not excessively different. Hospital admissions due to COVID-19 represent an opportunity for monitoring trends in disease severity.

Authors' statement

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Competing interests

The authors have no competing interests to declare.

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Appendix

Table A1: List of COVID-19-related diagnostic codes (ICD-10) used in provincial surveillance, Quebec

Code	Description
A090	Gastroentérite et colite autre et non précisée d'origine infectieuse
A099	Gastroentérite et colite d'origine non précisée
A418	Autres sepsies précisées
A419	Sepsie, sans précision
A498	Autres infections bactériennes, siège non précisé
A499	Infection bactérienne, sans précision
B348	Autres infections virales, siège non précisé
B349	Infection virale, sans précision
E860	Déshydratation
G430	Migraine sans aura [migraine commune]
G431	Migraine avec aura [migraine classique]
G432	État de mal migraineux
G433	Migraine compliquée
G438	Autres migraines
G439	Migraine, sans précision
G441	Céphalée vasculaire, non classée ailleurs
G442	Céphalée dite de tension
G444	Céphalée médicamenteuse, non classée ailleurs
G448	Autres syndromes précisés d'algies céphaliques
G933	Syndrome de fatigue post-virale
I260	Embolie pulmonaire, avec mention de coeur pulmonaire aigu
I269	Embolie pulmonaire, sans mention de coeur pulmonaire aigu
J00	Rhinopharyngite aiguë [rhume banal]
J010	Sinusite maxillaire aiguë
J011	Sinusite frontale aiguë
J012	Sinusite ethmoïdale aiguë
J013	Sinusite sphénoïdale aiguë
J014	Pansinusite aiguë
J018	Autres sinusites aiguës

Table A1: List of COVID-19-related diagnostic codes (ICD-10) used in provincial surveillance, Quebec (*continued*)

Code	Description
J019	Sinusite aiguë, sans précision
J020	Pharyngite à streptocoques
J028	Pharyngite aiguë due à d'autres micro-organismes précisés
J029	Pharyngite aiguë, sans précision
J040	Laryngite aiguë
J041	Trachéite aiguë
J042	Laryngo-trachéite aiguë
J050	Laryngite obstructive aiguë [croup]
J051	Épiglottite aiguë
J060	Laryngo-pharyngite aiguë
J068	Autres infections aiguës des voies respiratoires supérieures, à localisations multiples
J069	Infection des voies respiratoires supérieures, sans précision
J09	Grippe, due à un virus grippal zoonotique ou pandémique identifié
J110	Grippe avec pneumonie, virus non identifié
J111	Grippe avec d'autres manifestations respiratoires, virus non identifié
J118	Grippe avec d'autres manifestations, virus non identifié
J120	Pneumonie adénovirale
J121	Pneumonie due au virus respiratoire syncytial [VRS]
J122	Pneumonie due aux virus paragrippaux
J123	Pneumonie due au métapneumovirus humain
J128	Autre pneumonie virale
J129	Pneumonie virale, sans précision
J13	Pneumonie due à *Streptococcus pneumoniae*
J14	Pneumonie due à *Haemophilus influenzae*
J150	Pneumonie due à *Klebsiella pneumoniae*
J151	Pneumonie due à Pseudomonas
J152	Pneumonie due à des staphylocoques

Table A1: List of COVID-19-related diagnostic codes (ICD-10) used in provincial surveillance, Quebec (*continued*)

Code	Description
J153	Pneumonie due à des streptocoques, groupe B
J154	Pneumonie due à d'autres streptocoques
J155	Pneumonie due à *Escherichia coli*
J156	Pneumonie due à d'autres bactéries à Gram négatif
J157	Pneumonie due à *Mycoplasma pneumoniae*
J158	Autres pneumonies bactériennes
J159	Pneumonie bactérienne, sans précision
J160	Pneumonie due à Chlamydia
J168	Pneumonie due à d'autres micro-organismes infectieux
J170	Pneumonie au cours de maladies bactériennes classées ailleurs
J171	Pneumonie au cours de maladies virales classées ailleurs
J172	Pneumonie au cours de mycoses
J173	Pneumonie au cours de maladies parasitaires
J178	Pneumonie au cours d'autres maladies classées ailleurs
J180	Bronchopneumonie, sans précision
J181	Pneumonie lobaire, sans précision
J182	Pneumonie hypostatique, sans précision
J188	Autre pneumonie, micro-organisme non précisé
J189	Pneumonie, sans précision
J200	Bronchite aiguë due à *Mycoplasma pneumoniae*
J201	Bronchite aiguë due à *Haemophilus influenzae*
J202	Bronchite aiguë due à des streptocoques
J203	Bronchite aiguë due au virus Coxsackie
J204	Bronchite aiguë due aux virus paragrippaux
J205	Bronchite aiguë due au virus respiratoire syncytial [VRS]
J206	Bronchite aiguë due à des rhinovirus
J207	Bronchite aiguë due à des virus ECHO
J2080	Bronchite aiguë due au métapneumovirus humain
J2088	Bronchite aiguë due à d'autres micro-organismes précisés
J209	Bronchite aiguë, sans précision
J210	Bronchiolite aiguë due au virus respiratoire syncytial [VRS]
J211	Bronchiolite aiguë due au métapneumovirus humain
J218	Bronchiolite aiguë due à d'autres micro-organismes précisés
J219	Bronchiolite aiguë, sans précision
J22	Infection aiguë des voies respiratoires inférieures, sans précision
J398	Autres maladies des voies respiratoires supérieures précisées
J399	Maladie des voies respiratoires supérieures, sans précision
J40	Bronchite, non précisée comme aiguë ou chronique
J440	Maladie pulmonaire obstructive chronique avec infection aiguë des voies respiratoires inférieures
J441	Maladie pulmonaire obstructive chronique avec exacerbation aiguë, sans précision
J448	Autres maladies pulmonaires obstructives chroniques précisées

Table A1: List of COVID-19-related diagnostic codes (ICD-10) used in provincial surveillance, Quebec (*continued*)

Code	Description
J449	Maladie pulmonaire obstructive chronique, sans précision
J80	Syndrome de détresse respiratoire de l'adulte
J90	Épanchement pleural, non classé ailleurs
J91	Épanchement pleural au cours de maladies classées ailleurs
J960	Insuffisance respiratoire aiguë
J9600	Insuffisance respiratoire aiguë Type I [hypoxique]
J9601	Insuffisance respiratoire aiguë Type II [hypercapnique]
J9609	Insuffisance respiratoire aiguë, type non précisé
J961	Insuffisance respiratoire chronique
J9610	Insuffisance respiratoire chronique Type I [hypoxique]
J9611	Insuffisance respiratoire chronique Type II [hypercapnique]
J9619	Insuffisance respiratoire chronique, type non précisé
J969	Insuffisance respiratoire, sans précision
J9690	Insuffisance respiratoire, sans précision, type I [hypoxique]
J9691	Insuffisance respiratoire, sans précision, Type II [hypercapnique]
J9699	Insuffisance respiratoire, sans précision, type non précisé
J980	Affections des bronches, non classées ailleurs
J984	Autres affections pulmonaires
J988	Autres troubles respiratoires précisés
J989	Trouble respiratoire, sans précision
J998	Troubles respiratoires au cours d'autres maladies classées ailleurs
K290	Gastrite hémorragique aiguë
K291	Autres gastrites aiguës
K296	Autres gastrites
K297	Gastrite, sans précision
K298	Duodénite
K299	Gastroduodénite, sans précision
K523	Colite indéterminée
K528	Autres gastroentérites et colites non infectieuses précisées
K529	Gastroentérite et colite non infectieuses, sans précision
K591	Diarrhée fonctionnelle
P220	Syndrome de détresse respiratoire du nouveau-né (SDR)
P221	Tachypnée transitoire du nouveau-né
P228	Autres détresses respiratoires du nouveau-né
P229	Détresse respiratoire du nouveau-né, sans précision
P230	Pneumonie congénitale due à un agent viral
P231	Pneumonie congénitale à Chlamydia
P232	Pneumonie congénitale à staphylocoques
P233	Pneumonie congénitale due à des streptocoques, groupe B
P234	Pneumonie congénitale à *Escherichia coli*
P235	Pneumonie congénitale à Pseudomonas
P236	Pneumonie congénitale due à d'autres agents bactériens
P238	Pneumonie congénitale due à d'autres micro-organismes

Table A1: List of COVID-19-related diagnostic codes (ICD-10) used in provincial surveillance, Quebec (*continued*)

Code	Description
P239	Pneumonie congénitale, sans précision
P280	Atélectasie primitive du nouveau-né
P281	Atélectasies du nouveau-né, autres et sans précision
P282	Crises de cyanose du nouveau-né
P283	Apnée primitive du sommeil chez le nouveau-né
P284	Autres apnées du nouveau-né
P285	Insuffisance respiratoire du nouveau-né
P288	Autres affections respiratoires précisées chez le nouveau-né
P289	Affection respiratoire du nouveau-né, sans précision
P2918	Autre dysrythmie cardiaque néonatale
P358	Autres maladies virales congénitales
P359	Maladie virale congénitale, sans précision
P368	Autre sepsie bactérienne du nouveau-né
P369	Sepsie bactérienne du nouveau-né, sans précision
P741	Déshydratation du nouveau-né
R000	Tachycardie, sans précision
R002	Palpitations
R008	Anomalies des battements cardiaques, autres et non précisées
R030	Constatation d'une élévation de la tension artérielle, sans diagnostic d'hypertension
R031	Constatation d'une baisse non spécifique de la tension artérielle
R05	Toux
R060	Dyspnée
R061	Stridor
R062	Sifflement
R063	Respiration périodique
R064	Hyperventilation
R065	Respiration par la bouche
R067	Éternuement
R068	Anomalies de la respiration, autres et non précisées
R070	Douleur de la gorge
R071	Douleur thoracique respiratoire
R072	Douleur précordiale
R073	Autres douleurs thoraciques
R074	Douleur thoracique, sans précision
R093	Expectoration anormale
R098	Autres symptômes et signes précisés relatifs aux appareils circulatoire et respiratoire
R100	Syndrome abdominal aigu
R1010	Douleur localisée au quadrant supérieur droit
R1011	Douleur localisée au quadrant supérieur gauche
R1012	Douleur épigastrique
R1019	Douleur localisée à la partie supérieure de l'abdomen, sans précision

Table A1: List of COVID-19-related diagnostic codes (ICD-10) used in provincial surveillance, Quebec (*continued*)

Code	Description
R1030	Douleur localisée au quadrant inférieur droit
R1031	Douleur localisée au quadrant inférieur gauche
R1032	Douleur périombilicale
R1039	Douleur localisée à la partie inférieure de l'abdomen, sans précision
R104	Douleurs abdominales, autres et non précisées
R110	Vomissement en jet
R111	Nausées seules
R112	Vomissements seuls
R113	Nausées avec vomissements
R130	Dysphagie oro-pharyngée
R132	Dysphagie oesophagienne
R138	Dysphagie, autre et non précisée
R508	Autre fièvre précisée
R509	Fièvre, sans précision
R51	Céphalée
R520	Douleur aiguë
R529	Douleur, sans précision
R53	Malaise et fatigue
R5601	Convulsions fébriles complexes
R5602	Convulsions fébriles simples
R5609	Convulsions fébriles, sans précision
R5680	Trouble convulsif, décrit ainsi
R5688	Convulsions, autres et non précisées
R571	Choc hypovolémique
R572	Choc septique
R578	Autre choc
R579	Choc, sans précision
R590	Adénopathies localisées
R591	Adénopathies généralisées
R599	Adénopathie, sans précision
R650	Syndrome de réponse inflammatoire systémique d'origine infectieuse sans défaillance organique
R651	Syndrome de réponse inflammatoire systémique d'origine infectieuse avec défaillance organique aiguë
R652	Syndrome de réponse inflammatoire systémique d'origine non infectieuse sans défaillance organique
R653	Syndrome de réponse inflammatoire systémique d'origine non infectieuse avec défaillance organique aiguë
R659	Syndrome de réponse inflammatoire systémique, non spécifié
R91	Résultats anormaux d'imagerie diagnostique du poumon
U0490	Syndrome respiratoire aigu sévère [SRAS] suspect
U0491	Syndrome respiratoire aigu sévère [SRAS] probable
U071	COVID-19 virus identifié
U071NV	COVID-19 virus identifié avec ventilation

Table A1: List of COVID-19-related diagnostic codes (ICD-10) used in provincial surveillance, Quebec (*continued*)

Code	Description
U071S	COVID-19 virus identifié avec admission aux soins intensifs
U071SV	COVID-19 virus identifié avec admission aux soins intensifs et ventilation
U072	COVID-19, virus non identifié
U072NV	COVID-19 virus non identifié avec ventilation
U072S	COVID-19 virus non identifié avec admission aux soins intensifs
U072SV	COVID-19 virus non identifié admission aux soins intensifs et ventilation
U073	Syndrome inflammatoire multisystémique associé à la COVID-19
U074	Affection post-COVID-19
Z038	Mise en observation pour suspicion d'autres maladies et affections
Z039	Mise en observation pour suspicion de maladie ou affection, sans précision
Z048	Examen et mise en observation pour d'autres raisons précisées
Z049	Examen et mise en observation pour une raison non précisée
Z519	Soin médical, sans précision

Table A2: Number of intensive care unit admissions and in-hospital deaths by age group, sex, vaccination status, prior infection and presence of comorbidities

Variable	January 2 to 29, 2022					January 30 to February 26, 2022					February 27 to March 26, 2022					March 27 to April 23, 2022				
	Hospital admissions	ICU		In-hospital deaths		Hospital admissions	ICU		In-hospital deaths		Hospital admissions	ICU		In-hospital deaths		Hospital admissions	ICU		In-hospital deaths	
		N	% (95% CI)	N	% (95% CI)		N	% (95% CI)	N	% (95% CI)		N	% (95% CI)	N	% (95% CI)		N	% (95% CI)	N	% (95% CI)
Global	4,216	565	13.4 [12.4–14.4]	844	20 [18.8–21.2]	1,550	187	12.1 [10.4–13.7]	241	15.5 [13.7–17.4]	1,015	89	8.8 [7–10.5]	150	14.8 [12.6–17]	2,397	185	7.7 [6.6–8.8]	288	12 [10.7–13.3]
Age group (years)																				
0–45	469	65	13.9 [10.7–17]	5	1.1 [0.1–2]	247	24	9.7 [6–13.4]	3	1.2 [0–2.6]	121	7	5.8 [1.6–9.9]	1	0.8 [0–2.4]	248	24	9.7 [6–13.4]	5	2 [0.3–3.8]
44–55	254	50	19.7 [14.8–24.6]	11	4.3 [1.8–6.8]	89	18	20.2 [11.9–28.6]	5	5.6 [0.8–10.4]	39	8	20.5 [7.8–33.2]	2	5.1 [0–12.1]	68	4	5.9 [0.3–11.5]	0	0 [0–0]
56–65	544	131	24.1 [20.5–27.7]	60	11 [8.4–13.7]	171	34	19.9 [13.9–25.9]	16	9.4 [5–13.7]	103	18	17.5 [10.1–24.8]	10	9.7 [4–15.4]	200	28	14 [9.2–18.8]	15	7.5 [3.8–11.2]
66–75	911	176	19.3 [16.8–21.9]	161	17.7 [15.2–20.1]	316	57	18 [13.8–22.3]	51	16.1 [12.1–20.2]	186	27	14.5 [9.5–19.6]	28	15.1 [9.9–20.2]	446	60	13.5 [10.3–16.6]	43	9.6 [6.9–12.4]
Over 75 years	2,038	143	7 [5.9–8.1]	607	29.8 [27.8–31.8]	727	54	7.4 [5.5–9.3]	166	22.8 [19.8–25.9]	566	29	5.1 [3.3–6.9]	109	19.3 [16–22.5]	1,435	69	4.8 [3.7–5.9]	225	15.7 [13.8–17.6]
Sex																				
Male	2,252	350	15.5 [14–17]	502	22.3 [20.6–24]	809	108	13.3 [11–15.7]	130	16.1 [13.5–18.6]	538	55	10.2 [7.7–12.8]	88	16.4 [13.2–19.5]	1,243	103	8.3 [6.8–9.8]	166	13.4 [11.5–15.2]
Female	1,964	215	10.9 [9.6–12.3]	342	17.4 [15.7–19.1]	741	79	10.7 [8.4–12.9]	111	15 [12.4–17.5]	477	34	7.1 [4.8–9.4]	62	13 [10–16]	1,154	82	7.1 [5.6–8.6]	122	10.6 [8.8–12.3]
Vaccination																				
Adequate	2,864	312	10.9 [9.8–12]	628	21.9 [20.4–23.4]	1,027	96	9.3 [7.6–11.1]	171	16.7 [14.4–18.9]	785	63	8 [6.1–9.9]	126	16.1 [13.5–18.6]	1940	137	7.1 [5.9–8.2]	246	12.7 [11.2–14.2]
Inadequate	1,348	251	18.6 [16.5–20.7]	216	16 [14.1–18]	519	89	17.1 [13.9–20.4]	69	13.3 [10.4–16.2]	229	26	11.4 [7.2–15.5]	24	10.5 [6.5–14.4]	453	47	10.4 [7.6–13.2]	42	9.3 [6.6–11.9]
Missing	4	2	50 [1–99]	0	0 [0–0]	4	2	50 [1–99]	1	25 [0–67.4]	1	0	0 [0–0]	0	0 [0–0]	4	1	25 [0–67.4]	0	0 [0–0]
Prior infection according to laboratory tests																				
No	4,151	563	13.6 [12.5–14.6]	837	20.2 [18.9–21.4]	1,520	182	12 [10.3–13.6]	239	15.7 [13.9–17.6]	993	89	9 [7.2–10.7]	147	14.8 [12.6–17]	2,338	185	7.9 [6.8–9]	284	12.1 [10.8–13.5]
Yes	65	2	3.1 [0–7.3]	7	10.8 [3.2–18.3]	30	5	16.7 [3.3–30]	2	6.7 [0–15.6]	22	0	0 [0–0]	3	13.6 [0–28]	59	0	0 [0–0]	4	6.8 [0.4–13.2]
Comorbidities																				
None	521	104	20 [16.5–23.4]	38	7.3 [5.1–9.5]	219	29	13.2 [8.8–17.7]	13	5.9 [2.8–9.1]	122	10	8.2 [3.3–13.1]	7	5.7 [1.6–9.9]	236	30	12.7 [8.5–17]	18	7.6 [4.2–11]
At least one	3,526	448	12.7 [11.6–13.8]	798	22.6 [21.3–24]	1,247	152	12.2 [10.4–14]	225	18 [15.9–20.2]	846	77	9.1 [7.2–11]	140	16.5 [14–19.1]	2,066	148	7.2 [6.1–8.3]	267	12.9 [11.5–14.4]
Missing	169	13	7.7 [3.7–11.7]	8	4.7 [1.5–7.9]	84	6	7.1 [1.6–12.7]	3	3.6 [0–7.5]	47	2	4.3 [0–10]	3	6.4 [0–13.4]	95	7	7.4 [2.1–12.6]	3	3.2 [0–6.7]

Abbreviations: CI, confidence interval; ICU, intensive care unit

Table A3: Percentiles for the length of stay in hospital (days), by age group, sex, vaccination status, prior infection and presence of comorbidities

Variable	January 2 to 29, 2022				January 30 to February 26, 2022				February 27 to March 26, 2022				March 27 to April 23, 2022			
	Hospital admissions	Percentile			Hospital admissions	Percentile			Hospital admissions	Percentile			Hospital admissions	Percentile		
		25th	50th	75th		25th	75th	75th		25th	50th	75th		25th	50th	75th
Global	4,216	3	7	15	1,550	3	6	14	1,015	3	7	16.5	2,397	3	7	14
Age group (years)																
0–45	469	1	2	6	247	1	2	4	121	1	2	4	248	1	2	3
44–55	254	3	5	9	89	2	4	8	39	3	6	13.5	68	2	4	10.5
56–65	544	4	7	15	171	3	7	14	103	3.5	7	17	200	2	4.5	12.3
66–75	911	4	8	17	316	3	7	15	186	4	9	17.75	446	3	6	12
Over 75 years	2,038	4	8	17	727	4	9	18	566	4	9	19	1,435	4	9	17
Sex																
Male	2,252	3	7	15	809	2	6	13	538	3	7	15	1,243	3	7	14.5
Female	1,964	3	7	14	741	3	7	15	477	3	7	17	1,154	3	6	13
Vaccination																
Adequate	2,864	4	7	15	1,027	3	7	15.5	785	4	8	18	1,940	3	7	14
Inadequate	1,348	3	6	13	519	2	5	11	229	2	4	11	453	2	5	14
Missing	4	–	–	–	4	–	–	–	1	–	–	–	4	–	–	–
Prior infection according to laboratory tests																
No	4,151	3	7	15	1,520	3	6	14	993	3	7	16	2,338	3	7	14
Yes	65	4	8	11	30	4	8	11	22	2	6	21.75	59	3	7	15
Comorbidities																
None	521	2	5	11	219	1	3	10	122	2	4	10	236	1	3	10
At least one	3,526	4	7	16	1,247	3	7	15.5	846	4	8	19	2,066	3	7	15
Missing	169	1	2	4	84	1	2	3	47	1	2	4.5	95	1	2	3

EPIDEMIOLOGIC STUDY

Epidemiological characteristics of human infections with avian influenza A(H5N6) virus, China and Laos: A multiple case descriptive analysis, February 2014–June 2023

Simran Sandhu[1], Christina Ferrante[1], Aaron MacCosham[1], Nicole Atchessi[1]*, Christina Bancej[1]

Abstract

Background: The first human infection with highly pathogenic avian influenza A(H5N6) virus was reported in 2014. From then until June 30, 2023, 85 human cases with confirmed A(H5N6) infection have been reported worldwide.

Objective: To address the present gap in knowledge of the overall epidemiology of human A(H5N6) infections, the epidemiological characteristics of human infection with A(H5N6) in China from February 2014 to June 2023 are described.

Methods: Considering the severity of human infections with A(H5N6) virus (case fatality rate: 39%), the increased frequency of case reports from 2021 to present day, and lack of comprehensive epidemiologic analysis of all cases, we conducted a multiple-case descriptive analysis and a literature review to create an epidemiologic profile of reported human cases. Case data was obtained via a literature search and using official intelligence sources captured by the Public Health Agency of Canada's International Monitoring and Assessment Tool (IMAT), including Event Information Site posts from the World Health Organization.

Results: Most human A(H5N6) cases have been reported from China (China: 84; Laos: 1), with severe health outcomes, including hospitalization and death, reported among at-risk populations. The majority (84%) of cases reported contact with birds prior to illness onset. Cases were detected throughout the course of the year, with a slight decrease in illness incidence in the warmer months.

Conclusion: As A(H5N6) continues to circulate and cause severe illness, surveillance and prompt information sharing is important for creating and implementing effective public health measures to reduce the likelihood of additional human infections.

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Introduction

Avian influenza A(H5N6) is a highly pathogenic avian influenza (HPAI) reassortant virus (1,2). Waterfowl are a common reservoir for avian influenza viruses, including A(H5N6) (3). Transmission of A(H5N6) among birds can occur via infected secretions and droppings, and asymptomatic transmission of A(H5N6) among some wild bird species has been previously documented (4). Even though A(H5N6) mainly infects birds, humans have also been infected by the HPAI virus through zoonotic transmission of the virus. Humans can be exposed to A(H5N6) by both direct and indirect contact with infected poultry or contaminated environments. For example, a notable risk factor for human exposure to A(H5N6) and other avian influenza viruses are live poultry feeding and trading markets (5). When human cases of A(H5N6) are detected, these cases are reportable to the World

Health Organization (WHO) under the International Health Regulations (2005) (6).

Severe disease and high mortality are often associated with A(H5N6) infections among both animal and human populations (7,8). In Asia in 2014, A(H5N6) was first detected in domestic and wild bird populations. Since 2014, outbreaks have continued to be reported in bird populations worldwide. Detections have been reported to the World Organisation for Animal Health (WOAH) from 21 different countries in Asia, Europe, and Africa by the end of 2021. In 2022, an A(H5N6)-infected bird was reported in a 22nd country, Canada, marking the first such detection in the Americas. This event highlighted the spread of A(H5N6) virus in the animal population and the increased risk of exposure, and thus infection, in humans. As of June 30, 2023, 29 different countries have reported detections of A(H5N6) in animal or bird populations since 2014 (7,8).

Considering the prevalence of A(H5N6) in birds globally, the diversity of currently circulating avian influenza viruses (AIVs), and interactions between host species, conditions could be favourable for reassortment and continued zoonotic transmission (9,10). The earliest detection of a human case of A(H5N6) was in a poultry dealer from Sichuan Province, China in 2014, soon after outbreaks of A(H5N6) were initially reported in birds in Laos, China, and Vietnam (2,11). This fatal case had occupational exposure to poultry prior to illness onset. Human cases of A(H5N6) have continued to be reported every year since, with a marked increase in detections in 2021 (12). The diversity of circulating AIVs, along with continued interaction between host species, can allow for continued reassortment and transmission of A(H5N6) (9,10). Therefore, the reported increasing prevalence of A(H5N6) in bird populations may be related to the increase in human cases.

To the best of our knowledge, no recent study has presented the epidemiologic characteristics of a comprehensive group of human A(H5N6) infections. Previously assessed studies were either written as case reports or only included a select subset of cases, leaving a gap in knowledge of the overall epidemiology of human A(H5N6) infections (13–17). This study aims to address this gap by summarizing the epidemiology of reported laboratory-confirmed human cases of A(H5N6) with illness onset dates from February 2014 to June 30, 2023. Building a better understanding of human infections with A(H5N6) is key for the consideration of modern public health measures that may help mitigate AIV A(H5N6) disease transmission.

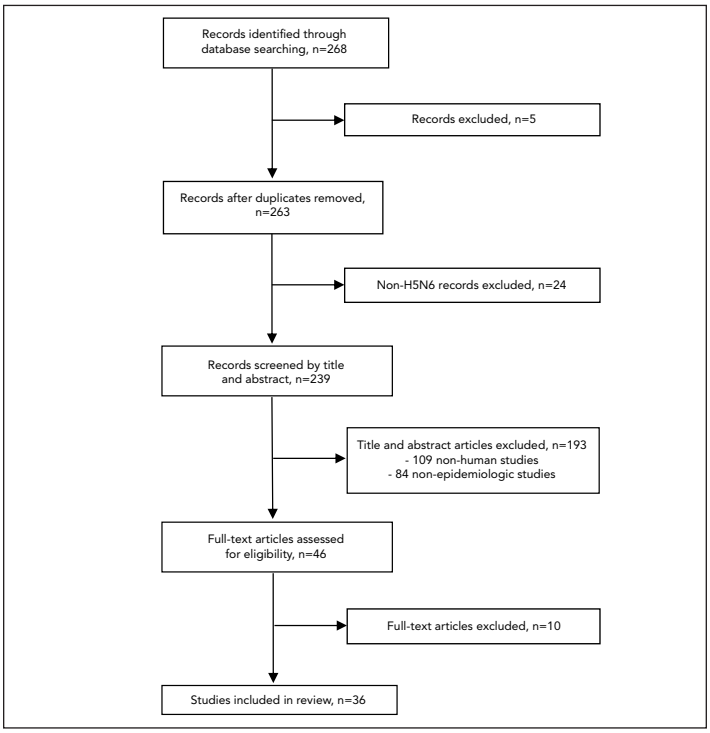
Methods

Search strategy and selection criteria

A literature review on the epidemiology of A(H5N6) infections in the human population was conducted. The literature review involved both published and grey literature, including primary studies, commentaries, and reviews that assessed the human epidemiology of A(H5N6), reviews of animal studies to provide an overview of what is currently known about reported animal infections with A(H5N6), and reports from well-recognized public health authorities like the WHO, WOAH, the European Centre for Disease Prevention and Control (ECDC), the United States Centers for Disease Control and Prevention (CDC), the Government of the Hong Kong Centre for Health Protection (CHP), and submissions from national laboratories to the Global Initiative on Sharing All Influenza Data (GISAID). The Public Health Agency of Canada's International Monitoring and Assessment Tool (IMAT) was also used to identify human cases of A(H5N6) and associated case information. The IMAT is a database that enables systematic documentation of information from event-based and other intelligence sources, as well as event verification and assessment of human emerging respiratory pathogens through official government sources. Trained epidemiologists conduct daily monitoring of these event-based surveillance sources and enter events as completely as possible into the IMAT using a standardized data capture form. These events are maintained and updated in the IMAT if or when more complete information becomes available from these sources.

The literature search, conducted by a Health Canada Librarian, contained research published up until October 6, 2021, in the following databases: Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions®, Embase, Global Health, and CAB Abstracts. Literature in both English and French was sought, with the following search terms specified to the time period of relevance: H5N6, AH5N6, A?H5N6, A H5N6, and influenza virus A H5N6. Following this literature search, pre-specified screening criteria were used to identify studies for inclusion in data extraction and synthesis (**Figure 1**). Screening exclusion criteria included: non-translated materials in a language other than English or French, duplications missed in the initial literature search, non-H5N6 records, non-human and/or non-epidemiology primary studies, publications with unretrievable full texts, and studies outside our predefined themes of interest (epidemiology, microbiology/virology/genomics, diagnostics/testing, vaccines/therapeutics, public health measures/response, and risk assessment). Independent reviewers screened citations in duplicate and reached a consensus on which materials to include after discussion of any conflicts. In total, 36 published studies were eligible for inclusion. During the study period, reports for new human cases of A(H5N6) were also reviewed and data was extracted from both grey literature (via the IMAT) and published literature. For cases of A(H5N6) identified after October 6, 2021, the IMAT's intelligence sources were used to assess and validate information about human cases of A(H5N6) that had a symptom onset date (or report date where symptom onset date was not available) after October 6, 2021.

Figure 1: Flow diagram for study inclusion and exclusion in systematic literature review of the epidemiology of A(H5N6) in the human population



Case definition

Human cases of A(H5N6) were considered to be those reported by the WHO through its Event Information Site (EIS) posts or those reported by Government of Hong Kong's CHP via an official publication. As the literature search was conducted, several journal articles that also referenced human A(H5N6) cases were cross-checked with the data available from official sources for validity and then included in the case line list. These referenced human A(H5N6) cases were either reported as or assumed to be laboratory-confirmed.

No standard case definition for human cases of A(H5N6) currently exists. The current WHO case definition for human cases of non-seasonal influenza are individuals with laboratory confirmation of a recent infection with non-seasonal influenza virus in a person, where the infection has been confirmed by positive results from the polymerase chain reaction (PCR), virus isolation, or paired acute and convalescent serological tests (18). This definition can be adapted to various non-seasonal influenza viruses, including A(H5N6). At this time, it is unclear if Government of Hong Kong's CHP case definition for human cases of A(H5N6) differs from the WHO's case definition.

Data elements and extraction

A case identification number (case ID) was assigned to each case and data was extracted for various administrative, demographic, exposure, course of illness, and outcome data elements such as report date, age, sex, occupation, comorbidities, reporting geographic regions, animal contact history, symptoms, symptom onset date, hospitalization status, hospitalization date, discharge date, current disposition, outcome, and outcome date. Information corresponding to the data elements for each case was input manually into a line list using Microsoft Excel. Whenever conflicting information pertaining to various extracted data elements was presented by different sources of information, the validity of the source was relied upon to determine which data to extract. For example, a publication by the WHO took precedence over journal articles because the data contained in the WHO EIS posts contain information from official and confirmed government sources.

Analysis

Descriptive analyses included all laboratory-confirmed human cases of A(H5N6) reported by symptom onset date from 2014 to June 30, 2023 (n=85). The descriptive analyses consisted of the calculation of median age and age range for cases, gender proportion, exposure proportion by age group, types of exposure sources, geographic distribution of cases, disease severity, and case outcomes. For all cases with available data, the main descriptive analysis consisted of seven variables: 1) median age; 2) age range; 3) proportion of males; 4) proportion hospitalized; 5) median hospitalization delay (days); 6) hospitalization delay (range); and 7) case fatality rate (CFR). The descriptive analyses were also stratified by sex: 1) male; 2) female; and by age group: 1) children (younger than 18 years); 2) adults (18 years or older). Case exposure source was also analyzed for cases with available exposure data.

Case data was analyzed by time period to have a better understanding of the characteristics and reported case incidence from 2021 to June 30, 2023, since there was a large increase in reported human A(H5N6) cases during 2021. For this analysis, the number of reported cases and geographic regions in which cases were reported were described by year, based on symptom onset or report date. Median age and age range for the cases, sex of cases, and case outcomes were described using Microsoft Excel.

Case data was also analyzed by season to understand if there is seasonality associated with reported human cases of A(H5N6), as has been suggested in the literature. For this analysis, months of the year were grouped into four seasons: 1) Spring: March, April, May; 2) Summer: June, July, August; 3) Fall: September, October, November; and 4) Winter: December, January, February. Reported human cases were then categorized according to symptom onset date or report date where symptom onset date was not available (n=1).

To assess disease severity, cases were analyzed by outcome, for which three variables were used: 1) survived; 2) deceased; and 3) unknown. For each category, the median case age and the age range, the proportion of cases for each category that were male, the proportion of cases hospitalized per outcome, the median and range of hospitalization delay (in days) per outcome, and

the proportion of cases that were critically ill at the last known disposition for each outcome were calculated using Microsoft Excel. Where hospitalization status and last known disposition of cases was unknown, these cases were removed from the analysis where this data was required.

Case data was also described by geographic location of the reported case. Geographic locations were extracted from case reports and pertinent articles from the literature search. Based on reported province, cases were assigned to their respective province. Cases were then stratified by symptom onset date or report date where symptom onset date was not available and summed. This analysis was conducted using Microsoft Excel. The figure depicting geographic distribution was created using RStudio.

Data manipulation and analyses were conducted using RStudio and Microsoft Excel 2016 software. No cases were dropped from the analytic dataset. Where case details required for a specific analysis were missing, these cases were dropped from the particular analysis. Symptom onset date was unavailable for one case, so where symptom onset date was required for the analysis, report date was used for this case instead.

Results

Demographic characteristics

A total of 85 human cases of A(H5N6) were reported from two countries worldwide from February 2014 to the end of June 2023 (**Table 1**). Thirteen of these cases were identified retrospectively from non-surveillance sources, such as research articles. The median age of these cases was 50 years, with an age range of 1–81 years. Thirteen (13/85; 15%) reported cases were children younger than 18 years of age. Approximately half (46/85; 54%) of the cases were male. Out of the cases with known exposure data (71/71; 100%), all reported contact with birds prior to illness onset. Contact methods included visiting live bird markets (LBMs), contact with or employment as poultry workers, and exposure to slain and cooked poultry and/or domestic or backyard poultry. Thirty-one cases reported occupational background, and the majority of these cases (22/31; 71%) were either farmers, dealers with LBM contact, or slaughterhouse workers, all of which are professions with obvious potential for poultry exposure.

Table 1: Distribution of human cases of A(H5N6) by country, February 1, 2014 to June 30, 2023

Country	Symptom onset date of first case	Symptom onset date of latest case	Number of reported cases	Number of reported deaths
China	2014-02-16	2023-05-19	84	33
Laos	2021-02-28	2021-02-28	1	0

Timeline and seasonality

On May 5, 2014, China reported one fatal A(H5N6) case from Sichuan Province, marking the first official report of a human A(H5N6) infection. However, an even earlier case was identified by researchers retrospectively, and case details published in a journal article (17). This case was a child who developed symptoms on February 16, 2014 (17). The case was identified in Hunan Province, a region that has reported nearly one fifth of all human cases to date (15/85; 18%) and the second-highest number of human cases total.

In 2021, a spike in case incidence was observed, with 37 cases (37/78; 47%) reporting symptom onset in this same year (**Figure 2**). The cases reported in 2021 from China were detected from six different regions in comparison to a median of three different regions annually in previous years (range: 1–5) (**Figure 3**). Furthermore, 2021 was the first year a human A(H5N6) case was detected outside of China. The cases with illness onset in 2021 had a similar profile to cases reported earlier: their median age was 54 years (range: 3–79) and 59% of the cases (22/37) were males. Outcome data were available for 15 of the cases from 2021 and indicated an annual CFR of 80% (12/15). Compared to 2021, fewer human cases with illness onset were reported in 2022 (18 cases), with a median age of 59 years (range: 3–68) and a similar sex distribution (13/18; 72% males). Outcome data were available for two cases from 2022, of which both cases (2/2; 100%) were fatalities. Human cases of A(H5N6) continue to be reported into 2023, and as of June 30, 2023, one case reported illness onset this year. Study results indicate that cases are detected throughout the course of the year, with a slight decrease in illness incidence into the spring and summer (**Figure 4**).

Figure 2: Epidemiologic curve of reported human cases of A(H5N6) by year of symptom onset, February 1, 2014 to June 30, 2023 (n=85)

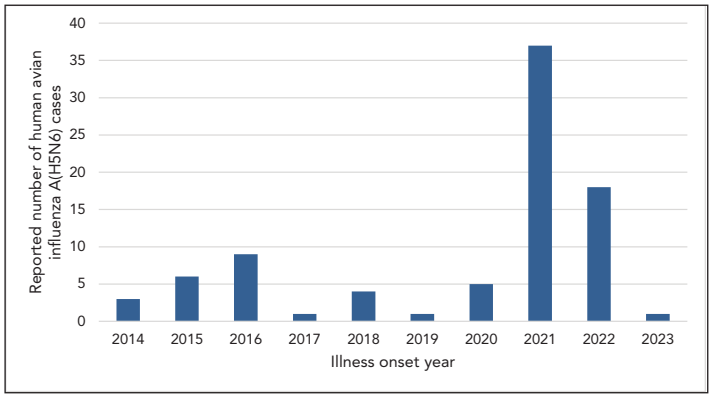


Figure 3: Geographic spread of human cases of avian influenza A(H5N6) in China by year of illness onset or report date, February 1, 2014 to June 30, 2023 (n=84)

	Provincial level division	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
North	Beijing	-	-	-	-	-	1	-	-	-	-
South	Hunan	1	-	3	-	-	-	1	9	1	-
	Guangdong	1	3	3	-	1	-	-	5	1	-
	Guangxi	-	-	1	-	2	-	-	11	5	-
	Sichuan	1	-	-	-	-	-	-	8	3	1
	Chongqing	-	-	-	-	-	-	1	2	-	-
	Jiangsu	-	-	-	-	1	-	1	-	3	-
	Jiangxi	-	1	-	-	-	-	-	-	2	-
	Anhui	-	-	1	-	-	-	1	-	-	-
	Yunnan	-	2	-	-	-	-	-	-	-	-
	Zhejiang	-	-	-	-	-	-	-	1	1	-
	Fujian	-	-	-	1	-	-	-	-	1	-
	Guizhou	-	-	-	-	-	-	1	-	-	-
	Henan	-	-	-	-	-	-	-	-	1	-
	Hubei	-	-	1	-	-	-	-	-	-	-

No. of cases: 1, 2, 3+

Figure 4: Epidemiologic curve of human avian influenza A(H5N6) infections, by season of illness onset date, February 1, 2014 to June 30, 2023 (n=85)

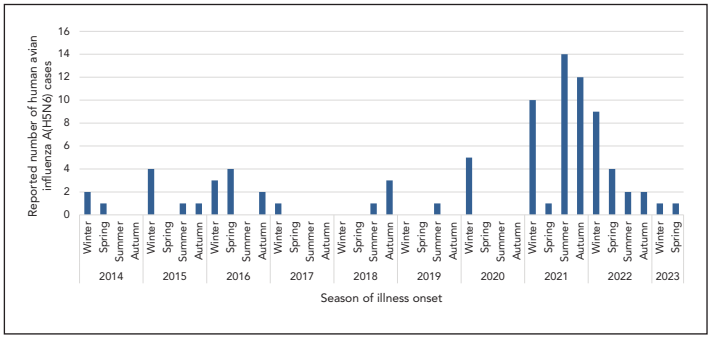
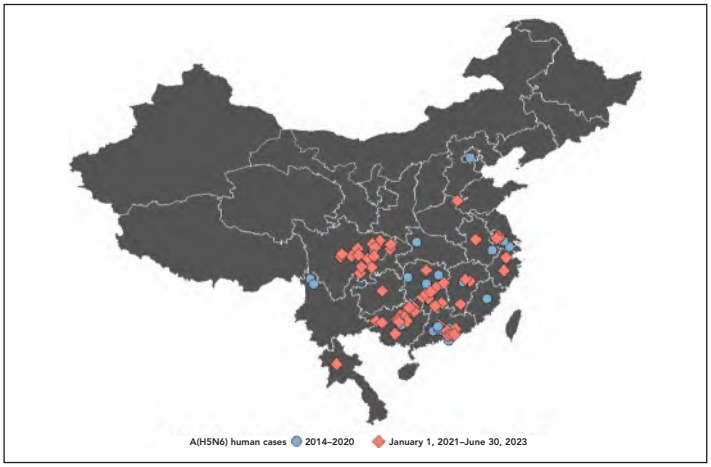


Figure 5: Spatial distribution of human cases of avian influenza A(H5N6) in China and Laos, February 1, 2014 to June 30, 2023 (n=85)



Geographic distribution

Almost all (84/85; 99%) human A(H5N6) infections have been reported from China, from 15 different regions: Guangxi Zhuang Autonomous Region (19 cases), Hunan Province (15 cases), Guangdong Province (14 cases), Sichuan Province (13 cases), Jiangsu Province (five cases), Chongqing Municipality (three cases), Jiangxi Province (three cases), Anhui Province (two cases), Yunnan Province (two cases), Fujian Province (two cases), Zhejiang Province (two cases), Beijing Municipality (one case), Guizhou Province (one case), Hubei Province (one case), and Henan Province (one case) (**Figure 5**). The majority of these cases were concentrated in south or southeast China, areas that have a high density and popularity of LBMs and free-range farming practices, and also areas rich in water resources that are habitats for AIV hosts (19). Geographic spread seems to be occurring, with not only the number of regions from which cases are reported from China increasing, but also with one case detected in northern China for the first time in August 2019 and one case reported from a bordering country, Laos, in March 2021 (16) (Figure 3).

Disease severity

Human cases of A(H5N6) have a clinical manifestation similar to human infections with other HPAI H5 viruses: symptoms often begin with fever, upper respiratory tract symptoms, and myalgia. Soon afterwards, a rapid progression to lower respiratory tract illness often results in pneumonia, multiple organ failure, acute respiratory distress syndrome (ARDs), and death (20). At least 33 case fatalities have been reported overall (CFR: 33/85; 39%) (21) and of the cases with unknown outcome but available disposition data, 90% (36/40) were in critical or severe condition at the time of the last report (**Table 2**). Among the 80 cases with available hospitalization data, 95% (76/80) required hospital admittance and of the 68 cases with available hospitalization and symptom onset dates, 91% (62/68) were admitted within one week (seven days) of illness onset (median hospitalization delay: four days; range: 0–13 days), further highlighting the severity of this disease (**Table 3**). Intensive care unit (ICU) admission details were too sparse to draw conclusions.

Table 2: Clinical characteristics of laboratory-confirmed human cases of avian influenza A(H5N6) by outcome status, February 1, 2014 to June 30, 2023

Outcome	Median age		Proportion male	Proportion hospitalized (n=78)	Hospitalization delay		Proportion critically ill at last known disposition[a] (n=39)
	n	range	%	%	days[b]	range	%
Survived (n=14)	31	1–65	36	71	3	0–10	14
Deceased (n=27)	49	3–81	48	100	5	0–13	N/A
Unknown (n=44)	53	3–72	64	100	3	0–10	90

Abbreviation: N/A, not applicable
[a] Proportion critically ill at last known disposition means the proportion of cases that were reported as critically ill (instead of stable, alive, or deceased) at the time of the last report, or at the time of the last report prior to final outcome
[b] Hospitalization delay (days) means time between symptom onset date and hospitalization date, in days

Table 3: Descriptive characteristics of human cases of A(H5N6) by sex and age groups, February 1, 2014 to June 30, 2023

Variable	All cases (n=85)	Sex		Age group	
		Male (n=46)	Female (n=39)	Children (<18 years) (n=13)	Adults (≥18 years) (n=72)
Median age (range)	51 (1–81)	51 (3–79)	47 (1–81)	5 (1–12)	52 (22–81)
Proportion males (%)	54	N/A	N/A	18	58
Proportion hospitalized (%)	95	98	92	69	100
Median hospitalization delay (days)[a] (range)	4 (0–13)	4 (0–13)	3 (0–10)	5 (1–10)	3 (0–13)
Case fatality rate (%)	39	72	61	44	72

Abbreviation: N/A, not applicable
[a] Hospitalization delay (days) means time between symptom onset date and hospitalization date, in days

Outcome data were only available for 48% of the cases (41/85), and of these individuals, two thirds (27/41; 66%) died. In comparison to nonfatal cases, fatal cases were older, had a higher proportion of males and hospitalizations, and experienced a greater delay in hospitalizations (Table 2). Of the fatal cases with known comorbidity information, half (3/6) reported the presence of comorbidities, as opposed to one third (1/3; 33%) of the non-fatal cases. However, comorbidity information was very infrequently reported.

Discussion

Avian influenza A(H5N6) remains a deadly virus, having killed approximately four out of every ten reported human cases (Table 3). Most of these cases, including those that survived, were severe and required hospitalization (Table 2 and Table 3). Existing evidence from serological studies of humans at high risk of exposure also suggests mild or asymptomatic illness is uncommon with A(H5N6) and less likely as compared with other AIVs (19). To date, 85 human cases of A(H5N6) have been reported worldwide, mostly from south or southeast China, but geographic spread is present with cases reported from other regions and Laos in recent years. Human infections have continually been reported since the emergence event in 2014, with an increase in cases in 2021 (Figure 2). It is possible that this increase in cases coincides with heightened surveillance and diagnostic systems resulting from the coronavirus disease 2019 (COVID-19) pandemic, but other factors, like the spread of AIVs in poultry populations, likely also play a role in the increased number of cases since most cases seem to be infected post-exposure to infected poultry or contaminated environments. Regardless, this increase in cases serves as a reminder that the epidemiology of human AIV infections may change at any time due to the transformative nature of these viruses. This further emphasizes the need to continue surveillance and situational assessments of human infections with AIVs. Each event should be scrutinized for changes that may result in increased infectivity or pathogenesis. In general, an increase in reported cases was observed in cooler seasons (Figure 4). These study results corroborate literature postulating an increased incidence in the winter and autumn months, coinciding with influenza A seasonality in humans and aligning with avian migratory pathways (22). The majority of cases were middle-aged, with a median age of 51 years, but viral infections have been reported in children and seniors as well (Table 3). Both sexes seem equally susceptible to infection (Table 3). Although avian influenza A(H5N6) rarely infects humans, certain populations are at an elevated risk of infection, such as those with exposure to birds. In the past, human A(H5N6) cases have been linked to local live poultry feeding and trading markets. through genetic analysis and comparison of viral case and environmental samples (21). Epidemiological investigations have also revealed positive H5 results from the backyards of several cases in China who kept domestic poultry or had wild birds frequent their residences (21). Workers with occupational exposures, such as poultry sellers, are also at higher risk of positive serology and investigators have observed positive A(H5N6) serology specimens from poultry

workers in the past, although this does not constitute a positive case. Since A(H5N6) is transmitted through secretions and droppings, exposure to birds in these environments may increase risk of infection through direct or indirect contact with infected poultry.

China is considered a hotspot for the emergence and spread of AIVs due to their widespread persistence, the well-established and growing poultry production and trading industry, and the mixing of host species in live bird markets (23–25). To mitigate the risk of animal-to-person transmission, the appropriate use of personal protective equipment is vital, and other biosecurity and preventive measures, such as antiviral prophylaxis after potential exposure, should be used as safeguards where applicable (26). Adhering to public health measures like regular thorough handwashing, staying home if feeling sick, and minimizing contact with wild, sick, and/or dead birds and contaminated and/or high-risk environments like LBMs may protect individuals from A(H5N6) infection. Seasonal influenza vaccination may also help prevent co-infections of novel and seasonal influenza, thereby potentially lessening the severity of the clinical course of illness and reducing the risk of reassortants. Population-specific health communication may be effective to disseminate these public health measures to at-risk populations (27).

Global surveillance of HPAI A(H5N6) and a OneHealth approach are recommended to detect virological, epidemiological, and clinical changes that can affect both animal and human health. As this pathogen continues to circulate in bird populations and contaminate various environments, additional detections of sporadic human cases of A(H5N6) are to be expected. Timely information sharing of these cases and relevant clinical, epidemiological, and virological findings under the International Health Regulations (2005) remains key for human A(H5N6) infection risk assessment and mitigation (21). Comprehensive data sharing is necessary for capturing a true picture of human A(H5N6) cases and the risks leading to infection. Only then will public health officials be able to implement protective measures that target those at increased risk of infection, illness, and death. The maintenance of a minimum dataset of International Health Regulations (2005) notified events could contribute positively to comprehensive data sharing and effective surveillance. Collection of basic epidemiological information on the A(H5N6) cases in this study required the triangulation of multiple event-based and official reports, genomic data banks, and research publications, which is an inefficient way to maintain essential situational awareness and to inform risk assessments.

Strengths and limitations

Although every effort was made to utilize valid and as complete as possible data element information on all cases, this study was limited by reliance on disseminated information from both official and unofficial sources. Incomplete data were often provided, with missing information for variables such as exposure history, comorbidities, or final outcome. The timing, types of case information, and the reporting formats that were shared varied widely from case to case, even in those reported by official sources. Analyses involving these data elements must thus be interpreted with caution due to the potential of demonstrating skewed population characteristics.

The A(H5N6) disease severity, highlighted by a relatively high CFR (39%) In humans, should be interpreted with caution as well, as this percentage may be subject to bias introduced by underreporting. It is possible that cases are tested more often when severe or hospitalized, and as a result of which a higher proportion of hospitalizations may be reported. In this scenario, an overestimation of the CFR in humans may occur, since the denominator might not capture mild or asymptomatic cases. It is also possible that community deaths are undercounted/underreported, such as instances in which individuals do not present to hospital and are not tested for AIV infections. However, current evidence suggests mild or asymptomatic illness is uncommon with A(H5N6), and less likely to occur as compared with other AIVs, such as A(H9N2) (19,28,29).

This study presented several strengths. For one, the information was gathered quickly due to the use of already published reports and articles; study authors did not need to wait for more sporadic cases to emerge to collate and analyze data. In addition, maintenance of an ongoing surveillance system (the IMAT), in which study authors collated daily respiratory events and created monthly reports on target pathogens, also supported the data collection stage. Conducting this study also highlighted the importance of not only sharing information in the international context, but also sharing complete information. Too often, case reports leave out several pertinent details about the case, resulting in potential misrepresentation of the susceptible population. However, case information was updated by study authors as more information became known through the maintenance of the IMAT, which supported the descriptive analyses, since the most complete case information possible was used.

Conclusion

This study contributes to the existing evidence base by providing an epidemiologic analysis of all human cases of A(H5N6) with symptom onset between February 2014 and June 30, 2023, to facilitate better understanding of the characteristics of these cases. Awareness of susceptible populations is vital in informing public health measures, such as public health communication and targeted communication to populations at increased risk of infection and/or severe outcomes. With an increased incidence of human A(H5N6) cases in recent years and a disease spectrum that includes severe disease or death, surveillance and timely and complete information sharing of human cases of A(H5N6) is critical for human A(H5N6) infection risk assessment and mitigation.

Authors' statement

SS — Conceptualization, data analysis, writing–original draft, writing–review and editing
CF — Conceptualization, updating data analysis, writing–original draft, writing–review and editing
AM — Conceptualization, data extraction, review
NA — Conceptualization, data extraction, review
CB — Conceptualization, data extraction, review

Competing interests

None.

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