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

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The cover photo represents a colony of *Streptococcus pneumonia* (or pneumococcus bacterias) that can cause many types of infections and can be life threatening. Some of these infections are "invasive" which means that they invade parts of the body that are normally free from germs. This image was taken from Adobe Stock #136685591.

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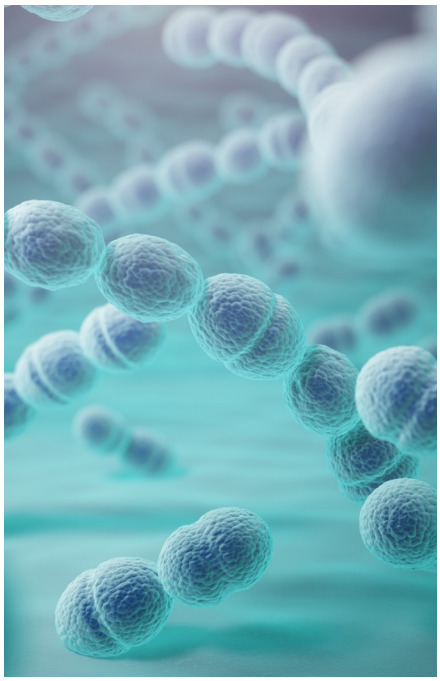

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Summary of the National Advisory Committee on Immunization (NACI) Seasonal Influenza Vaccine Statement for 2022–2023

Angela Sinilaite[1], Jesse Papenburg[2,3,4,5] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: The National Advisory Committee on Immunization (NACI) reviews the evolving evidence on influenza immunization and provides annual recommendations regarding the use of authorized seasonal influenza vaccines to the Public Health Agency of Canada.

Objective: To summarize the NACI seasonal influenza vaccine recommendations for 2022–2023 and to highlight new recommendations and supporting evidence.

Methods: In the preparation of the Statement on Seasonal Influenza Vaccine for 2022–2023, NACI's Influenza Working Group followed the NACI evidence-based process for developing recommendations. The recommendations were then considered and approved by NACI in light of the available evidence.

Results: The following key updates and new recommendations have been made for the 2022–2023 season: 1) updated information/guidance on influenza vaccination in the context of the coronavirus disease 2019 (COVID-19) has been incorporated; 2) Supemtek™ recombinant influenza vaccine may be considered for use among the quadrivalent influenza vaccines offered to adults 18 years of age and older for annual influenza immunization; and 3) Flucelvax® Quad may be considered among the quadrivalent influenza vaccines offered to adults and children two years of age and older.

Conclusion: NACI continues to recommend that an age-appropriate influenza vaccine should be offered annually for all individuals aged six months of age and older who do not have contraindications to the vaccine, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, and other groups for whom influenza vaccination is particularly recommended.

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Introduction

Seasonal influenza epidemics lead to significant morbidity and mortality in the Canadian population (1) and increase the demand on the healthcare system in the fall and winter months. Influenza circulation has been at a historical low since the onset of the coronavirus disease 2019 (COVID-19) pandemic, which has been associated with various reasons including the implementation of non-pharmaceutical public health measures (e.g. masking, social distancing) against COVID-19. Prior to the COVID-19 pandemic, the global annual attack rate was estimated to be 5%–10% in adults and 20%–30% in children (2). Although the burden of influenza can vary from year to year, it is estimated that in Canada there are an average of 12,200 hospitalizations related to influenza and approximately 3,500 deaths attributable to influenza annually (3,4). Current information on influenza activity internationally can be found on the World Health Organization's Global Influenza Program

website (5) and nationally on the Public Health Agency of Canada's (PHAC) FluWatch website (6).

The National Advisory Committee on Immunization (NACI) provides PHAC with annual recommendations regarding the use of seasonal influenza vaccines, which reflect identified changes in influenza epidemiology, immunization practices and influenza vaccine products authorized and available for use in Canada. The annual update of the *NACI Statement on Seasonal Influenza Vaccine* is led by the NACI Influenza Working Group (IWG), involves a thorough review and evaluation of the literature as well as discussion and debate at the scientific and clinical practice levels.

This article provides a concise summary of NACI's recommendations and supporting information for the 2022–2023 influenza season, including conclusions from evidence reviews on 1) a new, recombinant quadrivalent influenza vaccine (Supemtek™; RIV4) and 2) a mammalian cell-based influenza vaccine (Flucelvax® Quad; IIV4-cc). Updated guidance for use of influenza vaccines during the COVID-19 pandemic is also highlighted. Complete details can be found on the PHAC website in the *NACI Advisory Committee Statement: Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2022–2023* (the Statement) (7) and related publications.

Influenza vaccine abbreviations

The current abbreviations used by NACI to describe the defining features of various types of influenza vaccines are presented in **Table 1**. For the 2022–2023 Statement, recombinant influenza vaccine (RIV) has been added as a new category of influenza vaccines authorized for use in Canada.

Table 1: National Advisory Committee on Immunization influenza vaccine abbreviations

Influenza vaccine category	Formulation	Type	Current NACI abbreviation[a]
Inactivated influenza vaccine (IIV)	Trivalent (IIV3)	Standard dose[b], unadjuvanted, IM administered, egg-based	IIV3-SD
		Adjuvanted[c], IM administered, egg-based	IIV3-Adj
		High dose[d], unadjuvanted, IM administered, egg-based	IIV3-HD
	Quadrivalent (IIV4)	Standard dose[b], unadjuvanted, IM administered, egg-based	IIV4-SD
		Standard dose[b], unadjuvanted, IM administered, cell culture-based	IIV4-cc
		High dose[d], unadjuvanted, IM administered, egg-based	IIV4-HD
Recombinant influenza vaccine (RIV)	Quadrivalent (RIV4)	Recombinant[e], unadjuvanted, IM administered	RIV4
Live attenuated influenza vaccine (LAIV)	Trivalent (LAIV3)	Unadjuvanted, Nasal spray, egg-based	LAIV3
	Quadrivalent (LAIV4)	Unadjuvanted, Nasal spray, egg-based	LAIV4

Abbreviations: IM, intramuscular; IIV, inactivated influenza vaccine; IIV3, trivalent inactivated influenza vaccine; IIV3-Adj, adjuvanted egg-based trivalent inactivated influenza vaccine; IIV3-HD, high-dose egg-based trivalent inactivated influenza vaccine; IIV3-SD, standard-dose egg-based trivalent inactivated influenza vaccine; IIV4, quadrivalent 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; LAIV, live attenuated influenza vaccine; LAIV3, egg-based trivalent live attenuated influenza vaccine; LAIV4, egg-based quadrivalent live attenuated influenza vaccine; NACI, National Advisory Committee on Immunization; RIV, recombinant influenza vaccine; RIV4, quadrivalent recombinant influenza vaccine

[a] The numeric suffix denotes the number of antigens contained in the vaccine ("3" refers to the trivalent formulation and "4" refers to the quadrivalent formulation). The hyphenated suffix "-SD" is used when referring to IIV products that do not have an adjuvant, contain 15 µg hemagglutinin (HA) per strain and are administered as a 0.5 mL dose by intramuscular injection; "-cc" refers to an IIV product that is made from influenza virus grown in cell cultures instead of chicken eggs (Flucelvax® Quad); "-Adj" refers to an IIV with an adjuvant (IIV3-Adj for Fluad® or Fluad Pediatric®); and "-HD" refers to an IIV that contains higher antigen content than 15 µg HA per strain (IIV3-HD for Fluzone® High-Dose or IIV4-HD for Fluzone® High-Dose Quadrivalent)

[b] 15 µg HA per strain

[c] 7.5 µg (in 0.25 mL) or 15 µg (in 0.5 mL) HA per strain

[d] 60 µg HA per strain

[e] 45 µg HA per strain

Source: Table reproduced from NACI Seasonal Influenza Vaccine Statement for 2022–2023 (7)

Methods

In the preparation of the Statement on Seasonal Influenza Vaccine for 2022–2023, the NACI IWG identified the need for evidence reviews for new topics, and then reviewed and analyzed the available evidence, and proposed new or updated recommendations according to the NACI evidence-based process for developing recommendations (8). More details regarding the strength of NACI recommendations and the grading of evidence is available in **Table A1** in the **Appendix**. A published, peer-reviewed framework and evidence-informed tools (including the Ethics Integrated Filters, Equity Matrix, Feasibility Matrix, and Acceptability Matrix) was applied to ensure that issues related to ethics, equity, feasibility and acceptability were systematically assessed and integrated into guidance (9).

For the 2022–2023 influenza season, the NACI IWG reviewed evidence and developed new recommendations regarding the use of two vaccines: 1) Supemtek, a new, quadrivalent recombinant influenza vaccine (RIV4) and 2) Flucelvax Quad, a mammalian cell culture-based, inactivated seasonal influenza vaccine (IIV4-cc). Supemtek is the first and, to date, the only available recombinant influenza vaccine that was first authorized for use in Canada in adults 18 years of age and older on January 14, 2021. NACI has not previously made a recommendation on recombinant influenza vaccines in any population; therefore, the NACI IWG oversaw the completion of a systematic literature review and meta-analysis on the vaccine efficacy, effectiveness, immunogenicity and safety of RIV4 in adults 18 years of age and older to inform the development of guidance on its use among adults in Canada. The methodology was specified *a priori* in a written protocol that included the research questions, search strategy, inclusion and exclusion criteria and quality assessment. The search spanned publications from January 1, 2000, to January 12, 2021, with an update to August 8, 2021. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework (10) was used to organize and analyze the quality of the body of evidence across studies in developing recommendations. The strength and certainty of evidence included in syntheses were assessed by two independent reviewers using the GRADE system. NACI provided a new recommendation based on assessment of the available evidence.

Flucelvax Quad (IIV4-cc) is the first and, to date, the only mammalian cell culture-based inactivated seasonal influenza vaccine available for use in Canada. It was first authorized for use in Canada in adults and children nine years of age and older on November 22, 2019. In support of the original recommendation for use of the Flucelvax Quad in adults and children nine years of age and older, NACI conducted a systematic review of the literature to examine vaccine efficacy, effectiveness, immunogenicity and safety data for this age group. The systematic review methodology was developed with the NACI IWG and specified *a priori* in a written protocol that included review questions, search strategy, inclusion and exclusion criteria and quality assessment. Further details, recommendations and supporting evidence on the use of Flucelvax Quad in adults and children nine years of age and older can be found in the *NACI Supplemental Statement – Mammalian Cell Culture-Based Influenza Vaccines* (11) and have also been incorporated into the Statement on Seasonal Influenza Vaccine for 2021–2022. On March 8, 2021, Health Canada approved an expanded age indication for the use of Flucelvax Quad in children down to two years of age and older. Following the review and analysis of Health Canada's assessments of clinical trial evidence submitted by the manufacturer in support of the age extension, the NACI IWG proposed new recommendations for vaccine use to NACI. NACI critically appraised the available evidence and approved the specific recommendations brought forward.

Results

Use of seasonal influenza vaccine in the presence of COVID-19

Influenza vaccination remains a critical tool to minimize the morbidity and mortality related to potential influenza and COVID-19 co-circulation and to reduce the burden on the Canadian healthcare system to enhance the capacity to respond to ongoing COVID-19 activity. Public Health Agency of Canada guidance on seasonal influenza vaccination, developed in consultation with NACI and the Canadian Immunization Committee, to support provincial and territorial vaccine programs and primary care providers offering influenza vaccine during the COVID-19 pandemic, is available on the *Guidance on the use of influenza vaccine in the presence of COVID-19* web page (12). The web content will continue to be reviewed regularly and updates will be made as necessary to align with the currently available scientific evidence, expert opinion and public health context.

Administration of COVID-19 vaccines may occur at the same time as, or at any time before or after, influenza immunization (including all seasonal influenza vaccines or LAIV) for those aged 12 years and older as of September 2021. Readers should consult the Canadian Immunization Guide COVID-19 chapter (13) for updated NACI guidance on the concomitant administration of influenza and COVID-19 vaccines as the number of authorized COVID-19 vaccines and the age groups eligible to receive them expand.

Inclusion of quadrivalent recombinant seasonal influenza vaccine (RIV4)

Recombinant protein technology is a novel, alternative platform for influenza vaccine manufacturing that differs considerably from existing egg-based and mammalian cell culture-based

technologies. Although Supemtek is the first, and currently the only, recombinant seasonal influenza vaccine authorized in Canada, recombinant protein technology is a well-established vaccine-manufacturing platform that may allow for faster, more flexible production times, yields a highly pure product, and mitigates the risk of mismatch between the vaccine and circulating influenza virus strains. These advantages can help to overcome challenges associated with conventional egg-based influenza vaccine production and to improve the development process and quality of influenza vaccines for reducing and preventing future influenza epidemics and pandemics. However, they are also counterbalanced by barriers that may restrict feasibility, including limited RIV manufacturing infrastructure and higher cost of production (14).

Ten eligible studies were included in the evidence synthesis. Two vaccine efficacy and effectiveness outcomes were ranked as critical to decision making during the outcome prioritization process: efficacy or effectiveness against laboratory-confirmed influenza (LCI)-related mortality and efficacy or effectiveness against LCI. The peer-reviewed published evidence on the efficacy of RIV4 against LCI illness was sparse. No studies reporting on the efficacy of RIV4 against LCI-related mortality were identified. One randomized controlled trial (RCT) that assessed the efficacy of RIV4 against LCI in adults aged 50 years and older provided evidence that RIV4 may potentially offer improved protection against laboratory-confirmed influenza A infection compared to standard egg-based influenza vaccines (15). However, all the relative vaccine efficacy analyses were conducted using data only from the 2014–2015 influenza season in the United States (US), which was influenza A(H3N2)-dominant, and in adults aged 50 years and older. Peer-reviewed, published clinical data pertaining to the efficacy or effectiveness of vaccination with RIV4 during pregnancy or including breastfeeding were not available at the time of this review. Overall, there is fair evidence (of low certainty) that the efficacy of RIV4 is non-inferior to traditional egg-based comparators, based on data in adults aged 50 years and older.

Three vaccine immunogenicity outcomes were ranked as critical during the outcome prioritization process of this review: seroprotection rate; seroconversion rate; and geometric mean titre ratio. Eight RCTs that assessed the immunogenicity of RIV4 compared to different vaccines, including IIV3-HD, IIV3-Adj, IIV4-SD and IIV4-cc, were identified in this review. Of these studies, two were conducted during the 2014–2015 influenza season (15,16), three were conducted over the 2017–2018 influenza season (17–19) and three were conducted over the 2018–2019 influenza season (20–22). The RCTs were of good quality overall. Non-inferiority was assessed using the criteria specified by the US Food and Drug Administration (23). Across studies, RIV4 demonstrated non-inferiority compared to egg-based influenza vaccines against influenza A(H1N1), most strains of A(H3N2), and B/Yamagata lineage (15–22). Findings differed across studies regarding the non-inferiority of RIV4 compared to egg-based influenza vaccines against influenza B/Victoria lineage based on seroconversion rates, seroprotection rates and geometric mean titre ratio (15,16). Overall, there is fair evidence (of moderate certainty) that the immunogenicity for RIV4 is non-inferior to traditional egg-based comparators, based on data in adults aged 18 years and older.

Two vaccine safety outcomes were ranked as critical during the outcome prioritization process for this review: serious adverse events (SAEs) and solicited systemic adverse events (AEs). Six eligible studies were identified that assessed the safety of RIV4 in adults, including five RCTs and one review of post-marketing surveillance data from the US. Of these studies, two were conducted during the 2014–2015 influenza season (15,16), two were conducted during the 2017–2018 influenza season (18,24), one was conducted during the 2018–2019 influenza season (21) and one study (25) reported data from the Vaccine Adverse Event Reporting System (VAERS) from July 1, 2017, through June 30, 2020. The five RCTs found that Supemtek is a safe, well-tolerated and immunogenic alternative to conventional egg-based influenza vaccines for adults (noting that no published clinical data pertaining to the safety of vaccination with RIV4 during pregnancy were available at the time of this review to inform vaccine-associated risks) (15,16,18,21,24). No elevated risk of severe allergic reactions compared to traditional egg-based influenza vaccines was identified; however, lack of egg proteins in RIV4 does not eliminate the risk of allergic reactions following vaccine administration, as allergic reactions can occur following exposure to any drug or vaccine (26). Overall, there is evidence of moderate certainty that RIV4 is a safe and well-tolerated alternative to conventional egg-based influenza vaccines for adults.

Based on the review of available pre-licensure and post-market clinical trial and surveillance data, NACI made the following recommendation, supplementing NACI's overarching recommendation for influenza vaccination, which is available in the NACI Seasonal Influenza Vaccine Statement (7):

NACI recommends that Supemtek may be considered among the seasonal influenza vaccines offered to adults 18 years of age and older (Discretionary NACI Recommendation).

- **NACI concludes that there is fair evidence to recommend vaccination of adults 18 years of age and older with Supemtek (Grade B Evidence)**

For complete details of this review, rationale, relevant considerations and additional information supporting this recommendation, refer to the *NACI Supplemental Statement: Recombinant Influenza Vaccines* (27). NACI will continue to monitor the evidence related to recombinant influenza vaccines and will update this supplemental statement as needed and as data on Supemtek from several different influenza seasons accumulates.

Updated recommendations on mammalian cell culture-based quadrivalent influenza vaccine (IIV4-cc)

The age extension for the use of Flucelvax Quad in adults and children two years of age and older was based on a phase 3/4 randomized clinical trial of efficacy, immunogenicity and safety of the vaccine in children two years to less than 18 years of age. The clinical trial was conducted in eight countries in Europe and South East Asia over three influenza seasons (Southern Hemisphere 2017 influenza season and Northern Hemisphere 2017–2018 and 2018–2019 influenza seasons). Overall, the quality of the evidence was considered good. NACI concluded that Flucelvax Quad is effective and safe compared to comparable vaccines, and elicits a robust immune response based on direct evidence in children two years to less than nine years of age. The quantity of direct safety and immunogenicity evidence for Flucelvax Quad in children two years to less than nine years of age is limited; however, the currently reviewed and previous clinical trial evidence provided fair evidence of efficacy, immunogenicity, and safety in children. Therefore, NACI recommended that **Flucelvax Quad may be considered among the IIV4 offered to adults and children two years of age and older (Discretionary NACI Recommendation).**

Additional information supporting this recommendation can be found in Section IV.1 of the NACI Seasonal Influenza Vaccine Statement for 2022–2023 (7). Notably, Flucelvax Quad was recently authorized by Health Canada for use in adults and children six months of age and older. This updated authorized age indication supersedes the information for Flucelvax Quad found in relevant sections within the NACI Statement on Seasonal Influenza Vaccine for 2022–2023. Further details are available in the new product monograph for this vaccine (28).

Summary of National Advisory Committee on Immunization recommendations for the use of influenza vaccines for the 2022–2023 influenza season

NACI continues to recommend influenza vaccination to anyone six months and older who does not have contraindications to the vaccine. Vaccination should be offered as a priority to people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk of complications, and others as indicated in **List 1**.

Recommended influenza vaccine options by age group and by dosage and route of administration by age are summarized in **Table 2** and **Table 3**, respectively.

List 1: Groups for whom influenza vaccination is particularly recommended

People at high risk of influenza-related complications or hospitalization

- All children 6–59 months of age
- Adults and children with the following chronic health conditions[a]:
  - Cardiac or pulmonary disorders (includes bronchopulmonary dysplasia, cystic fibrosis and asthma)
  - Diabetes mellitus and other metabolic diseases
  - Cancer, immune compromising conditions (due to underlying disease, therapy, or both, such as solid organ transplant or hematopoietic stem cell transplant recipients)
  - Renal disease
  - Anemia or hemoglobinopathy
  - Neurologic or neurodevelopment conditions (includes neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders [and, for children, includes febrile seizures and isolated developmental delay], but excludes migraines and psychiatric conditions without neurological conditions)
  - Morbid obesity (body mass index of 40 kg/m^2 and over)
  - Children six months to 18 years of age undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza
- All pregnant individuals
- People of any age who are residents of nursing homes and other chronic care facilities
- Adults 65 years of age and older
- Indigenous peoples

People capable of transmitting influenza to those at high risk

- Healthcare and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk
- Household contacts, both adults and children, of individuals at high risk, whether or not the individual at high risk has been vaccinated:
  - Household contacts of individuals at high risk
  - Household contacts of infants less than six months of age, as these infants are at high risk but cannot receive influenza vaccine
  - Members of a household expecting a newborn during the influenza season
- Those providing regular childcare to children 0–59 months of age, whether in or out of the home
- Those who provide services within closed or relatively closed settings to people at high risk (e.g. crew on a ship)

Others

- People who provide essential community services
- People who are in direct contact with poultry infected with avian influenza during culling operations

[a] Refer to Immunization of Persons with Chronic Diseases and Immunization of Immunocompromised Persons in Part 3 of the CIG for additional information about vaccination of people with chronic diseases (29)

Source: Table reproduced from NACI Seasonal Influenza Vaccine Statement for 2022–2023 (7)

Table 2: Recommendations on choice of influenza vaccine type for individual and public health program-level decision making by age group

Recipient by age group	Vaccine types authorized for use	Recommendations on choice of influenza vaccine	
6–23 months	IIV3-SD[a] IIV3-Adj IIV4-SD	• A quadrivalent influenza vaccine licensed for this age group should be used in infants and young children without contraindications, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine • If a quadrivalent vaccine is not available, any of the available trivalent vaccines licensed for this age group should be used	
2–17 years[b]	IIV3-SD[a] IIV4-SD IIV4-cc LAIV4	• An age-appropriate quadrivalent influenza vaccine (IIV4-SD, LAIV4 or IIV4-cc) should be used in children without contraindications or precautions (see text below applicable to LAIV), including those with chronic health conditions, given the burden of influenza B disease in this age group and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine • LAIV4 may be given to children with: ◦ Stable, non-severe asthma ◦ Cystic fibrosis who are not being treated with immunosuppressive drugs (e.g. prolonged systemic corticosteroids) ◦ Stable HIV infection, if the child is currently being treated with ART (i.e. HAART) and has adequate immune function • LAIV should not be used in children or adolescents for whom it is contraindicated or for whom there are warning and precautions such as those with: ◦ Severe asthma (defined as currently on oral or high dose inhaled glucocorticosteroids or active wheezing) ◦ Medically attended wheezing in the seven days prior to vaccination ◦ Current receipt of aspirin or aspirin-containing therapy ◦ Immune compromising conditions, with the exception of stable HIV infection, i.e. if the child is treated with HAART (for at least 4 months) and has adequate immune function ◦ Pregnancy ◦ In pregnancy, IIV4-SD or IIV4-cc should be used instead • If IIV4-SD, IIV4-cc and LAIV4 are not available, IIV3-SD should be used	
18–59 years	IIV3-SD[a] IIV4-SD IIV4-cc RIV4 LAIV4	• Any of the available influenza vaccines authorized for this age group should be used in adults 18–59 years without contraindications or precautions, noting the following consideration and exceptions: ◦ There is some evidence that IIV may provide better efficacy than LAIV in healthy adults • LAIV is not recommended for: ◦ Pregnant individuals ◦ Adults with any of the chronic health conditions identified in List 1, including immune compromising conditions ◦ Healthcare workers	
60–64 years	IIV3-SD[a] IIV4-SD IIV4-cc RIV4	• Any of the available influenza vaccines authorized for this age group should be used in adults 60–64 years without contraindications	
65 years and older[c]	IIV3-SD[a] IIV3-Adj IIV3-HD[d] IIV4-SD IIV4-cc RIV4	**Individual-level decision-making** • IIV-HD should be used over IIV-SD, given the burden of influenza A(H3N2) disease and the good evidence of IIV3-HD providing better protection compared to IIV3-SD in adults 65 years of age and older ◦ Other than a recommendation for using IIV-HD over IIV-SD formulations, NACI has not made comparative individual-level recommendations on the use of the other available vaccines in this age group. In the absence of a specific product, any of the available age-appropriate influenza vaccines should be used	**Public health program-level decision-making** • Any of the available influenza vaccines authorized in this age group should be used ◦ There is insufficient evidence on the incremental value of different influenza vaccines (i.e. cost-effectiveness assessments have not been performed by NACI) to make comparative public health program-level recommendations on the use of the available vaccines

Abbreviations: ART: antiretroviral therapy; HAART, highly active antiretroviral therapy; IIV, inactivated influenza vaccine; IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4-cc, quadrivalent mammalian cell-culture based inactivated influenza vaccine; IIV4-HD, high-dose quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine; NACI, National Advisory Committee on Immunization; RIV4, quadrivalent recombinant influenza vaccine

[a] IIV3-SD formulations will not be available for use in Canada during the 2022–2023 influenza season

[b] Refer to Table 4 of the NACI Seasonal Influenza Vaccine Statement for 2022–2023 for a summary of vaccine characteristics of LAIV compared with IIV in children 2–17 years of age

[c] Refer to Table 5 of the NACI Seasonal Influenza Vaccine Statement for 2022–2023 for a comparison of the vaccine characteristics of influenza vaccine types available for use in adults 65 years of age and older

[d] IIV3-HD formulations will not be authorized or available for use in Canada during the 2022–2023 influenza season

Source: Table reproduced from NACI Seasonal Influenza Vaccine Statement for 2022–2023 (7)

Table 3: Recommended dose and route of administration, by age, for influenza vaccine types authorized for the 2022–2023 influenza season

Age group	Influenza vaccine type (route of administration)						Number of doses required
	IIV3-SD[a] or IIV4-SD[b] (IM)	IIV4-cc[c] (IM)	IIV3-Adj[d] (IM)	IIV4-HD[e] (IM)	RIV4[f] (IM)	LAIV4[g] (intranasal)	
6–23 months	0.5 mL[h]	-	0.25 mL	-	-	-	1 or 2[i]
2–8 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1 or 2[i]
9–17 years	0.5 mL	0.5 mL	-	-	-	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	0.5 mL	-	-	0.5 mL	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	0.5 mL	-	-	0.5 mL	-	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	0.7 mL	0.5 mL	-	1

Abbreviations: IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4-cc, quadrivalent mammalian cell-culture based inactivated influenza vaccine; IIV4-HD, high-dose quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; IM, intramuscular; LAIV4, quadrivalent live attenuated influenza vaccine; RIV4:quadrivalent recombinant influenza vaccine

[a] IIV3-SD formulations (Agriflu® [six months and older], Fluviral® [six months and older] and Influvac® [three years and older]) are authorized but will not be available for use in Canada during the 2021–2022 influenza season

[b] Afluria® Tetra (five years and older), Flulaval® Tetra (six months and older), Fluzone® Quadrivalent (six months and older), Influvac® Tetra (three years and older)

[c] Flucelvax® Quad (two years and older)

[d] Fluad Pediatric® (6–23 months) or Fluad® (65 years and older)

[e] Fluzone® High-Dose Quadrivalent (65 years and older)

[f] Supemtek™ (18 years and older)

[g] FluMist® Quadrivalent (2–59 years)

[h] Evidence suggests moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines (29,30). This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to Statement on Seasonal Influenza Vaccine for 2011–2012

[i] Children six months to less than nine years of age receiving seasonal influenza vaccine for the first time in their life should be given two doses of influenza vaccine, with a minimum interval of four weeks between doses. Children six months to less than nine years of age who have been properly vaccinated with one or more doses of seasonal influenza vaccine in the past should receive one dose of influenza vaccine per season thereafter

Source: Table reproduced from NACI Seasonal Influenza Vaccine Statement for 2022–2023 (7)

Conclusion

NACI continues to recommend annual influenza vaccination for all individuals aged six months and older (noting product-specific age indications and contraindications), with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, people who provide essential community services and people in direct contact during culling operations with poultry infected with avian influenza. For the 2022–2023 influenza season, NACI newly recommend that Supemtek recombinant influenza vaccine may be considered for use among the quadrivalent influenza vaccines offered to adults 18 years of age and older. NACI also newly recommends that Flucelvax Quad may be considered among the quadrivalent influenza vaccines offered to adults and children two years of age and older.

Authors' statement

AS — Writing, original draft, review, editing
JP — Review, editing

The *NACI Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2022–2023* was prepared by A Sinilaite, R Stirling and R Harrison, on behalf of the NACI Influenza Working Group, and was approved by NACI.

Competing interests

J Papenburg reports grants to his institution from MedImmune, Sanofi Pasteur, Merck and AbbVie and personal fees from AbbVie, Astra-Zeneca and Merck; all of which were outside of the submitted work.

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Appendix

Table A1: National Advisory Committee on Immunization recommendations: strength of recommendation and grade of evidence

Strength of NACI recommendation (based on factors not isolated to strength of evidence; e.g. public health need)	Strong	Discretionary
Wording	"**should/should not** be offered"	"**may be** considered"
Rationale	Known/anticipated advantages outweigh known/anticipated disadvantages ("should"), OR known/anticipated disadvantages outweigh known/anticipated advantages ("should not")	Known/anticipated advantages closely balanced with known/anticipated disadvantages, OR uncertainty in the evidence of advantages and disadvantages exists
Implication	A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present	A discretionary recommendation may be considered for some populations/individuals in some circumstances Alternative approaches may be reasonable
Grade of evidence (based on assessment of the body of evidence)	A: good evidence to recommend B: fair evidence to recommend C: conflicting evidence, however other factors may influence decision-making D: fair evidence to recommend against E: good evidence to recommend against I: insufficient evidence (in quality or quantity), however other factors may influence decision-making	

Abbreviation: NACI, National Advisory Committee on Immunization

RAPID COMMUNICATION

Summary of the National Advisory Committee on Immunization (NACI) Supplemental Statement on Recombinant Influenza Vaccines

Anabel Gil[1], Angela Sinilaite[1], Jesse Papenburg[2,3,4,5] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Recombinant protein technology is a novel platform for influenza vaccine manufacturing that differs significantly from existing egg-based and mammalian cell culture-based technologies. Supemtek™ is the first and, to date, the only recombinant quadrivalent influenza vaccine (RIV4) authorized for use in Canada in adults aged 18 years and older. The objective is to review the available evidence for efficacy, effectiveness, immunogenicity and safety of RIV4, and to summarize the National Advisory Committee on Immunization (NACI) recommendation regarding the use of Supemtek.

Methods: A systematic literature review and meta-analysis on the vaccine efficacy, effectiveness, immunogenicity and safety of RIV4 in adults was conducted according to methodology specified *a priori* in a written protocol. NACI evidence-based process was used to assess the available evidence and develop a recommendation regarding the use of Supemtek.

Results: Ten eligible studies were included in the evidence synthesis. One randomized controlled trial (RCT) in adults aged 50 years and older provided evidence that RIV4 may potentially offer improved protection against laboratory-confirmed influenza A infection compared to standard egg-based influenza vaccines. Data from eight RCTs assessing immunogenicity and five RCTs and one post-marketing surveillance study assessing safety indicated that Supemtek is a safe, well tolerated, and immunogenic alternative to conventional egg-based influenza vaccines for adults.

Conclusion: There is fair evidence that Supemtek is effective, safe, and has non-inferior immunogenicity to comparable vaccines, based on direct evidence in adults 18 years of age and older; thus, NACI recommends that Supemtek may be considered among the seasonal influenza vaccines offered to adults 18 years of age and older for their annual influenza vaccination.

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Keywords: National Advisory Committee on Immunization, NACI, recombinant vaccine, influenza, immunization

Introduction

Recombinant protein technology is an established vaccine-manufacturing platform that has been used to produce vaccines approved for use in Canada against various vaccine-preventable diseases (1). This platform is a new, alternative method for influenza vaccine production, which is significantly different from existing egg-based and mammalian cell culture-based technology. The production of recombinant influenza vaccine (RIV) involves the expression of recombinant hemagglutinin in a proprietary insect cell line using a baculovirus expression vector system (1). This process does not rely on egg supply nor the availability of an avian or canine kidney cell substrate, as it does not require propagation of candidate vaccine virus in egg

or mammalian cell (2), thus allowing for more rapid scale-up of vaccine production in the event of an epidemic, pandemic or egg shortage. The flexible and quick manufacturing process of RIV and the continued diversification of influenza vaccine platforms may be helpful in overcoming influenza supply vulnerabilities and improving vaccine-production capacity for a prompt response to rapid and emerging circulating seasonal influenza strains in a post-coronavirus disease 2019 (COVID-19) pandemic setting. Recombinant influenza vaccines may also offer other advantages related to vaccine quality compared to conventional platforms for influenza vaccine manufacturing, including high vaccine purity, three times higher hemagglutinin content than standard-dose vaccines, and reduced risk of a mismatch between vaccines and circulating viral strains because it is not subject to adaptive mutations acquired from growth in eggs or in cells (3–6).

Supemtek™ (Sanofi Pasteur, Ltd.) is the first and, to date, the only recombinant quadrivalent influenza vaccine (RIV4) licensed in Canada for use in adults 18 years of age and older (1). The RIV4 (licensed in the United States under the trade name Flublok® Quadrivalent) builds on the clinical development of its trivalent predecessor, Flublok (RIV3), an inactivated, recombinant influenza vaccine developed by Protein Sciences, Inc. (currently operating as Sanofi Pasteur, Ltd.). The trivalent and quadrivalent RIV formulations have the same manufacturing process; however, the quadrivalent RIV formulation comprises proteins from four strains of influenza virus A (H1N1), A (H3N2), B/Victoria lineage, B/Yamagata lineage) (1,3).

The National Advisory Committee on Immunization (NACI) has not previously made a recommendation on recombinant influenza vaccines in any population; therefore, the objective of the advisory committee supplemental statement was to review the available evidence on the efficacy, effectiveness, immunogenicity and safety of RIV4, and to provide provincial and territorial health authorities and healthcare professionals with guidance on its use among adults in Canada. This article provides a concise summary of NACI's recommendation for RIV4, supporting information and conclusions from the evidence review. Complete details can be found on the Public Health Agency of Canada website in the *NACI Supplemental Statement – Recombinant Influenza Vaccines* (7).

Methods

A systematic literature review and meta-analysis on the vaccine efficacy, effectiveness, immunogenicity and safety of RIV4 in adults 18 years of age and older was performed. The methodology was specified *a priori* in a written protocol that included the research questions, search strategy, inclusion and exclusion criteria, and quality assessment. The NACI's Influenza Working Group reviewed and approved the protocol. A search strategy based on the objective was developed in consultation with a federal Reference Librarian from the Health Library of Health Canada and the Public Health Agency of Canada.

Searches were restricted to primary research studies from peer-reviewed journals and case reports published in English or French. Evidence was retrieved from the EMBASE, MEDLINE, Cochrane Central, Scopus, ProQuest Public Health and ClinicalTrials.gov electronic databases. Registered clinical trials and grey literature from international public health authorities and National Immunization Technical Advisory Groups were also considered. The search spanned publications from January 1, 2000, to January 12, 2021, with an update to August 8, 2021. Two reviewers independently screened the titles, abstracts and eligible full-text articles.

Studies were included if they met the following criteria:

- Study population or sub-population consisted of adults 18 years of age and older
- Study assessed efficacy and effectiveness, immunogenicity, or safety of RIV4
- Primary research studies from peer-reviewed scientific literature
- Case reports and case series
- Registered clinical trials and grey literature from international public health authorities (Australian Technical Advisory Group on Immunisation; Centers for Disease Control and Prevention; clinicaltrials.gov; European Centre for Disease Prevention and Control; European Medicines Agency; Department of Health Services Research & Policy; International Clinical Trials Registry Platform; World Health Organization)
- Study was published in English or French
- Study was published in 2000 or later

Studies were excluded if they met one or more of the following criteria:

- Study did not present data on the efficacy, effectiveness, immunogenicity or safety of RIV4
- Study is in a language other than English or French
- Study is a non-human or *in vitro* study
- Article is not a primary research study
- Article is an editorial, opinion, commentary or news report
- Article is an economic study, clinical practice guideline, consensus conference, health technology assessment report
- Article was a doctoral dissertation, master's thesis, conference summary
- Article is a duplicate

Data were extracted from the included studies into an evidence table using a piloted data abstraction template. The quality (internal validity) of included studies was assessed using Cochrane tools (RoB 2.022 for randomized trials and ROBINS-I23 for non-randomized studies of interventions). The Joanna Briggs Institute checklist was used to evaluate case reports or case series. Data extraction and quality assessment were completed by one reviewer and independently validated by a second reviewer.

Results from included studies were synthesized narratively and analyzed according to NACI evidence-based process to develop a new recommendation. The results of studies deemed to be clinically and methodologically similar were also pooled using random effects meta-analyses. Subgroup analyses were conducted by age group, vaccine strains, and influenza vaccine type. Forest plots illustrating the results of the meta-analyses are presented in the **Appendix**.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework (8) was used to organize and analyze the quality of the body of evidence across studies in developing recommendations. The strength and certainty of evidence included in syntheses were assessed by two independent reviewers using the GRADE system. GRADE assessment was reserved for the following outcomes deemed to be critical for decision-making by the Influenza Working Group through a prioritization exercise:

- Serious adverse event (SAE): Any untoward medical occurrence that at any dose results in death requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is life-threatening
- Laboratory-confirmed influenza (LCI)-related mortality: A death during an influenza season resulting from a clinically compatible illness that was confirmed to be influenza by an appropriate laboratory test (e.g. reverse transcription polymerase chain reaction [RT-PCR], virus culture or antigen detection); all influenza (A and B)
- Laboratory-confirmed influenza (LCI): Symptoms of influenza with a positive laboratory diagnosis by RT-PCR, virus culture or antigen detection; all influenza (A and B)
- Solicited systemic adverse event (AE): Intentionally solicited systemic reactions including but not limited to fever, malaise, muscle pain, headache or loss of appetite
- Seroprotection: Proportion of subjects achieving a haemagglutination inhibition (HI) titre of at least 1:40 post-vaccination
- Seroconversion: Proportion of subjects achieving an increase from equal or less than 1:10 HI titre pre-vaccination to at least 1:40 post-vaccination or achieving at least a four-fold rise in HI titres
- Geometric mean titre ratio (GMTR): Ratio of geometric mean titre post-vaccination of licensed vaccine to geometric mean titre post-vaccination of new vaccine

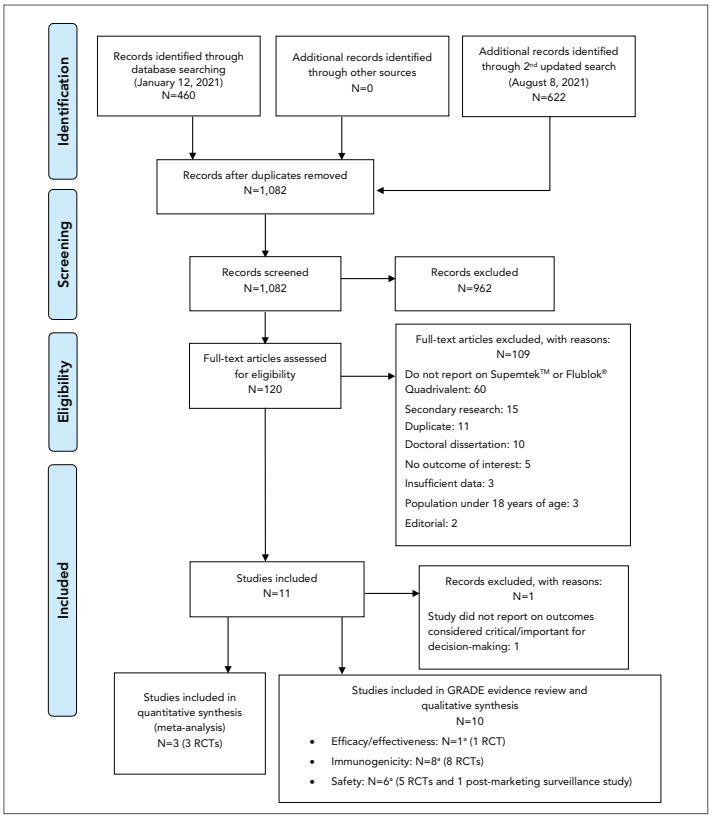
NACI's peer-reviewed framework and evidence-informed tools (9) were also used to assess the implications of ethics, equity, feasibility and acceptability (EEFA) of the recommendation for the use of Supemtek (RIV4) for the prevention of influenza in adults aged 18 years and older in Canada.

Following a thorough review of the evidence according to NACI's evidence-based process, NACI approved the recommendation.

Results

A total of 1,082 articles were retrieved after removing duplicates, of which ten were retained for data extraction and analysis; however, only three of the 10 studies could be pooled through a meta-analysis. One randomized controlled trial (RCT) that reported on the efficacy of RIV4 was identified (10). Eight RCTs investigated the immunogenicity of RIV4 (10–17). Six studies assessed the safety of RIV4, including five RCTs (10,13–15,18) and one post-marketing surveillance study (19). Studies reporting critical outcomes related to the effectiveness of RIV4 were not available at the time of this review. Notably, at the time of this Statement's development, studies reporting on vaccination with RIV4 during pregnancy or during breastfeeding were not available. A flow diagram of the study selection process is presented in **Figure 1** and key study characteristics are summarized in **Table 1**.

Figure 1: PRISMA flow diagram of the study selection process for the systematic review on the efficacy, effectiveness, immunogenicity and safety of Supemtek™



Abbreviations: GRADE, grading of recommendations, assessment, development and evaluation; PRISMA, preferred reporting items for systematic review and meta-analyses; RCT, randomized controlled trial

[a] Some studies fit into more than one outcome category

Table 1: Characteristics of RIV4 studies included in the systematic review

Study	Design	Study	Intervention/Control	Outcomes
Dunkle *et al.* (10) NCT02285998	• RCT • 2014–2015 influenza season	Adults 50 years of age or older	RIV4 (n=4,498) IIV4-SD (n=4,505)	Efficacy • LCI infection Immunogenicity • GMTR 28 days post-vaccination • Seroconversion rate 28 days post-vaccination • Seroprotection rate 28 days post-vaccination Safety • SAEs reporting within 182 days (6 months) post-vaccination
Dawood *et al.* (17) NCT03722589	• RCT • 2018–2019 influenza season	Adult healthcare personnel aged 18–64 years	RIV4 (n=202) IIV4-cc (n=283) Fluarix IIV4-SD (n=120) Fluzone IIV4-SD (n=122)	Immunogenicity • GMTR 1 month post-vaccination • Seroconversion rate 1 month post-vaccination • Seroprotection rate 1 month post-vaccination
Belongia *et al.* (12) NCT02872311	• RCT • 2017–2018 influenza season	Adults 65–74 years of age	RIV4 (n=30) IIV3-HD (n=29) IIV3-Adj (n=30)	Immunogenicity • Seroconversion 28±5 days post-vaccination • Seroprotection rate 28±5 days post-vaccination
Shinde *et al.* (14) NCT03658629	• RCT • 2018–2019 influenza season	Adults 65 years of age or older	RIV4 (n=153) IIV3-HD (n=154)	Immunogenicity • Seroconversion 28, 56 and 182 days post-vaccination • Seroprotection 28, 56 and 182 days post-vaccination Safety • SAEs 181 days post-vaccination • Solicited systemic AEs 6 days post-vaccination
Dunkle *et al.* (15) NCT02290509	• RCT • 2014–2015 influenza season	Adults 18–49 years of age or older	RIV4 (n=1,011) IIV4-SD (n=339)	Immunogenicity • GMTR 28 days post-vaccination • Seroconversion rate 28 days post-vaccination Safety • SAEs reporting within 182 days (6 months) post-vaccination • Solicited systemic AEs 7 days post-vaccination
Wang *et al.* (11) NCT03734237	• RCT • 2018–2019 influenza season	Adults 18–83 years of age	RIV4 (n=51) IIV4-SD (n=46) IIV4-cc (n=36)	Immunogenicity • Seroconversion 21–35 days post-vaccination
Cowling *et al.* (13) NCT03330132	• RCT • 2017–2018 influenza season	Community-dwelling adults 65–82 years of age	RIV4 (n=355) IIV4-SD (n=508) IIV3-Adj (n=508) IIV3-HD (n=510)	Immunogenicity • Seroconversion rate 30 days post-vaccination Safety • SAE (hospitalizations) reporting throughout the study
Cowling *et al.* (18) NCT03330132	• RCT • 2017–2018 influenza season	Community-dwelling adults 65–82 years of age	RIV4 (n=355) IIV4-SD (n=508) IIV3-Adj (n=508) IIV3-HD (n=510)	Safety • Solicited systemic AEs 1, 3–4, 7–9, and 14–16 days post-vaccination
Gouma *et al.* (16) NCT03068949	• RCT • 2017–2018 influenza season	Adults 18–49 years of age	RIV4 (n=23) IIV4-SD (n=23) IIV3-HD (n=16) IIV4-cc (n=23)	Immunogenicity • Seroconversion rate 28 days post-vaccination
Woo *et al.* (19)	• Post-marketing safety surveillance of cases identified through VAERS • 2017–2018, 2018–2019, 2019–2020 influenza seasons	Persons vaccinated with RIV4 July 1, 2017–June 30, 2020	Reports on SAEs: N=39 Reports on systemic AEs: N=300	Safety • SAEs post-vaccination • Systemic AEs identified from non-serious reports post-vaccination

Abbreviations: AE, adverse event; GMTR, geometric mean titre ratio; IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV4-cc, cell-culture based quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; LCI, laboratory-confirmed influenza; NCT, national clinical trial number; RCT, randomized controlled trial; RIV4, quadrivalent recombinant influenza vaccine; SAE, serious adverse event; VAERS, Vaccine Adverse Event Reporting System

An overview of the key efficacy and effectiveness, immunogenicity, and safety findings for this review is provided below. Further details are available in the *NACI Supplemental Statement on Recombinant Influenza Vaccines* (7).

Vaccine efficacy

One RCT assessed the relative vaccine efficacy (rVE) of RIV4 compared to egg-based standard-dose quadrivalent inactivated influenza vaccines (IIV4) against LCI infection. The RCT was conducted indults 50 years of age and older during the 2014–2015 influenza season in the United States (US) (10). Data from this study demonstrated that RIV4 was statistically significantly more efficacious than egg-based IIV4 influenza vaccines in preventing LCI type A infection, but not LCI type B infection in older adults.

Overall, there was fair evidence (of low certainty) that the efficacy of RIV4 is non-inferior to traditional egg-based comparators, based on direct data in adults aged 50 years and older.

Immunogenicity

Eight RCTs reported on the immunogenicity of RIV4 compared to different influenza vaccines, including IIV3-HD, IIV3-Adj, IIV4-SD and IIV4-cc. Two studies were from the 2014–2015 influenza season (10,15), three from the 2017–2018 influenza season (12,13,16) and three from the 2018–2019 influenza season (11,14,17). For all immunogenicity outcomes, non-inferiority was assessed using the criteria specified by the US Food and Drug Administration (20), which are also used in Canada. Critical immunogenicity outcomes reported by these studies included seroconversion rates, seroprotection rates and GMTR.

Eight RCTs assessed seroconversion rates of RIV4 compared to IIV3-HD, IIV3-Adj, IIV4-SD and IIV4-cc in adults aged 18 years and older (10–17). In four (12–14,17) of the eight studies, seroprotection rates were similar among all vaccine groups against all influenza strains. The remaining four studies reported different results. In two studies (10,15) RIV4 did not meet the non-inferiority threshold compared to IIV4-SD against the B/Victoria lineage in adults 18 to 64 years of age. Additionally, rates of seroconversion following RIV4 did not meet the non-inferiority threshold compared to IIV4-SD against influenza A(H1N1) in adults 64 and older (10). Two RCTs (11,16) did not report confidence intervals and non-inferiority could not be assessed. Pooled seroconversion estimates from three RCTs (10,13,14) suggested that RIV4 induced similar antibody responses compared to IIV4-SD, IIV3-HD, and IIV3-Adj in adults 50 years of age and older (**Figure A1**).

Four RCTs examined seroprotection rates of RIV4 compared to IIV3-HD, IIV3-Adj, IIV4-SD and IIV4-cc in adults 18 years of age and older (10,12,14,17). Similar seroprotection rates were observed among the five treatment groups. Across these studies, non-inferiority of the RIV4 vaccine was demonstrated for five of seven tested A (H3N2) strains (10,12,14,17). In two of the four studies, RIV4 demonstrated non-inferiority for all influenza strains (14,17). In one study (12), RIV4 demonstrated lower rates of seroprotection for two of four tested A (H3N2) influenza strains in older adults aged 65–74 years. In the study by Dunkle *et al.* (10), non-inferiority of RIV4 seroprotection rate was demonstrated for influenza A (H1N1), A (H3N2) and B/Yamagata lineage, but not for the B/Victoria lineage in adults aged 50 years and older.

Three RCTs evaluated GMTR of RIV4 compared to IIV4-SD in adults aged 18 years and older (10,15,17,21). In one study, RIV4 demonstrated non-inferiority for all influenza strains (17). In the other two studies (10,15,21), the GMTR against influenza A and B/Yamagata lineage were comparable in both vaccine groups. However, GMTR against B/Victoria lineage for IIV4-SD recipients compared to RIV4 recipients did not meet the non-inferiority criteria.

Overall, there was fair evidence (of moderate certainty) that the immunogenicity for RIV4 is non-inferior to traditional egg-based vaccines, based on data in adults aged 18 years and older.

Safety

Six studies reported on the safety of RIV4 compared to IIV3-HD, IIV3-Adj and IIV4-S in adults aged 18 years of age and older. Of the six studies, five were RCTs (10,13–15,18) and one study was a post-marketing surveillance study (19). Of the included RCTs, two were conducted during the 2014–2015 influenza season (10,15), two were conducted during the 2017–2018 influenza season (13,18), and one was conducted during the 2018–2019 influenza season (14). The post-marketing surveillance study reported data from the US Vaccine Adverse Event Reporting System (VAERS) from July 1, 2017, through June 30, 2020 (19). Limited safety data were available on the use of RIV4 during pregnancy. Critical safety outcomes reported by these studies included solicited systemic AEs and SAEs. Systemic reactions were transient, mild to moderate in intensity and similar in frequency between RIV4 and comparator vaccines. The SAEs reported across the RCTs were comparable between the study vaccines and were not considered to be vaccine-related by the investigators. Most AEs reported to VAERs were non-serious; 39 out of 849 AEs reports were SAEs reports (19). Data from two RCTs (10,14) conducted among adults aged 50 years and older receiving RIV4, IIV3-HD and IIV4-SD vaccines, were pooled in a meta-analysis and there was no difference in the odds of experiencing a SAE between RIV4 and egg-based vaccine comparators (**Figure A2**).

Overall, there was fair evidence (of moderate certainty) that RIV4 is a safe and well-tolerated alternative to egg-based influenza vaccines, based on data in adults aged 18 years and older.

Discussion

The RIV4 is considered effective, immunogenic and safe in adults 18 years of age and older and has a comparable immunogenicity and safety profile to egg-based and cell-based vaccines already licensed in Canada. The immunogenicity evidence for RIV4 builds on the clinical development program of RIV3, which is a trivalent recombinant influenza vaccine that has been licensed in the US since 2013 (22). Recombinant technology is a vaccine manufacturing process that is considerably different from traditional egg-based production and mammalian cell-culture-based technology. Recombinant technology can allow for faster production times, yields a highly pure product, and mitigates the risk of a mismatch between manufactured vaccines and circulating influenza strains.

There were no factors identified through the EEFA Framework (9) that could contribute to inequity or ethical issues related to the recommendation of RIV4; however, potential perceived risks and unknowns of a new influenza vaccine platform could influence people's acceptance of RIV4. Additionally, barriers that may restrict feasibility include limited manufacturing infrastructure and higher cost of production of recombinant influenza vaccine compared to egg-based vaccines.

Given the novelty of recombinant influenza vaccines, there is sparse peer-reviewed literature on the use of RIV4 in pregnant individuals (23) and in other vulnerable populations; however, available data on the use of RIV3 in pregnant individuals (24) may be used to supplement the safety evidence base of recombinant vaccines as both trivalent and quadrivalent vaccine formulations have the same manufacturing process and overlapping compositions.

Seasonal influenza vaccination remains the best strategy for preventing influenza infection. Efforts to diversify influenza vaccine development, manufacturing and promotion of innovative technologies are critical for reducing and preventing future influenza epidemics and pandemics. Nevertheless, a more robust, comprehensive and consistent body of evidence is needed on influenza recombinant vaccines to further evaluate the effectiveness, efficacy, immunogenicity and safety of RIV4 compared with other seasonal influenza vaccines.

Limitations

There were limited peer-reviewed studies available at the time of the review that evaluated the relative efficacy and effectiveness of RIV4 compared to other injectable influenza vaccines. The study evaluating the rVE against LCI analyses identified in this review was conducted using data from a single influenza season in the US and in adults aged 50 years and older. As influenza seasons vary from year to year, interpretation of the data is limited and further data on multiple influenza seasons, and a wider age range that includes adults aged 18 and older, are needed. Moreover, no studies reporting on vaccine effectiveness against LCI were identified. Additionally, no data on the use of RIV4 in pregnancy were included in this review. A more robust, comprehensive and consistent body of evidence, including data on comorbidities, pregnant individuals, health status and other potential confounders, is needed to evaluate the efficacy, effectiveness, immunogenicity and safety of RIV4 compared to other licensed seasonal influenza vaccines.

NACI recommendation for individual level decision-making

Based on the review of the available evidence summarized above and the assessment of ethics, equity, feasibility and acceptability considerations with the EEFA Framework regarding the use of RIV4 in adults, NACI made the following recommendation, supplementing NACI's overarching recommendation for influenza vaccination, which is available in the NACI Seasonal Influenza Statement (25):

NACI recommends that Supemtek may be considered among the seasonal influenza vaccines offered to adults 18 years of age and older (Discretionary NACI Recommendation)

- **NACI concludes that there is fair evidence to recommend vaccination of adults 18 years of age and older with Supemtek (Grade B Evidence)**

The complete details of this review, rationale, relevant considerations and additional information supporting this recommendation can be found in the *NACI Supplemental Statement – Recombinant Influenza Vaccines* (7).

Conclusion

There is fair evidence that RIV4 is effective, safe and has non-inferior immunogenicity to comparable vaccines, based on direct evidence in adults 18 years of age and older. NACI recommends that RIV4 may be considered among the seasonal influenza vaccines offered to adults 18 years of age and older for their annual influenza vaccination. NACI will continue to monitor the evidence on RIV and update the supplemental statement as needed and as data on the use of RIV4 from several different influenza seasons accumulate.

Authors' statement

AG — Writing, original draft, review, editing
AS — Writing, review, editing
JP — Review, editing

The *NACI Supplemental Statement – Recombinant Influenza Vaccines* was prepared by A Gil, A Sinilaite, M Xi, R Harrison and J Papenburg, on behalf of the NACI Influenza Working Group, and was approved by NACI.

Competing interests

J Papenburg reports grants to his institution from MedImmune, Sanofi Pasteur, Merck and AbbVie, and personal fees from AbbVie, AstraZeneca and Merck, which were all outside of the submitted work.

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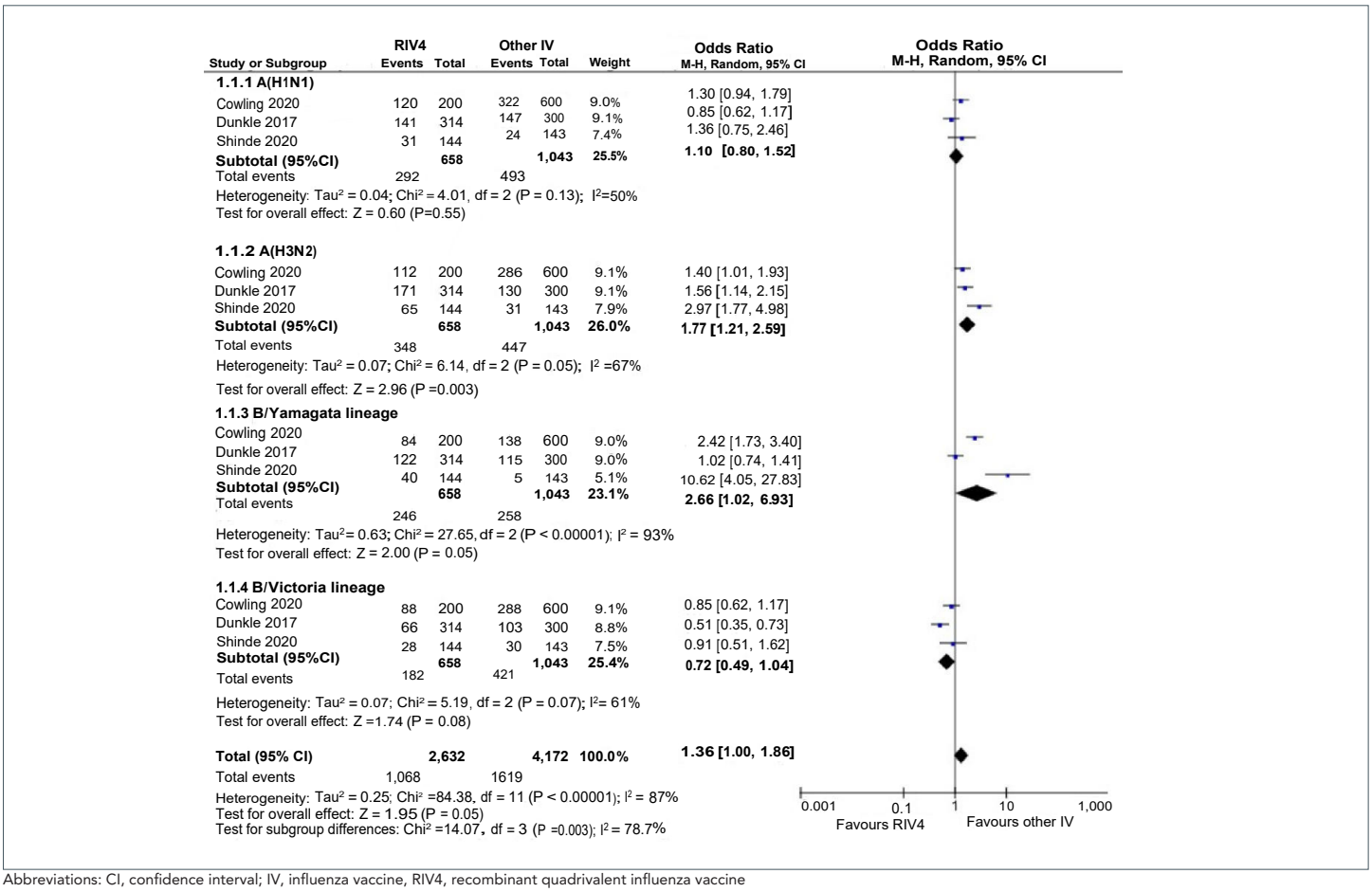
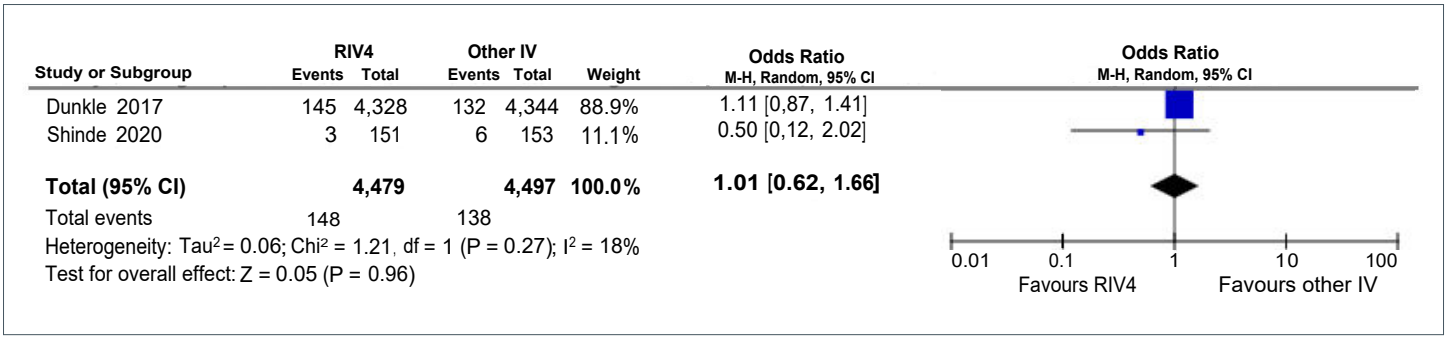
Appendix

Figure A1: Odds of seroconversion on days 28–30 post-vaccination between RIV4 and other seasonal influenza vaccine recipients 50 years and older



Abbreviations: CI, confidence interval; IV, influenza vaccine, RIV4, recombinant quadrivalent influenza vaccine

Figure A2: Odds of experiencing a serious adverse event within 180 days of vaccination between RIV4 and other seasonal influenza vaccine recipients 50 years and older



Abbreviations: CI, confidence interval; IV, influenza vaccine, RIV4, recombinant quadrivalent influenza vaccine

Evaluation of influenza case definitions for use in real-world evidence research

Pamela Doyon-Plourde[1,2], Élise Fortin[1,3], Caroline Quach[1,2,4,5]*

Abstract

Background: Laboratory confirmation of influenza is not routinely done in practice. With the advent of big data, it is tempting to use healthcare administrative databases for influenza vaccine effectiveness studies, which often rely on clinical diagnosis codes. The objective of this article is to compare influenza incidence curves using international case definitions derived from clinical diagnostic codes with influenza surveillance data from the United States (US) Centers for Disease Control and Prevention (CDC).

Methods: This case series describes influenza incidence by CDC week, defined using International Classification of Disease diagnostic codes over four influenza seasons (2015–2016 to 2018–2019) in a cohort of US individuals three years of age and older who consulted at least once per year between 2015 and 2019. Results were compared to the number of influenza-positive specimens or outpatient visits for influenza-like illness obtained from the CDC flu surveillance data.

Results: The incidence curves of influenza-related medical encounters were very similar to the CDC's surveillance data for laboratory-confirmed influenza. Conversely, the number of influenza-like illness encounters was high when influenza viruses started to circulate, leading to a discrepancy with CDC-reported data.

Conclusion: A specific case definition should be prioritized when data for laboratory-confirmed influenza are not available, as a broader case definition would conservatively bias influenza vaccine effectiveness toward the null.

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Keywords: influenza, influenza-like-illness, laboratory-confirmed influenza, real-world data, surveillance

Introduction

Although a vaccine-preventable disease, influenza causes annually approximately three to five million cases of severe illness and 290,000 to 650,000 deaths worldwide (1). Due to the high mutation rate of influenza viruses, vaccine formulations are updated annually, requiring constant surveillance of influenza worldwide. Influenza vaccine effectiveness (IVE) has been studied extensively, producing estimates that vary widely. This can be explained by several factors, including study design and influenza case definition (2).

Evaluation of IVE is commonly conducted using a test-negative design that compares vaccination rates in individuals with a positive test for laboratory-confirmed influenza (LCI) to those with a negative test. This is considered the gold standard for IVE study, but requires proper recruitment into a cohort, which is resource intensive. It may thus be tempting, with the advent of big data, to use healthcare administrative databases for IVE studies. As laboratory confirmation of influenza-like illness (ILI) is not routinely done, one must rely on clinical diagnosis codes as an alternate case definition for real-world evidence research on influenza.

Over the years, several influenza case definitions have been proposed with varying levels of sensitivity and specificity (3). The choice of case definitions depends on several factors such as data sources, study population and the purpose of the surveillance: high sensitivity may be suitable for early detection of disease outbreak whereas higher specificity may be required for vaccine effectiveness studies. International Classification of Diseases (ICD) diagnostic codes specific to influenza are easily retrieved from electronic medical records (EMR); however, EMR data must be able to accurately and comprehensively capture

cases, especially when clinical diagnostic codes are used for identification of influenza.

The study aims to determine if alternate influenza case definitions correlate with standard case definitions used for surveillance, by comparing influenza incidence curves using case definitions derived from clinical diagnostic codes to the United States (US) Centers for Disease Control and Prevention (CDC) flu surveillance data.

Methods

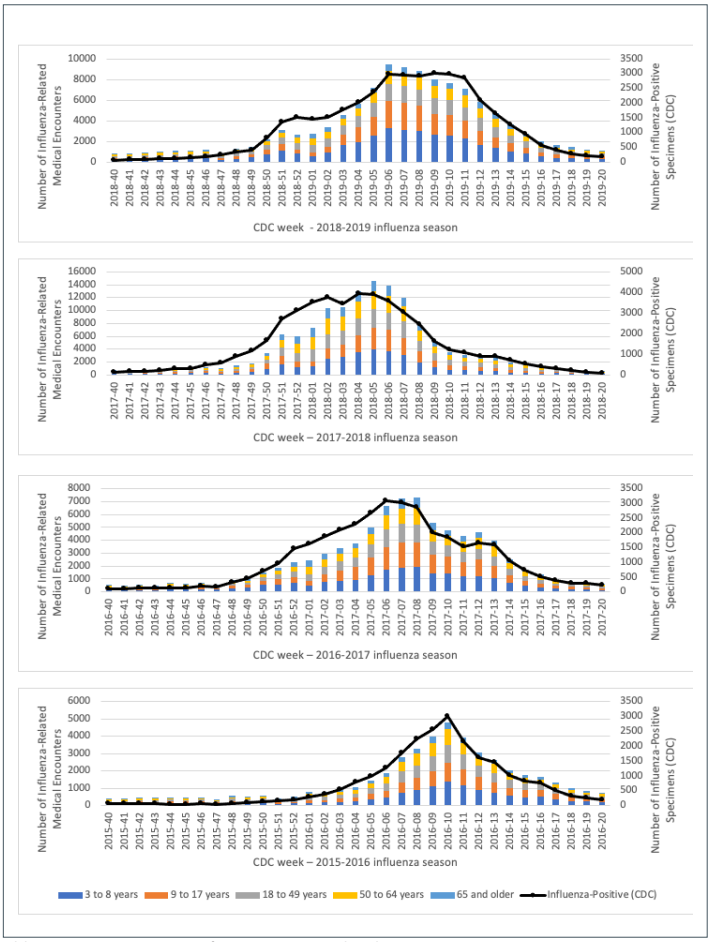
This case series describes influenza incidence by CDC week, defined using ICD diagnostic codes, over four influenza seasons (from 2015–2016 to 2018–2019) in a cohort of US individuals three years of age and older who consulted at least once per year between 2015 and 2019. Study data were derived from an integrated dataset including linked primary care EMRs from Veradigm Health Insights database, supplemented with pharmacy and medical claims data from Komodo Health Inc., New York, New York. Data sources and linkage processes have been described previously (4).

We used the case definitions developed by the US Armed Forces Health Surveillance Center (AFHSC) for specific and sensitive surveillance of influenza (5). The primary outcome was a record of influenza-related medical encounter in a hospital or primary care setting, defined by ICD codes specific to influenza (AFHSC code set B) (5). As the AFHSC code set B definition was developed for specific influenza surveillance, results were compared to the number of influenza-positive specimens from the CDC flu surveillance data (5,6). The secondary outcome was an ILI encounter using a sensitive case definition (AFHSC code set A) (5). Results were compared to the number of outpatient visits for ILI from the CDC flu surveillance data as AFHSC code set A was developed to identify ILI cases (5,6). The incidence date was the date of the first encounter meeting the outcome definition during the influenza seasons (from CDC week 40 to CDC week 20 of the following year). A qualitative analysis of incidence curves was conducted to assess if alternate influenza case definitions derived from clinical diagnostic codes correlated with standard influenza case definitions used by the CDC long-established nationally representative surveillance system (7).

Results

Incidence curves of influenza-related medical encounters derived from ICD codes specific to influenza, using AFHSC code set B, compared to the incidence of influenza-positive specimens reported by the CDC flu surveillance data over four influenza seasons are shown in **Figure 1**. Incidence curves of influenza-related medical encounters were very similar to the CDC's surveillance data for LCI over the four influenza seasons. At the beginning of each season, numbers of influenza-related medical encounters were low and gradually increased, reaching a peak between CDC weeks 05 and 10, as seen with the CDC's surveillance data. Levels then decreased for the remainder of each season, following a pattern similar to the number of influenza-positive specimens.

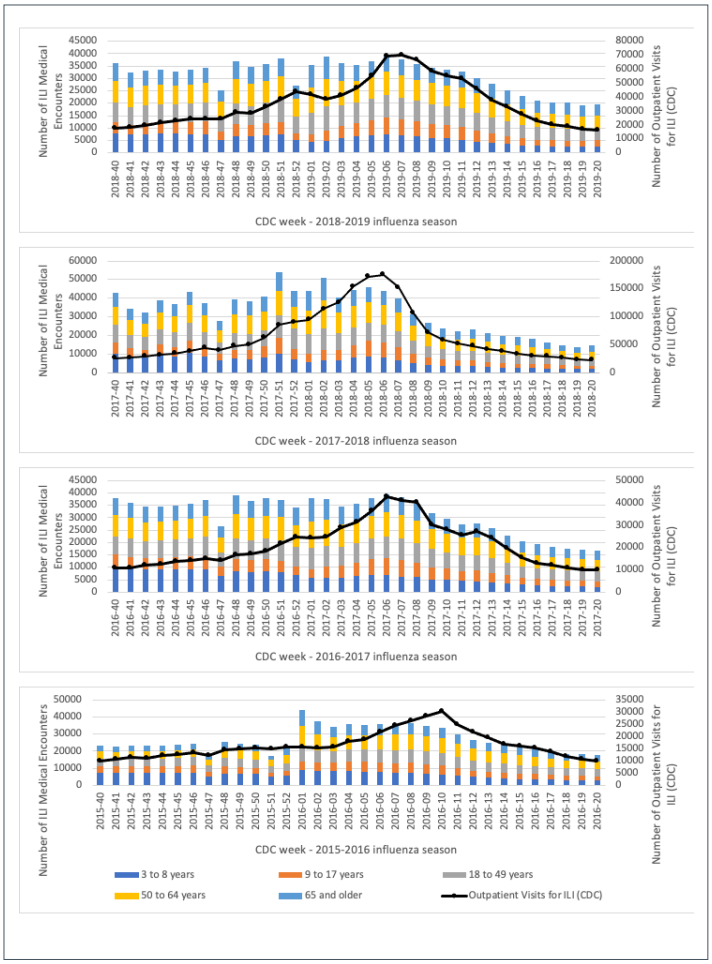
Figure 1: Distribution of influenza-related medical encounters[a] in the study cohort by age groups overlapped with the incidence of influenza-positive specimens reported by public health laboratories over four influenza seasons[b]



Abbreviation: CDC, Centers for Disease Control and Prevention
[a] Specific definition
[b] Influenza surveillance data from the United States CDC

Incidence curves of ILI medical encounters derived from AFHSC code set A case definition for sensitive surveillance, compared to the incidence of outpatient visits for ILI reported by the CDC are shown in **Figure 2**. Incidence curves for ILI encounters did not follow the same pattern as ILI outpatient visits at the national level. Numbers of ILI medical encounters started and remained high over the first half of the season. Conversely, national levels gradually increased until a peak around CDC weeks 05 and 10 is observed, as for LCI reported by the CDC flu surveillance data. Afterward, both curves decreased for the remainder of each season.

Figure 2: Distribution of influenza-like illness medical encounters[a] in the study cohort by age groups overlapped with the national incidence of outpatient visits for influenza-like illness reported by sentinel providers over four influenza seasons[b]



Abbreviations: CDC, Centers for Disease Control and Prevention; ILI, influenza-like illness
[a] Sensitive definition
[b] Reported to the United States CDC

Discussion

We found that incidence curves of the CDC-reported LCI and influenza-related medical encounters obtained from EMRs overlapped well over the four influenza seasons studied (Figure 1); therefore, the AFHSC definition for specific influenza surveillance is a good proxy for LCI, when only clinical diagnostic codes are available to identify influenza-related medical encounters. In contrast, the number of ILI encounters was high when influenza viruses started to circulate, leading to a discrepancy with CDC-reported data for both LCI and outpatient visits for ILI. The case definition for ILI from the AFHSC was broad, and included ICD codes for fever, cough, otitis media, acute nasopharyngitis, acute sinusitis and pneumonia, thus including cases not related to influenza. Conversely, the CDC ILI definition was limited to fever and cough and/or sore throat without a known cause other than influenza (7).

Other studies have investigated the use of clinical diagnostic codes for the identification of influenza cases (3,8). A multicenter validation study found that influenza-specific ICD codes were highly specific to the identification of LCI in children admitted to tertiary care pediatric facilities with 73% of LCI cases being identified by discharge diagnostic code specific to influenza (8). Another validation study found that AFHSC code set B that only used codes with greater than 75% positivity for influenza led to very high specificity (96%) but moderate sensitivity (62%) in identifying LCI (3). Moreover, studies have shown that physicians can accurately diagnose influenza cases on the basis of clinical symptoms alone when the pre-test probability is high, such as when influenza viruses are circulating in the community (9,10). Together, influenza-specific clinical case definition and knowledge of influenza seasonality can lead to accurate identification of influenza infection.

Limitations

The study is limited by its retrospective design and the lack of data on days from symptoms onset; a criteria commonly used in influenza case definition. Thus, previously validated outcome definitions that only required clinical diagnostic codes were used.

Conclusion

Our results suggest that it is more appropriate to use the influenza AFHSC standard case definition for specific surveillance rather than a broad ILI definition, when only clinical diagnostic codes are available for the evaluation of influenza, because its trends are more closely related to CDC-reported data. Although our work was oriented towards surveillance needs, we believe specific case definition should also be prioritized for IVE research when LCI are not available. A broader case definition could conservatively bias IVE towards the null by including cases unrelated to influenza, which cannot be prevented by influenza vaccination. This validation exercise should be repeated now that COVID-19 also cause ILIs.

Authors' statement

PDP — Writing–original draft, writing–review & editing, conceptualization, methodology, investigation, formal analysis, visualization, funding acquisition
EF — Writing–review & editing, conceptualization, methodology, supervision
CQ — Writing–review & editing, conceptualization, methodology, supervision

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Competing interests

None.

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Invasive pneumococcal disease surveillance in Canada, 2020

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Abstract

Background: Invasive pneumococcal disease (IPD), which is caused by *Streptococcus pneumoniae*, has been a nationally notifiable disease in Canada since 2000. The use of conjugate vaccines has markedly decreased the incidence of IPD in Canada; however, the distribution of serotypes has shifted in favour of non-vaccine types. This report summarizes the demographics, serotypes and antimicrobial resistance of IPD infections in Canada in 2020.

Methods: The Public Health Agency of Canada's National Microbiology Laboratory (Winnipeg, Manitoba) collaborates with provincial and territorial public health laboratories to conduct national surveillance of IPD. A total of 2,108 IPD isolates were reported in 2020. Serotyping was performed by Quellung reaction and antimicrobial susceptibilities were determined in collaboration with the University of Manitoba/Canadian Antimicrobial Resistance Alliance. Population-based IPD incidence rates were obtained through the Canadian Notifiable Disease Surveillance System.

Results: Overall incidence of IPD in Canada decreased significantly from 11.5 (95% confidence interval [CI]: 10.1–13.1) to 6.0 (95% CI: 5.0–7.2), and from 10.0 (95% CI: 9.7–10.3) to 5.9 (95% CI: 5.7–6.2) cases per 100,000 from 2019 to 2020; in those younger than five years and those five years and older, respectively. The most common serotypes overall were 4 (11.2%, n=237), 3 (10.9%, n=229) and 8 (7.2%, n=151). From 2016 to 2020, serotypes with increasing trends ($p<0.05$) included 4 (6.4%–11.2%), 3 (9.5%–10.9%), 8 (5.2%–7.2%) and 12F (3.6%–5.7%). The overall prevalence of PCV13 serotypes increased over the same period (30.3%–34.9%, $p<0.05$). Antimicrobial resistance rates in 2020 included 23.0% clarithromycin and 9.9% penicillin (IV meningitis breakpoints). Multidrug-resistant IPD has significantly increased since 2016 (4.2%–9.5%, $p<0.05$).

Conclusion: Though the incidence of IPD decreased in 2020 in comparison to previous years across all age groups, disease due to PCV13 serotypes 3 and 4, as well as non-PCV13 serotypes such as 8 and 12F, increased in prevalence. Continued surveillance of IPD is imperative to monitor shifts in serotype distribution and antimicrobial resistance.

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Introduction

Invasive pneumococcal disease (IPD) causes severe infections such as meningitis and bacteraemia, with children and the elderly being at greatest risk for infection (1). Of the approximately 100 distinct pneumococcal serotypes currently recognized, the majority of disease worldwide is caused by only a few serotypes (1,2). Vaccination has proven effective in reducing the incidence of IPD. A 7-valent pneumococcal conjugate vaccine (PCV7), consisting of serotypes 4, 6B, 9V, 14, 18C, 19F and 23F, was introduced in all Canadian provincial and territorial vaccination programs between 2002 and 2006 (3). Though PCV7 use led to a dramatic decrease in incidence of disease caused by the constituent serotypes (3–5), a subsequent increase in non-PCV7 serotype infections occurred, including serotypes 7F and 19A (3,6). In 2009, a 10-valent pneumococcal conjugate vaccine (PCV10) program (consisting of all PCV7 serotypes plus serotypes 1, 5 and 7F) was implemented in Québec, Ontario, Yukon and Newfoundland and Labrador. The 13-valent pneumococcal conjugate vaccine (PCV13, consisting of all PCV10 serotypes plus serotypes 3, 6A and 19A) was recommended for use in Canada in 2010 and introduced by all provinces and territories during 2010 and 2011, though specific immunization schedules vary by jurisdiction (5,7,8). In 2018, Québec replaced PCV13 with PCV10 for paediatric IPD immunization; subsequently Québec introduced a mixed schedule in late 2020: two doses of PCV10 (two and four months of age); and one dose of PCV13 (one year old). A 23-valent pneumococcal polysaccharide vaccine (PPV23 which includes all PCV13 serotypes except 6A, plus serotypes 2, 8, 9N, 10A, 11A, 12F, 15B/C, 17F, 20, 22F and 33F) has been available for use in Canada since 1989, particularly in older adults and children over two years of age at high risk of IPD (7,9).

Surveillance of the distribution of *Streptococcus pneumoniae* serotypes is important to monitor serotype replacement and inform future vaccine composition. Several higher valency pneumococcal conjugate vaccines (PCVs) are in development. These incorporate emerging serotypes, including PCV15 (consisting of all PCV13 serotypes plus serotypes 22F and 33F) and PCV20 (all PCV15 serotypes plus serotypes 8, 10A, 11A, 12F and 15BC) (10,11). The objective of this annual surveillance report is to provide a summary of the serotypes and antimicrobial resistance associated with IPD in Canada in 2020.

Methods

Surveillance program

Surveillance of IPD in Canada consists of a passive laboratory-based system where all invasive isolates from all provincial/territorial public health laboratories are serotyped by the National Microbiology Laboratory (NML), Winnipeg; the *Laboratoire de santé publique du Québec* (LSPQ); or the Provincial Laboratory for Public Health, Edmonton, Alberta (ProvLab Alberta). In 2019, surveillance of IPD in Québec was expanded to all invasive strains. A total of 2,108 IPD isolates were reported in 2020, including 1,408 submitted to NML by provincial and territorial public health laboratories; as well as data for 426 and 274 IPD isolates serotyped by LSPQ and ProvLab Alberta, respectively (**Table 1**). Sterile clinical isolation sites include blood, cerebrospinal fluid, peritoneal, pericardial or joint fluid, internal body sites and deep tissue including surgical or biopsy samples. Although *S. pneumoniae* isolated from the pleural cavity does not currently meet the national case definition for invasive disease, these isolates are included for the analyses in this report as *S. pneumoniae* isolated from pleural fluid is widely considered as invasive in other jurisdictions (3).

Table 1: Number of invasive *Streptococcus pneumoniae* isolates submitted by province in 2020

Province	Age groups (years)						Not given	Total
	Younger than 2	2–4	5–14	15–49	50–64	65 or older		
British Columbia[a]	2	3	6	88	115	74	1	289
Alberta	7	3	0	115	80	68	1	274
Saskatchewan	3	2	1	41	41	21	2	111
Manitoba	6	3	2	79	48	29	0	167
Ontario	26	13	8	150	229	246	4	676
Québec	38	14	9	71	117	225	1	475[b]
Atlantic[c]	0	0	2	14	21	51	6	94
Northern[d]	0	0	1	9	8	4	0	22
Total	82	38	29	567	659	718	15	2,108

[a] Includes isolates from the Yukon
[b] Québec provincial surveillance program expanded in 2019
[c] Includes isolates from New Brunswick, Prince Edward Island, Nova Scotia and Newfoundland and Labrador
[d] Includes isolates from Northwest Territories and Nunavut

Preliminary population-based incidence of disease data for 2020 were obtained through the Canadian Notifiable Disease Surveillance System (CNDSS). Population data for incidence rates were obtained from Statistics Canada's July 1st annual population estimates.

Isolate testing

All IPD isolates were screened using bile solubility and optochin disc susceptibility (Oxoid) (12). Serotyping of IPD at NML, LSPQ and ProvLab Alberta was performed by the Quellung reaction using pool, group, type and factor commercial antisera (SSI Diagnostica; Statens Serum Institute, Copenhagen, Denmark) (13). Isolates for which a Quellung reaction was not observed were confirmed as *S. pneumoniae* by *rpoB* gene sequencing (14,15). For this study serotypes 15B and 15C were grouped together as 15B/C because of reported reversible switching between them *in vivo* during infection, making it difficult to precisely differentiate between the two types (16,17).

In 2011, the NML began a collaboration with the University of Manitoba/Canadian Antimicrobial Resistance Alliance to provide antimicrobial susceptibility testing for *S. pneumoniae* isolates submitted to NML. All IPD isolates (n=1,022) submitted to NML for serotyping by the provincial public health laboratories of Saskatchewan, Manitoba, Ontario, Québec, Nova Scotia, Prince Edward Island, Newfoundland and Labrador and six of seven health regions in New Brunswick were included in the study. Tested antimicrobials included penicillin, amoxicillin/clavulanate, ceftriaxone, chloramphenicol, clarithromycin, clindamycin, doxycycline, imipenem, meropenem, levofloxacin, trimethoprim/sulfamethoxazole, linezolid and vancomycin. Minimum inhibitory concentrations were determined by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method using 96-well custom designed microtitre plates prepared by Canadian Antimicrobial Resistance Alliance (18). Minimum inhibitory concentration interpretive standards were defined according to CLSI breakpoints (19). Multidrug resistance (MDR) was defined as resistance to three or more classes of antimicrobials. Antimicrobial susceptibility testing results from other laboratories are not included in this report.

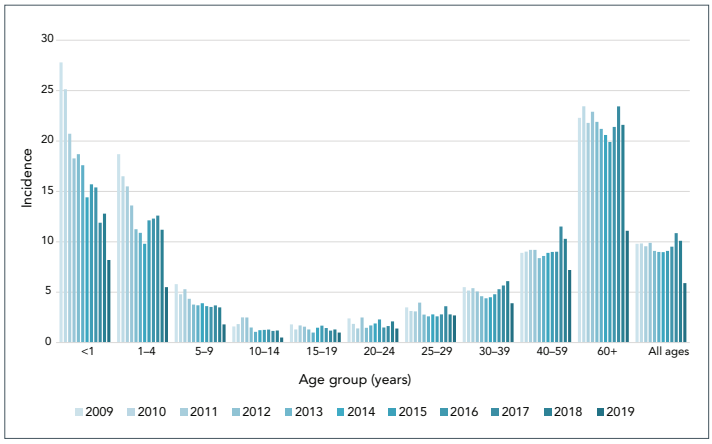
Data analysis

Data submitted with bacterial isolates included patient age, sex, clinical source, province and date of collection. Multiple isolates with the same serotype and collected from the same patient within 14 days were counted once with the most invasive isolation site assigned. Meningitis related isolates were regarded as most invasive, followed by blood and then other sterile sites. The laboratory data were aggregated by age into younger than two, 2–4, 5–14, 15–49 and 50–64 years and 65 years and older age groups and regionally into Western (British Columbia, Alberta, Saskatchewan, Manitoba), Central (Ontario and Québec), Eastern (New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador) and Northern (Yukon Territories, Northwest Territories and Nunavut) regions of Canada. Statistical significance of trends was assessed using the Cochran-Armitage test for trend, with a *p*-value of <0.05 considered significant.

Results

Prior to 2020, the overall IPD incidence rates in Canada have remained stable since 2009. In 2020 the national incidence rate was 5.9 cases per 100,000 population (95% CI: 5.7–6.2); this was a significant decrease compared to 10.1 cases per 100,000 population in 2019 (95% CI: 9.8–10.4) (**Figure 1**; **Supplemental material Table S1**). Though IPD incidence declined across all age groups from 2019 to 2020, the largest absolute decline in incidence was seen in seniors aged 60 years and older. It remained around 20 cases per 100,000 population between 2009 and 2019 but declined from 21.6 cases per 100,000 population in 2019 (95% CI: 20.6–22.6) to 11.1 cases per 100,000 population in 2020 (95% CI: 10.4–11.8).

Figure 1: Annual incidence of invasive pneumococcal disease cases per 100,000 population in Canada by age group, 2010–2020

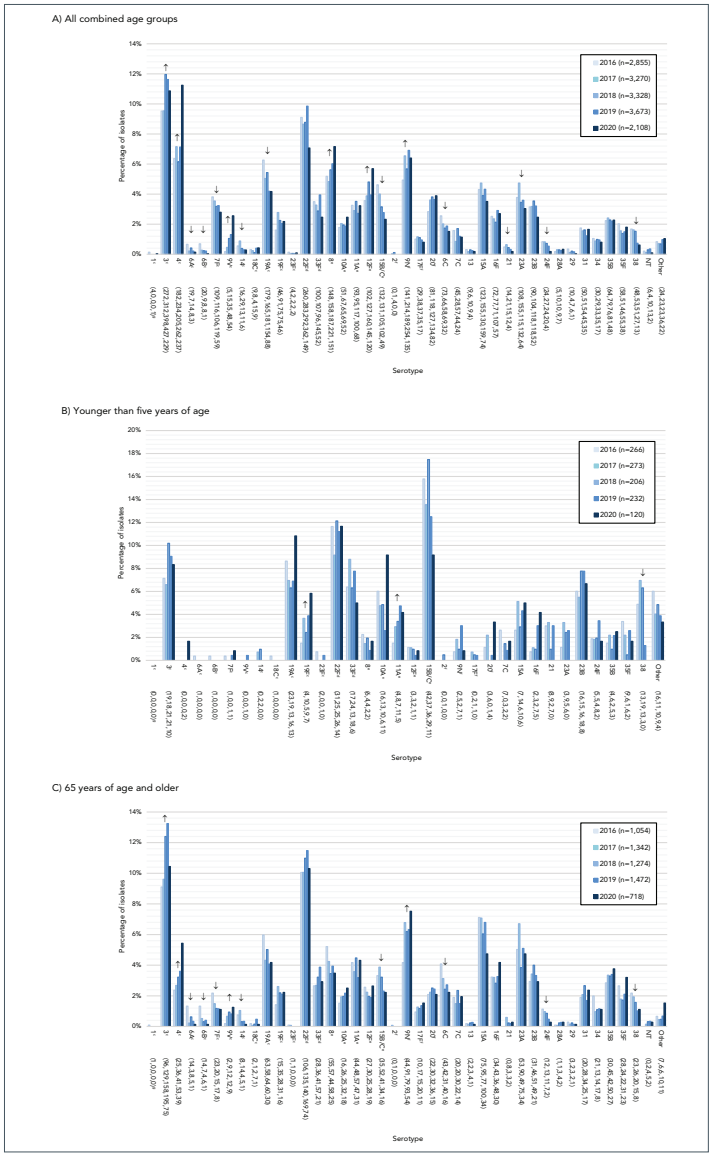


Of the 2,108 IPD isolates serotyped in 2020, 2,098 had patient ages. Infants younger than two years of age accounted for 3.9% (n=82), toddlers aged 2–4 years for 1.8% (n=38), children aged 5–14 years for 1.4% (n=29), adults aged 15–49 years for 26.9% (n=567), older adults aged 50–64 years for 31.3% (n=659) and seniors aged 65 years and older for 34.1% (n=718). Sex information was specified for 2,066 isolates of which 58.2% (n=1,203) were from male patients. Blood was the most frequent clinical isolation site accounting for 92.3% (n=1,945) of all isolates collected in 2020. Additional information on serotypes by specimen source can be found in **Figures S1 to S4**.

The most commonly collected serotypes overall in 2020 were 4 (11.2%, n=237), 3 (10.9%, n=229), 8 (7.2%, n=151),

22F (7.1%, n=149), 9N (6.4%, n=135) and 12F (5.7%, n=120). Serotypes that demonstrated significant increasing trends in prevalence from 2016 to 2020 (**Figure 2**; A) include PCV13 serotypes 4 (6.4%–11.2%, $p<0.001$), 3 (9.5%–10.9%, $p=0.004$) and 9V (0.2%–2.6%, $p<0.001$), as well as PPV23 serotype 9N (4.9%–6.4%, $p=0.02$) and PCV20/PPV23 serotypes 8 (5.2%–7.2%, $p<0.001$) and 12F (3.6%–5.7%, $p=0.002$). Vaccine serotypes that significantly decreased in prevalence from 2016 to 2020 include 6A, 6B, 7F, 14, 15B/C and 19A ($p\leq0.04$).

Figure 2: Invasive *Streptococcus pneumoniae* serotype prevalence trends by age, 2016–2020[a,b]



[a] For serotypes with an overall (2016–2020) N≥30: up or down arrows indicate statistically significant trends toward increasing or decreasing prevalence for the 2016–2020 timespan, using the chi-squared test for trend. Serotypes with no arrow either did not demonstrate a statistically significant trend or did not have an overall N≥30. Trends for more detailed age groups can be found in the Supplemental material as **Figures S5 to S9**

[b] Serotypes 15B and 15C were grouped together as 15B/C because of reported reversible switching between them *in vivo* during infection, making it difficult to precisely differentiate between the two types (16,17)

[c] Component of PCV13

[d] Component of PCV15

[e] Component of PCV20

[f] Component of PPV23

[g] Number of isolates for 2016, 2017, 2018, 2019 and 2020 respectively

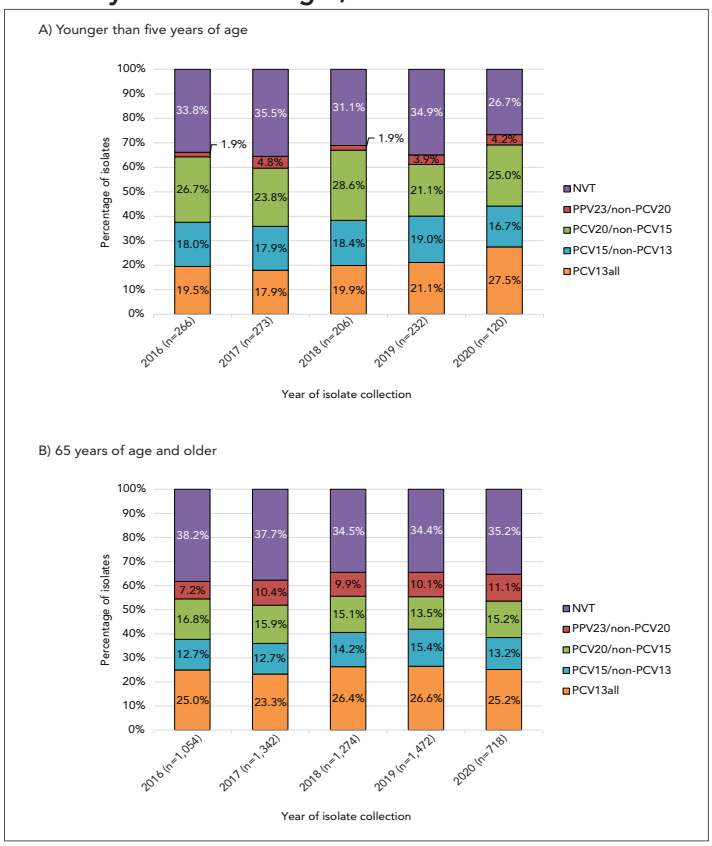
The most common serotypes in children younger than two years of age during 2020 included 19A, 15B/C and 22F, all at 12.2% (n=10), while the most common for children 2–4 years old were serotypes 3 (15.8%, n=6), 10A (13.2%, n=5) and 22F (10.5%, n=4). Serotypes 3 (17.2%, n=5), 8 (13.8%, n=4) and 10A (13.8%, n=4) were the most common in those 5–14 years old. Serotype 4 was the most prevalent serotype in those 15–49 years old (20.8%, n=118) followed by serotypes 8 (11.1%, n=63) and 12F (10.9%, n=62). Serotypes 3 (12.6%, n=83) and 4 (11.4%, n=75) were the most common in those 50–64 years old, while serotypes 3 (10.4%, n=75) and 22F (10.3%, n=74) were dominant in adults over 65 years of age (**Figure S10** and **Figure S11**).

From 2016 to 2020 in children younger than five years of age, significant increases of serotypes 19F (1.5%–5.8%, $p=0.04$) and 11A (1.5–4.2%, $p=0.04$) were observed (Figure 2; B). The proportion of serotype 4 isolates increased significantly in adults 15–49 years of age (14.6%–20.8%, $p<0.05$) (Figure S8) and those 65 years of age and older (2.4%–5.4%, $p<0.001$) (Figure 2; C). Significant increases of serotype 8 were noted for adults 15–49 years (7.6%–11.1%, $p=0.02$) and 50–64 years (4.2%–8.6%, $p<0.001$) (Figure S10 and Figure S11). The 15–49 years of age group saw a significant increase of serotype 12F (6.5%–10.9%, $p=0.02$), while the 65 years and older age group also demonstrated increases of serotypes 3 (9.1%–10.4%, $p=0.007$) and 9N (4.2%–7.5%, $p=0.02$). The PCV13 vaccine serotype 9V increased significantly in all adult age groups ($p\leq0.01$), whereas previously common vaccine serotypes 19A and 7F decreased significantly from 2016 to 2020 in the 50–64 years (7.7%–3.8%, $p<0.001$) and 65 years and older (2.2%–1.1%, $p=0.03$) groups, respectively.

Serotypes prevalent in Western Canada during 2020 included 4 (18.2%, n=153), 12F (9.2%, n=77), 3 (8.6%, n=72) and 8 (8.2%, n=69). In Central regions, serotype 3 continued to be the most prevalent (13.0%, n=150), followed by 22F (8.0%, n=92) and 9N (6.8%, n=78). Serotypes 9N (10.6%, n=10) and 22F (10.6%, n=10) were predominant in Eastern Canada. Northern Canada had very few isolates overall, but 63.6% (n=14) were serotype 4 (**Figures S12 to S16**).

Serotypes belonging to the currently recommended PCV13 formulation have significantly increased in prevalence overall from 2016 to 2020 (30.3%–34.9%, $p=0.0034$). There were no significant changes in prevalence in child age groups (**Figure 3**; A). However an increase from 38.7% to 46.9% was observed in the 15–49 years age group ($p=0.02$). Proportions of PCV15-specific and PCV20-specific serotypes have not significantly changed from 2016 to 2020 among the age groups. The proportion of PPV23 unique serotypes increased in the older than or 65 years age group (7.2%–11.1%, $p=0.02$) (Figure 3; B) and the number of non-vaccine serotypes (NVTs) overall has decreased from 2016 to 2020 (29.9%–23.6%, $p<0.001$) (**Figures S17 to S21** and **Tables S2 to S7**).

Figure 3: Invasive *Streptococcus pneumoniae* serotype trends by vaccine and age[a], 2016–2020



Abbreviation: NVT, non-vaccine serotype

[a] Vaccine serotypes include PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, 23F); PCV15 (all PCV13 plus 22F and 33F); PCV20 (all PCV15 plus 8, 10A, 11A, 12F, 15B/C) and PPV23 (PCV20 serotypes except 6A, plus 2, 9N, 17F, 20); NVT=all serotypes not included in PCV13, PCV15, PCV20 and PPV23. Serotypes 15B and 15C were grouped together as 15B/C because of reported reversible switching between them *in vivo* during infection, making it difficult to precisely differentiate between the two types (16,17). Trends for more detailed age groups can be found in the Supplemental material as Figures S17 to S21 and Tables S2 to S7

Antimicrobial susceptibility testing was performed on 1,022 *S. pneumoniae* isolates collected in 2020 (**Table 2, Figure S22**). The highest rate of resistance during 2020 was observed for clarithromycin at 23.0% (n=235); a decrease from 25.0% (n=453) reported in 2019, though the decrease from 2016 to 2020 was not statistically significant. Penicillin resistance decreased over the 2016 to 2020 timespan, from 12.2% (n=136) to 9.9% (n=101) (p=0.003). Other antimicrobial resistance rates for 2020 included doxycycline at 11.4% (n=117), trimethoprim-sulfamethoxazole at 11.1% (n=113), clindamycin at 7.0% (n=72) and chloramphenicol at 4.1% (n=42). All isolates were susceptible to linezolid and vancomycin. Resistance rates for specific serotypes in 2020 are listed in **Table 3**.

Multidrug resistant IPD increased from 4.2% (n=47) of the isolates tested in 2016 to 9.5% (n=97) in 2020 (p<0.001) (**Figure 4, Table S8**). Of the serotypes where 10 or more isolates were collected in 2020, the highest rates of MDR were identified in 15A (66.7%, n=18), 19A (34.3%, n=12), 19F (27.3%, n=6) and 12F (25.9%, n=14) (Table 3, **Figure S23**). The most common MDR pattern for serotypes 15A and 19F was macrolide-clindamycin-tetracycline (n=16 and n=13, respectively). Multidrug resistant serotype 19A isolates were most commonly resistant to five antimicrobial classes (β-lactam, macrolide, clindamycin, tetracycline and trimethoprim/sulfamethoxazole; n=9), while the most common MDR pattern for serotype 12F was tetracycline-trimethoprim/sulfamethoxazole-chloramphenicol (n=13) (**Table S9**).

Table 2: Proportion of antimicrobial resistant[a] invasive *Streptococcus pneumoniae* isolates by year, 2016–2020

Antimicrobial	Year									
	2016		2017		2018		2019		2020	
	%	n	%	n	%	n	%	n	%	n
AMC	0.1%	1	0.4%	5	1.2%	22	0.4%	7	1.4%	14
PEN	12.2%	136	15.0%	169	11.2%	199	10.7%	194	9.9%	101
AXO	0.4%	4	0.7%	8	0.7%	13	0.2%	4	0.4%	4
IMI	0.3%	3	1.3%	15	1.4%	25	0.2%	4	1.2%	12
MER	0.7%	8	1.6%	18	2.0%	36	0.9%	17	2.0%	20
LEV	0.3%	3	0.4%	5	0.3%	5	0.6%	10	0.1%	1
CLA	21.5%	240	25.8%	291	25.9%	462	25.0%	453	23.0%	235
CLI	4.2%	47	7.9%	89	6.8%	122	7.3%	133	7.0%	72
CHL	1.2%	13	2.0%	23	5.6%	100	3.1%	57	4.1%	42
DOX	8.5%	95	10.7%	121	8.5%	151	10.5%	191	11.4%	117
SXT	8.8%	98	10.6%	120	7.7%	137	9.5%	172	11.1%	113
Total tested	-	1,114	-	1,130	-	1,784	-	1,815	-	1,022

Abbreviations: AMC, amoxicillin/clavulanic acid; AXO, ceftriaxone using the parenteral meningitis interpretive standard; CHL, chloramphenicol; CLA, clarithromycin; CLI, clindamycin; DOX, doxycycline; IMI, imipenem; LEV, levofloxacin; MER, meropenem; PEN, penicillin using the parenteral meningitis CLSI interpretive standard; SXT, trimethoprim/sulfamethoxazole; -, not applicable

[a] All isolates were susceptible to linezolid and vancomycin

Table 3: Percentage of antimicrobial resistance and multidrug resistance of invasive *Streptococcus pneumoniae* serotypes collected in 2020

Serotype	Percent resistance[a]										
	PEN	AXO	IMI	MER	LEV	CLA	CLI	CHL	DOX	SXT	MDR
3[b] (n=112)	-	-	-	-	-	8.9	3.6	8.9	10.7	3.6	3.6
4[b] (n=133)	0.8	-	-	-	-	14.3	10.5	10.5	13.5	0.75	11.3
6A[b] (n=2)	100	-	-	-	-	100	-	-	-	-	-
7F[b] (n=24)	-	-	-	-	-	-	-	-	-	-	-
9V[b] (n=7)	14.3	-	-	-	-	14.3	-	-	14.3	14.3	14.3
14[b] (n=5)	60.0	-	20.0	20.0	-	100	80.0	20.0	20.0	80.0	80.0
18C[b] (n=9)	11.1	-	-	-	-	11.1	-	-	11.1	11.1	11.1
19A[b] (n=35)	37.1	5.7	25.7	28.6	-	60.0	31.4	-	34.3	34.3	34.3
19F[b] (n=22)	18.2	4.5	4.5	9.1	-	27.3	22.7	-	27.3	13.6	27.3
23F[b] (n=1)	-	-	-	-	-	-	-	-	-	-	-
22F[c] (n=64)	1.6	1.6	1.6	1.6	-	50.0	3.1	1.6	4.7	6.3	4.7
33F[c] (n=32)	-	-	-	-	-	84.4	6.3	-	9.4	71.9	6.3
8[d] (n=85)	1.2	-	-	-	-	-	-	-	-	1.2	-
10A[d] (n=22)	-	-	-	-	-	22.7	-	-	-	-	-
11A[d] (n=33)	6.1	-	-	-	-	39.4	3.0	-	3.0	9.1	3.0
12F[d] (n=54)	1.9	-	-	-	-	51.9	1.9	25.9	35.2	35.2	25.9
15B/C[d,e] (n=27)	3.7	-	-	-	-	14.8	-	-	3.7	3.7	-
9N[f] (n=71)	2.8	-	-	-	-	2.8	1.4	-	4.2	2.8	2.8
17F[f] (n=10)	-	-	-	-	-	-	-	-	-	-	-
20[f] (n=45)	-	-	-	-	-	4.4	2.2	-	6.7	6.7	2.2
6C (n=16)	12.5	-	-	-	-	25.0	-	-	-	18.8	-
7C (n=14)	7.1	-	-	-	-	-	-	7.1	7.1	57.1	7.1
9A (n=2)	-	-	-	-	-	-	-	-	-	-	-
9L (n=1)	-	-	-	-	-	-	-	-	-	-	-
10B (n=1)	-	-	-	-	-	-	-	-	-	-	-
13 (n=3)	-	-	-	-	-	100	33.3	-	66.7	66.7	66.7
15A (n=27)	74.1	-	-	3.7	-	77.8	66.7	-	77.8	3.7	66.7
16F (n=25)	-	-	-	-	-	-	-	-	-	-	-
21 (n=2)	-	-	-	-	-	-	-	-	-	-	-
23A (n=28)	42.9	-	-	-	-	32.1	17.9	-	17.9	3.6	14.3
23B (n=21)	57.1	-	-	-	-	-	-	-	-	14.3	-
24F (n=1)	-	-	-	-	-	-	-	-	-	100	-
28A (n=4)	-	-	-	-	-	-	-	25.0	25.0	-	-
29 (n=1)	-	-	-	-	-	-	-	-	-	-	-
31 (n=19)	5.3	-	-	-	-	10.5	5.3	-	-	-	-
34 (n=12)	-	-	-	-	-	8.3	8.3	-	8.3	41.7	8.3
35B (n=28)	64.3	-	-	17.9	3.6	53.6	-	-	3.6	17.9	14.3
35D (n=2)	50	-	-	-	-	50	-	-	-	50	-
35F (n=15)	-	-	-	-	-	-	-	-	-	-	-
38 (n=5)	-	-	-	-	-	-	-	-	-	-	-
45 (n=1)	100	-	-	-	-	100	-	-	100	100	100
NT (n=1)	-	-	-	-	-	-	-	-	-	-	-
All (n=1,022)	9.9	0.4	1.2	2.0	0.1	23.0	7.0	4.1	11.4	11.1	9.5

Abbreviations: AXO, ceftriaxone using the parenteral meningitis interpretive standard; CHL, chloramphenicol; CLA, clarithromycin; CLI, clindamycin; DOX, doxycycline; IMI, imipenem; LEV, levofloxacin; MER, meropenem; PEN, penicillin using the parenteral meningitis CLSI interpretive standard; SXT, trimethoprim/sulfamethoxazole

[a] "-" denotes no resistance (0%) to the antimicrobial

[b] Component of PCV13

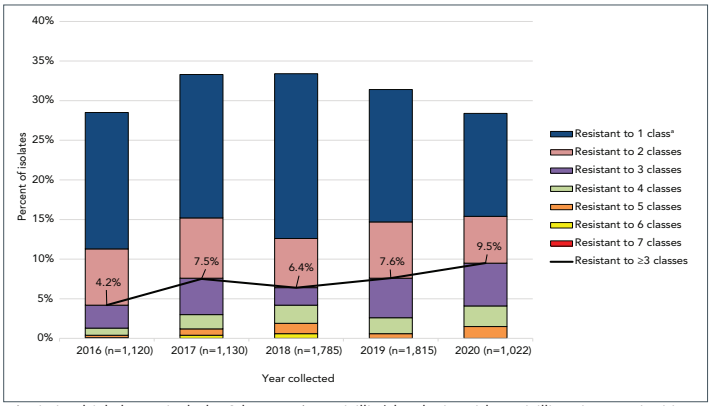
[c] Component of PCV15

[d] Component of PCV20

[e] Serotypes 15B and 15C were grouped together as 15B/C because of reported reversible switching between them *in vivo* during infection, making it difficult to precisely differentiate between the two types (16,17)

[f] Component of PPV23

Figure 4: Annual trend of multidrug resistance of invasive *Streptococcus pneumoniae*, 2016–2020



[a] Antimicrobial classes include: β-lactams (amoxicillin/clavulanic acid, penicillin using meningitis breakpoints, ceftriaxone using meningitis breakpoints, imipenem and meropenem); macrolides (clarithromycin); fluoroquinolones (levofloxacin); tetracyclines (doxycycline); folate pathway inhibitors (trimethoprim-sulfamethoxazole); phenicols (chloramphenicol); lincosamides (clindamycin); oxazolidinones (linezolid)

Discussion

In 2020, the national incidence rate of IPD in Canada was 5.9 cases per 100,000 population; this was a dramatic decrease in the incidence of IPD in comparison with previous years. After the first case of coronavirus disease 2019 (COVID-19) was recorded in Canada in late January 2020, the first national intervention strategies to prevent the spread of the virus were announced in March/April 2020, including border closures, isolation requirements, masking and work-from-home recommendations. Closures of schools, non-essential businesses and recreational activities followed at the discretion of provincial and territorial governments (20). Like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), *S. pneumoniae* is transmitted via respiratory droplets; the same measures put in place to prevent the spread of COVID-19 likely also prevented significant transmission of *S. pneumoniae*, possibly accounting for the reduction of IPD cases. The Invasive Respiratory Infection Surveillance Initiative studied the incidence of respiratory-transmitted pathogens associated with invasive disease in the early months of the COVID-19 pandemic; 26 countries submitted data for IPD (21). The study noted that there was a marked decrease in IPD among all participating countries due to containment measures, though the stringency of said measures varied by country. The Invasive Respiratory Infection Surveillance Initiative also estimated that social changes caused by the pandemic resulted in an initial 38% decrease in the incidence of IPD, followed by an additional 13% average weekly reduction up to the end of May 2020 when the study concluded (21). Canada has gone through periods of both increased mobility and restrictive containment measures due to the various pandemic waves; therefore, it is expected that decreased IPD incidence will continue in the near future.

The PCV13 serotypes 3 and 4 continued to be significant sources of IPD in Canada during 2020. Serotype 3 was the second most common serotype collected in 2020 and continued to be a substantial cause of IPD in all age groups. Studies have noted poor immunogenicity of PCV13 against serotype 3, possibly due to the abundant capsule polysaccharide produced during growth that ultimately overwhelms any PCV13-generated protective response (22,23). Early immunogenicity studies of the PCV15 formulation have noted a superior immune response to serotype 3 in comparison to PCV13, though it is currently unclear if this will translate to increased clinical effectiveness (24). Some real-world effectiveness data should be available in the near future; as of late 2021, the United States Advisory Committee on Immunization Practices now recommends using PCV15 (or PCV20) in PCV-naive adults 65 years or older, or older than 18 years with certain underlying conditions (25). If PCV15 is administered, the Advisory Committee on Immunization Practices recommends that it be followed by PPSV23 (25).

PCV13 serotype 4 overtook serotype 3 as the most predominant IPD serotype in 2020. Serotype 4 has been associated with IPD outbreaks in vulnerable groups of adults and is regionally biased in Western regions of Canada. A study of serotype 4 associated with shipyard outbreaks in Northern Europe found an emergent sequence type (ST801) to be responsible for disease across different countries, though there was significant diversity (26). Another study of serotype 4 in Alberta, Canada observed that this serotype was overrepresented in adults experiencing homelessness and those using illicit drugs. This study also noted genetic diversity within serotype 4, including an emergent sequence type (ST244) associated with the outbreak (27). Similarly, ST244 was found to be responsible for outbreaks of serotype 4 IPD in adults experiencing homelessness in the United States (28). Few serotype 4 isolates were identified in paediatric age groups (n=2) in 2020, where there is also wide uptake of PCV13 (29). According to the 2019 childhood National Immunization Coverage Survey, uptake for pneumococcal conjugate vaccines was 84.4% among those younger than two years of age (29).

Despite the COVID-19 pandemic topping the list of health crises in 2020, antimicrobial resistant pathogens still remain an imminent threat and a significant source of morbidity and mortality worldwide. In general, our surveillance of IPD isolates collected in 2020 noted relatively low rates of antimicrobial resistance. The only resistance rate of concern was that for clarithromycin (23.0%), which has been relatively stable since 2016. Of note is the decrease in penicillin resistance during the same period, which can be speculatively attributed to the PCV13-driven decrease in the overall prevalence of high penicillin-resistant and MDR serotype 19A, a finding observed in other countries such as Portugal (30). In contrast, serotype 19F has been included in all PCV formulations to date. However it has been increasing in prevalence in children younger than five years

of age since 2016 (5.8% of isolates in 2020). This will be crucial to monitor going forward, as a steady increase of a common MDR serotype could have a significant impact on patient outcomes in the future.

Strengths and limitations

Caution should be exercised when interpreting the data presented in this report. Only a subset of laboratory isolates from each province may have been submitted for testing; therefore, this report does not reflect the true incidence or rates of disease in Canada. The representativeness of the proportions of isolates submitted to the NML for testing as compared to information submitted to CNDSS are presented in **Table S10**. Not all provinces and territories report line list data to CNDSS; therefore, only aggregated data were available at the national level. For this reason, CNDSS and NML laboratory data are presented differently in terms of age grouping. Age groups are consistent with literature and current immunization recommendations.

Conclusion

Although the incidence of IPD in Canada decreased significantly in 2020, likely in part due to the intervention strategies used to contain the SARS-CoV-2 virus, several PCV13 vaccine serotypes have increased in prevalence: serotypes 3 and 4 in adult age groups, and 19F in children younger than five years of age. Continued surveillance of IPD serotypes and antimicrobial resistance in Canada is important to monitor existing trends, identify new trends, and assess the effect of the COVID-19 pandemic on the pneumococcal serotype distribution in Canada.

Authors' statement

ARG — Formal analysis, data curation, visualization, writing–original draft, review and editing of final version
AG — Formal analysis, validation, investigation, data curation, visualization, writing–review and editing
WHBD — Formal analysis, validation, investigation, data curation, visualization, writing–review and editing
BL — Resources, methodology, writing–review and editing
AM — Resources, methodology, writing–review and editing
GJT — Resources, methodology, writing–review and editing
GGZ — Resources, methodology, writing–review and editing
JVK — Resources, methodology, writing–review and editing
LH — Resources, methodology, writing–review and editing
JM — Resources, methodology, writing–review and editing
PVC — Resources, methodology, writing–review and editing
HS — Resources, methodology, writing–review and editing
DH — Resources, methodology, writing–review and editing
GZ — Resources, methodology, writing–review and editing
KM — Resources, methodology, writing–review and editing
LS — Resources, methodology, writing–review and editing
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MRM — Methodology, writing–review and editing
IM — Conceptualization, validation, methodology, supervision, project administration, writing–review and editing

Competing interests

None.

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Supplementary material

These documents can be accessed on the Supplemental material file.

Table S1: Annual incidence of invasive pneumococcal disease cases per 100,000 population in Canada by age group, 2010–2020
Figure S1: Clinical isolation site of invasive *Streptococcus pneumoniae* isolates collected in 2020, by age
Figure S2: Percentage of invasive *Streptococcus pneumoniae* isolates from blood in 2020, by serotype
Figure S3: Percentage of invasive *Streptococcus pneumoniae* isolates from cerebrospinal fluid in 2020, by serotype
Figure S4: Percentage of invasive *Streptococcus pneumoniae* isolates from other sterile sites in 2020, by serotype
Figure S5: Prevalence of invasive *Streptococcus pneumoniae* serotypes in those younger than two years old, 2016–2020
Figure S6: Prevalence of invasive *Streptococcus pneumoniae* serotypes in those 2–4 years old, 2016–2020
Figure S7: Prevalence of invasive *Streptococcus pneumoniae* serotypes in those 5–14 years old, 2016–2020
Figure S8: Prevalence of invasive *Streptococcus pneumoniae* serotypes in those 15–49 years old, 2016–2020
Figure S9: Prevalence of invasive *Streptococcus pneumoniae* serotypes in those 50–64 years old, 2016–2020
Figure S10: Prevalence of invasive *Streptococcus pneumoniae* serotypes isolated in 2020 for those younger than two, 2–4 and 5–14 years old
Figure S11: Prevalence of invasive *Streptococcus pneumoniae* serotypes isolated in 2020 for those 15–49 and 50–64 years and 65 years and older
Figure S12: Number of invasive *Streptococcus pneumoniae* isolates collected in 2020, by region and serotype

Figure S13: Prevalence of the ten most common invasive *Streptococcus pneumoniae* serotypes collected from Western Canada in 2020
Figure S14: Prevalence of the ten most common invasive *Streptococcus pneumoniae* serotypes collected from Central Canada in 2020
Figure S15: Prevalence of the ten most common invasive *Streptococcus pneumoniae* serotypes collected from Eastern Canada in 2020
Figure S16: Prevalence of invasive *Streptococcus pneumoniae* serotypes collected from Northern Canada, 2020
Figure S17: Proportion of invasive pneumococcal disease isolates by vaccine for those younger than two years old, 2016–2020
Figure S18: Proportion of invasive pneumococcal disease isolates by vaccine for those 2–4 years old, 2016–2020
Figure S19: Proportion of invasive pneumococcal disease isolates by vaccine for those 5–14 years old, 2016–2020
Figure S20: Proportion of invasive pneumococcal disease isolates by vaccine for those 15–49 years old, 2016–2020
Figure S21: Proportion of invasive pneumococcal disease isolates by vaccine for those 50–64 years old, 2016–2020
Table S2: Proportion of vaccine serotypes for those younger than two years old, 2016–2020
Table S3: Proportion of vaccine serotypes for those 2–4 years old, 2016–2020
Table S4: Proportion of vaccine serotypes for those 5–14 years old, 2016–2020
Table S5: Proportion of vaccine serotypes for those 15–49 years old, 2016–2020
Table S6: Proportion of vaccine serotypes for those 50–64 years old, 2016–2020
Table S7: Proportion of vaccine serotypes for those 65 years and older, 2016–2020
Figure S22: Antimicrobial resistance trends of invasive *Streptococcus pneumoniae* isolates, 2016–2020
Figure S23: Invasive *Streptococcus pneumoniae* serotypes by resistance to different antimicrobial classes, 2020
Table S8: Multidrug resistance of invasive *Streptococcus pneumoniae* isolates, 2016–2020
Table S9: Multidrug resistance profiles of invasive *Streptococcus pneumoniae* serotypes in 2020
Table S10: Number of invasive *Streptococcus pneumoniae* isolates serotyped by the National Microbiology Laboratory (NML) in comparison to the total number of cases reported to Canadian Notifiable Diseases Surveillance System (CNDSS), 2020

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Invasive group A streptococcal disease surveillance in Canada, 2020

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Abstract

Background: Invasive group A streptococcal (iGAS) disease (caused by *Streptococcus pyogenes*) has been a nationally notifiable disease in Canada since 2000. This report summarizes the demographics, *emm* types and antimicrobial resistance of iGAS infections in Canada in 2020.

Methods: The Public Health Agency of Canada's National Microbiology Laboratory (Winnipeg, Manitoba) collaborates with provincial and territorial public health laboratories to conduct national surveillance of invasive *S. pyogenes*. *Emm* typing was performed on all isolates using the Centers for Disease Control and Prevention *emm* sequencing protocol. Antimicrobial susceptibilities were determined using Kirby-Bauer disk diffusion according to Clinical and Laboratory Standards Institute guidelines. Population-based iGAS disease incidence rates up to 2019 were obtained through the Canadian Notifiable Disease Surveillance System.

Results: Overall, the incidence of iGAS disease in Canada has increased from 4.0 to 8.1 cases per 100,000 population from 2009 to 2019. The 2019 incidence represents a slight decrease from the 2018 rate of 8.6 cases per 100,000 population. A total of 2,867 invasive *S. pyogenes* isolates that were collected during 2020 are included in this report, representing a decrease from 2019 (n=3,194). The most common *emm* types in 2020 were *emm*49 (16.8%, n=483) and *emm*76 (15.0%, n=429), both increasing significantly in prevalence since 2016 ($p<0.001$). The former most prevalent type, *emm*1, decreased to 7.6% (n=217) in 2020 from 15.4% (n=325) in 2016. Antimicrobial resistance rates in 2020 included 11.5% resistance to erythromycin, 3.2% resistance to clindamycin and 1.6% nonsusceptibility to chloramphenicol.

Conclusion: Though the number of collected invasive *S. pyogenes* isolates decreased slightly in 2020 in comparison to previous years, iGAS disease remains an important public health concern. The *emm* distribution in Canada has been subtly shifting over the past five years, away from common and well-known *emm*1 and towards *emm*49 and *emm*76. It is important to continue surveillance of *S. pyogenes* in Canada to monitor expanding replacement *emm* types, as well as outbreak clones and antimicrobial resistance.

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Introduction

Invasive group A Streptococcus (*Streptococcus pyogenes*) is responsible for a wide range of human diseases, the most serious of which include bacteraemia, streptococcal toxic shock syndrome, necrotizing fasciitis and endocarditis (1). In Canada, the incidence of invasive group A streptococcal (iGAS) infections is increasing; doubling from 4.0 cases per 100,000 population in 2009 to 8.1 cases per 100,000 in 2019 (2). Though iGAS disease is a global cause of morbidity and mortality (3), many studies have indicated that certain populations are at particular risk of disease, including those who are disadvantaged or living in overcrowded conditions (4,5).

The M protein, encoded by the *emm* gene, is an important virulence factor and an epidemiological marker used to characterize *S. pyogenes* isolates (1). A significant amount of iGAS disease is caused by a small number of *emm* types; however, shifts in prevalence can cause substantial temporal and geographic variability. Studies have noted frequent fluctuations in *emm* type prevalence in so-called "epidemic behaviour", where new, emerging strains ultimately replace those previously circulating (1,6). Furthermore, the accumulation of mutations through acquisition of exogenous DNA may result in more virulent clones expanding in prevalence or causing new outbreaks of disease in vulnerable populations (6).

As rapid clonal spread and outbreaks of iGAS disease continue to occur in Canada (4–6), it has become increasingly important to monitor the constantly shifting virulence patterns associated with this organism. This report provides a summary of invasive *S. pyogenes* isolates collected in Canada in 2020.

Methods

Surveillance program

Surveillance of iGAS infections in Canada consists of a passive, laboratory-based system where invasive *S. pyogenes* isolates from all provincial and territorial public health laboratories (except Alberta) are sent to the National Microbiology Laboratory (NML) in Winnipeg for further testing. A total of 2,867 invasive *S. pyogenes* isolates were reported in 2020, including 1) 2,409 isolates submitted directly to NML by provincial and territorial public health laboratories and 2) data for a further 458 isolates collected and tested by the Provincial Laboratory for Public Health in Edmonton, Alberta (ProvLab Alberta) (**Table 1**). Isolates are collected from sterile clinical isolation sites, which include blood, cerebrospinal fluid, deep tissue, biopsy and surgical samples, bone and any clinical sources associated with necrotizing fasciitis or toxic shock syndrome.

Population-based incidence of iGAS disease up to 2019 was obtained through Canadian Notifiable Disease Surveillance System (CNDSS). Population data for incidence rates were obtained from Statistics Canada's July 1st annual population estimates.

Isolate testing

Streptococcus pyogenes isolates were confirmed by a positive PYR (pyrrolidonyl-β-naphthylamide) reaction and susceptibility to bacitracin (7). *Emm* typing was performed on all iGAS isolates submitted to NML and ProvLab Alberta using the Centers for Disease Control and Prevention (CDC) *emm* sequencing protocol. The sequences obtained were compared with the CDC *emm* database and results reported to the subtype level.

Table 1: Number of invasive *Streptococcus pyogenes* isolates collected by each Canadian province/region, 2020

Province	Age group (years)						Not given	Total
	Younger than 2	2–4	5–14	15–49	50–64	65 and older		
British Columbia	2	1	4	159	104	67	1	338
Alberta	16	3	9	248	121	61	0	458
Saskatchewan	13	2	3	168	58	28	0	272
Manitoba	12	10	4	114	70	58	0	268
Ontario	10	6	18	458	274	294	3	1,063
Quebec	12	7	8	143	74	101	0	345
New Brunswick	2	0	3	25	14	8	1	53
Atlantic[a]	2	1	5	48	25	17	1	99
Northern[b]	0	1	0	11	11	1	0	24
Total	67	31	51	1,349	737	627	5	2,867

[a] Includes isolates from New Brunswick, Prince Edward Island, Nova Scotia and Newfoundland and Labrador
[b] Includes isolates from Yukon, Northwest Territories and Nunavut

Antimicrobial susceptibilities for *S. pyogenes* (n=2,375) were determined using Kirby-Bauer disk diffusion for chloramphenicol (30 µg), erythromycin (15 µg), clindamycin (2 µg), penicillin (10 µg), ceftriaxone (30 µg) and vancomycin (30 µg) according to Clinical and Laboratory Standards Institute (CLSI) guidelines (8).

Supplementary testing was performed on a subset of *emm*1 isolates to determine the prevalence of the novel $M1_{UK}$ lineage. Genotypes for $M1_{UK}$ isolates were determined by mapping whole genome sequencing reads against reference strain MGAS5005 and identifying 27 characteristic genomic single-nucleotide variants (SNVs), as previously described (9,10).

Data analysis

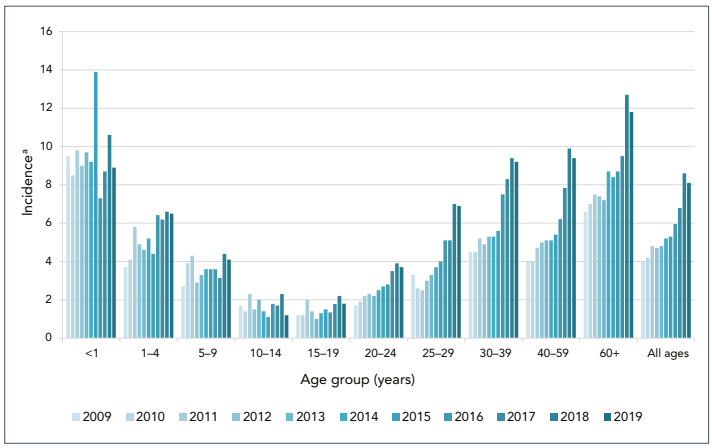
Data submitted with bacterial isolates included patient age, sex, clinical source, province and date of collection. Multiple isolates with the same *emm* type and collected from the same patient within 14 days were counted once with the most invasive isolation site assigned. Meningitis-related isolates were regarded as most invasive, followed by blood and then other sterile sites. The laboratory data were aggregated by age into younger than two, 2–4, 5–14, 15–49, 50–64 and 65 years and older age groups, and regionally into Western (British Columbia, Alberta, Saskatchewan, Manitoba), Central (Ontario and Québec), Eastern (New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador) and Northern (Yukon Territories, Northwest Territories and Nunavut) regions of Canada. Statistical significance of trends was assessed using the Cochran Armitage test of trend, with a *p*-value of <0.05 considered significant.

Results

The overall incidence of iGAS disease in Canada decreased slightly in 2019 after successive annual increases from 2009 to 2018. The overall incidence rate in 2019 was 8.1 cases per 100,000 population—twice the rate observed in 2009 (**Figure 1, Supplemental material Table S1**). In 2020, 2,867 isolates of invasive *S. pyogenes* were collected, representing a decrease from 2019 (n=3,194).

Of the 2,867 invasive *S. pyogenes* isolates tested in 2020, 2,862 (99.8%) had patient ages. Infants younger than two years of age accounted for 1.7% (n=67), toddlers aged 2–4 years for 1.1% (n=31), children aged 5–14 years for 1.8% (n=51), teens/adults aged 15–49 years for 47.1% (n=1,349), adults aged 50–64 years for 25.7% (n=737) and seniors aged 65 years and older for 21.9% (n=627). Five isolates had no ages provided. Isolates from male patients represented 58.1% (n=1,635) of the isolates for which sex information was available. Blood was the main clinical isolation site, accounting for 67.9% (n=1,947) of isolates collected. Additional information on *emm* types by specimen source can be found in **Figures S1 to S5**.

Figure 1: Annual incidence rates of invasive *Streptococcus pyogenes* cases in Canada by age group, 2010–2019

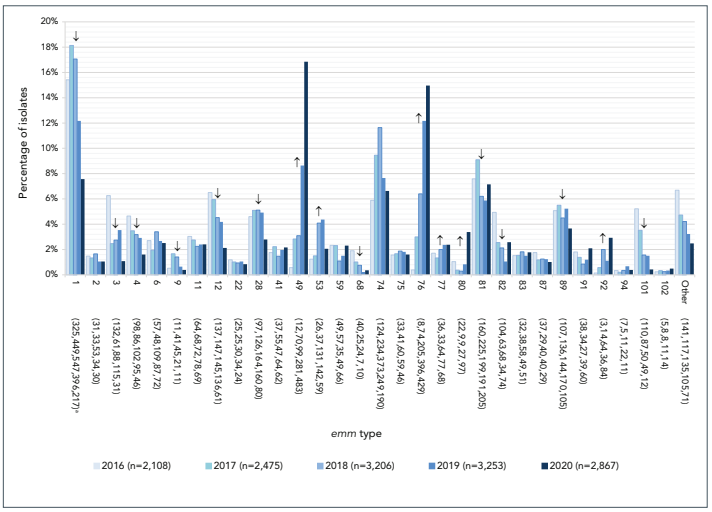


[a] Cases per 100,000 population

The most predominant *emm* types overall in 2020 were *emm*49 (16.8%, n=483) and *emm*76 (15.0%, n=429), which have increased significantly in prevalence since 2016 (from 0.6%, n=12 and 0.4%, n=8, respectively; $p<0.001$) (**Figure 2**). Other *emm* types that demonstrated significantly increasing trends from 2016 to 2020 include *emm*53 (1.2% to 2.1%, $p<0.001$), *emm*77 (1.7% to 2.4%, $p=0.005$), *emm*80 (1.0% to 3.4%, $p<0.001$) and *emm*92 (0.1% to 2.9%, $p<0.001$). Other *emm* types demonstrated significantly decreasing trends (see Figure 2), such as *emm*1 from 15.4% (n=325) of all invasive *S. pyogenes* isolates collected in 2016, to only 7.6% (n=217) in 2020 ($p<0.001$). Of note, 33% (n=138) of *emm*1 isolates sequenced in 2019 were the novel $M1_{UK}$ lineage; in comparison, only three $M1_{UK}$ isolates were identified in 2015.

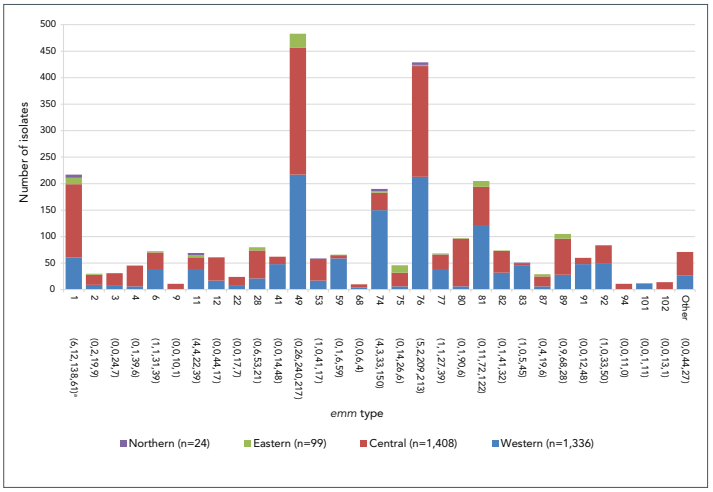
In 2020, the most common *emm* type from children younger than two years of age was *emm*49 (20.9%, n=14), while *emm*1 predominated for children 2–4 years (41.9%, n=13) and 5–14 years (37.3%, n=19) (**Figure S6**). In patients aged 15–49 and 50–64 years, *emm*49 was most common (17.9%, n=242; 17.9%, n=132, respectively), followed by *emm*76 (16.3%, n=220; 14.2%, n=105). For adults 65 years and older, *emm*76 (14.4%, n=90) and *emm*49 (14.2%, n=89) were also most common, but *emm*1 was also frequently identified (12.0%, n=75) (**Figure S7**). *Emm* types associated with Western Canada (**Figure 3**) included *emm*49 (16.2%, n=217), *emm*76 (15.9%, n=213), *emm*74 (11.2%, n=150) and *emm*81 (9.1%, n=122). In Central Canada, *emm*49 (17.1%, n=240) and *emm*76 (14.8%, n=209) were predominant, while *emm*49 (26.3%, n=26) and *emm*75 (14.1%, n=14) were most common in Eastern Canada. Isolates from Northern Canada were highly represented by *emm*1 at 25.0% (n=6), though only 24 isolates were submitted from this region (**Figures S8 to S11**).

Figure 2: Prevalence of invasive *Streptococcus pyogenes emm* types in Canada, 2016–2020[a,b,c]



[a] Number of isolates for 2016, 2017, 2018, 2019 and 2020, respectively
[b] Increase in 2016 and 2017 totals from previous annual reports is due to inclusion of submitted data from Alberta
[c] For *emm* types with an overall (2016–2020) n≥30: up or down arrows indicate statistically significant trends toward increasing or decreasing prevalence for the 2016–2020 timespan, using the chi-squared test for trend. *Emm* types with no arrow either did not demonstrate a statistically significant trend, or did not have an overall n≥30

Figure 3: Regional distribution of invasive *Streptococcus pyogenes* isolates collected in 2020, by *emm* type[a]

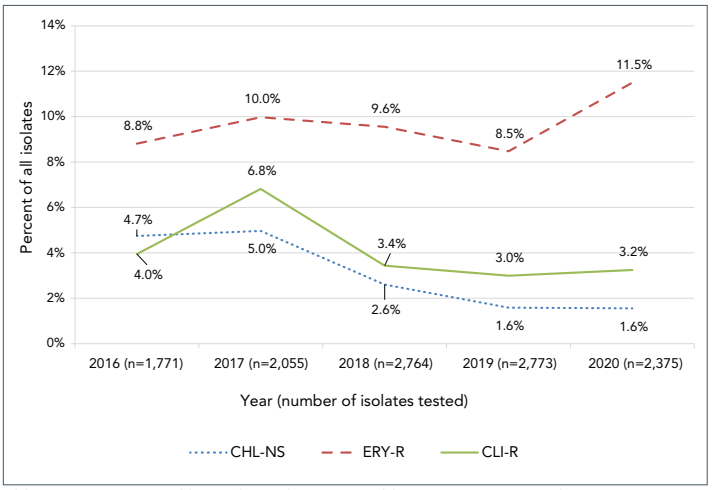


[a] Number of isolates in the Northern, Eastern, Central and Western regions of Canada, respectively

Upon request, NML provides assistance to provincial and territorial public health laboratories for *S. pyogenes* outbreak investigations. During 2020, NML assisted in six outbreak investigations from various jurisdictions, including *emm*6.4 (n=224 cases), *emm*74 (n=3), *emm*81 (n=9), *emm*92 (n=5) and two multi-*emm* type outbreaks (*emm*1, *emm*74, *emm*76 and *emm*92, n=14; *emm*1, *emm*76 and *emm*77, n=10).

Antimicrobial resistance among invasive *S. pyogenes* isolates remained low in 2020 (**Figure 4, Table S2**). After dropping to 8.5% (n=235) in 2019, erythromycin resistance increased to 11.5% (n=273) in 2020; however, the overall increase from 2016 to 2020 was not statistically significant. Chloramphenicol nonsusceptibility decreased significantly from 4.7% in 2016 to 1.6% in 2020 ($p<0.001$), and clindamycin resistance has remained relatively stable over the previous three years (3.0%–3.4%). There was no resistance observed to penicillin or vancomycin. *Emm* types associated with erythromycin and clindamycin resistance included *emm*11 (88.6%, n=39; 79.5%, n=35); *emm*77 (80.8%. n=42; 78.8%, n=41) *emm*83 (45.7%, n=21; 47.8%, n=22) and *emm*92 (97.4%, n=74; 93.4%, n=71; respectively) (**Figure S12, Table S3**).

Figure 4: Antimicrobial resistance of invasive *Streptococcus pyogenes* in Canada, 2016–2020



Abbreviation: CHL-NS, chloramphenicol-nonsusceptible (resistant or intermediate); CLI-R, constitutively clindamycin-resistant; ERY-R, erythromycin-resistant

Discussion

In 2019, 3,054 cases of iGAS disease were reported to CNDSS, with a national incidence rate of 8.1 cases per 100,000 population; more than double the lowest recorded national incidence (2.7 cases per 100,000 population in 2004) since iGAS disease became notifiable in Canada in 2000. Other countries have noted similar increases in iGAS disease over time (11–14), and have hypothesized that the overall increase could be due to increasing molecular diversity of the M protein, or expansion of particularly virulent strains of *S. pyogenes* (13,14). Horizontal gene transfer of large regions of genetic material has resulted in a number of unusually virulent clones that have become dominant worldwide, such as the pandemic *emm*1 clone that resulted from acquisition of a 36kb region, resulting in increased expression of the cytotoxins *nga* (NADase) and *slo* (streptolysin O) (15). It has also been shown that in addition to

increased toxin expression, no or low capsule production may also support the expansion of successful lineages (16); examples include *emm*89, *emm*28 and *emm*87 (16,17).

The number of invasive *S. pyogenes* isolates collected by NML decreased from 3,194 in 2019 to 2,867 in 2020. Though 2020 incidence data for iGAS disease was unavailable at the time of writing, it is likely there was a slight decrease between 2019 and 2020. This decrease may have been an indirect effect of the containment measures put in place in 2020 to prevent the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic virus. Several studies have noted that there was decreased invasive disease due to respiratory-transmitted pathogens in 2020; among other routes, *S. pyogenes* may also be transmitted via respiratory droplets, so the same non-pharmaceutical public health measures put in place to prevent the spread of coronavirus disease 2019 (COVID-19) may have prevented some spread of *S. pyogenes*, resulting in fewer cases of iGAS disease. The Invasive Respiratory Infection Surveillance Initiative noted worldwide decreases in invasive diseases caused by respiratory pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis* due to containment measures and social changes caused by the pandemic (18). A Houston, Texas area hospital also identified a decrease in invasive pneumococcal disease and iGAS disease in 2020 due to COVID-19 containment measures (19).

The most prevalent *emm* type collected in Canada over the past decade was *emm*1, accounting for over 25% of reported iGAS cases in the early 2010s and reflecting levels reported in Europe and North America (20). Although *emm*1 has decreased in prevalence in Canada since 2014, an increasing number of sequenced isolates (138 isolates in 2019 in comparison to three in 2015) are the novel, hypertoxigenic $M1_{UK}$ lineage originally described by Lynskey *et al*. (10). Recent publications indicated that the prevalence of this lineage is variable: 64% of sequences *emm*1 isolates in the Netherlands grouped with $M1_{UK}$, while the United States has not seen significant expansion (21,22). It will be crucial to monitor the expansion of this lineage in Canada and determine whether it results in increasing prevalence or outbreaks of *emm*1.

Despite decreasing in prevalence for a number of years, *emm*1 has only been surpassed by *emm*76 in 2019 (2), and by *emm*49 in 2020, each of which accounted for fewer than 1% of reported iGAS cases in 2016. Many outbreaks of iGAS disease across Canada in recent years have been due to *emm*76 and *emm*49 (*unpublished data*). *Emm* type replacements such as these may often be driven by low population immunity to rare *emm* types, and intensified transmission of disease within at-risk populations such as people experiencing homelessness (PEH), people who inject drugs (PWID) and other closed/semi-closed populations; in fact, it has been noted that the distribution of *emm* types varies between non-risk and at-risk groups, and even between different risk groups (14,23). Valenciano *et al*. observed that the *emm* distribution in the United States varied between PEH, PWID and those with both risk factors (23). Rapid expansion of previously uncommon *emm* types has been noted recently in a number of countries: *emm*74 in various disadvantaged groups across Canada; *emm*6 in a semi-closed population of military trainees in Canada; *emm*26.3 in PEH in the United States; and *emm*66 in PEH/PWID in England (4,5,24,25).

Streptococcus pyogenes remains susceptible to penicillin—the most commonly chosen antimicrobial treatment for iGAS infections, however, there is growing resistance to second-line agents such as macrolides and clindamycin (1). In 2020, common *emm* types in Canada that had high levels (more than 40%) of erythromycin and clindamycin resistance included *emm*11, *emm*77, *emm*83 and *emm*92, and two of these types (*emm*77, *emm*92) also demonstrated increasing prevalence from 2016 to 2020. These *emm* types were also found to be significant sources of macrolide/lincosamide resistance in countries such as Spain and the United States (26,27), with the latter study also noting increases over time of *emm*11, *emm*77 and *emm*92 (27). Importantly, all four *emm* types are included in an investigational 30-valent M-protein-based vaccine currently undergoing clinical trials (28). Further clinical development and eventual use of this vaccine worldwide could help to reduce the burden of disease associated with antimicrobial resistant *emm* types.

Strengths and limitations

Caution should be exercised when interpreting the data presented in this report as the overall interpretation of the results is limited to only isolates available for testing. Only a subset of laboratory isolates from each province may have been submitted for testing and therefore this report does not reflect the true incidence or rates of disease in Canada. The representativeness of the proportions of isolates submitted for testing to NML as compared to the CNDSS are presented in **Table S4**. Not all provinces and territories report line list data to CNDSS and therefore only aggregated data are available at the national level; therefore, CNDSS data and NML laboratory data are presented differently in terms of age grouping.

Conclusion

Although the number of isolates collected decreased in 2020 in comparison to previous years, iGAS disease remains an important public health concern. In the past five years the *emm* distribution in Canada has shifted away from the common and well-known *emm*1 and towards previously uncommon *emm*49 and *emm*76. Continued surveillance of invasive *S. pyogenes* in Canada is imperative to monitor these expanding replacement *emm* types, as well as outbreak clones and antimicrobial resistance.

Authors' statement

ARG — Formal analysis, data curation, visualization, writing–original draft, review and editing of final version
AG — Formal analysis, validation, investigation, data curation, visualization, writing–review and editing
WHBD — Formal analysis, validation, investigation, data curation, visualization, writing–review and editing
GJT — Resources, methodology, writing–review and editing
JVK — Resources, methodology, writing–review and editing
AM — Resources, methodology, writing–review and editing
MCD — Resources, methodology, writing–review and editing
LH — Resources, methodology, writing–review and editing
JM — Resources, methodology, writing–review and editing
PVC — Resources, methodology, writing–review and editing
HS — Resources, methodology, writing–review and editing
DH — Resources, methodology, writing–review and editing
GZ — Resources, methodology, writing–review and editing
KM — Resources, methodology, writing–review and editing
LS — Resources, methodology, writing–review and editing
LS — Resources, methodology, writing–review and editing
AYL — Writing–review and editing
MRM — Methodology, writing–review and editing
IM — Conceptualization, validation, methodology, supervision, project administration, writing–review and editing

Competing interests

None.

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Supplemental material

These documents can be accessed on the Supplemental material file.

Table S1: Annual incidence rates of invasive *Streptococcus pyogenes* cases in Canada by age group, 2009–2019
Figure S1: Clinical isolation sites of invasive *Streptococcus pyogenes* from children younger than 15 years of age in 2020 (n=149)
Figure S2: Clinical isolation sites of invasive *Streptococcus pyogenes* from patients 15 years of age and older in 2020 (n=2,718)
Figure S3: Percentage of invasive *Streptococcus pyogenes* isolates from blood in 2020, by *emm* type (n=1,947)
Figure S4: Percentage of invasive *Streptococcus pyogenes* isolates from other sterile sites in 2020, by *emm* type (n=910)
Figure S5: Percentage of invasive *Streptococcus pyogenes* isolates from cerebrospinal fluid in 2020, by *emm* type (n=10)
Figure S6: Prevalence of invasive *Streptococcus pyogenes emm* types isolated in 2020 for those younger than two, 2–4 and 5–14 years old
Figure S7: Prevalence of invasive *Streptococcus pyogenes emm* types isolated in 2020 for those 15–49, 50–64 and 65 years and older
Figure S8: Prevalence of the ten most common invasive *Streptococcus pyogenes emm* types collected from Western Canada in 2020
Figure S9: Prevalence of the ten most common invasive *Streptococcus pyogenes emm* types collected from Central Canada in 2020
Figure S10: Prevalence of the ten most common invasive *Streptococcus pyogenes emm* types collected from Eastern Canada in 2020
Figure S11: Prevalence of invasive *Streptococcus pyogenes emm* types collected from Northern Canada in 2020
Table S2: Antimicrobial resistant invasive *Streptococcus pyogenes* isolates by year, 2016–2020
Figure S12: Percentage of macrolide and lincosamide resistant invasive *Streptococcus pyogenes* isolates collected in 2020, by *emm* type
Table S3: Percentage of macrolide and lincosamide resistant invasive *Streptococcus pyogenes* isolates collected in 2020, by *emm* type
Table S4: Number of invasive *Streptococcus pyogenes* isolates typed by the National Microbiology Laboratory (NML) in comparison to the total number of cases reported to Canadian Notifiable Diseases Surveillance System (CNDSS) in 2019, by patient age group

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In-person learning low risk for COVID-19 acquisition: Findings from a population-based analysis of the 2020–2021 school year in Saskatchewan, Canada

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic has caused substantial disruption to in-person learning, often interfering with the social and educational experience of children and youth across North America, and frequently impacting the greater community by limiting the ability of parents and caregivers to work outside the home. Real-world evidence related to the risk of COVID-19 transmission in school settings can help inform decisions around initiating, continuing, or suspending in-person learning.

Methods: We analyzed routinely collected case-based surveillance data from Saskatchewan's electronic integrated public health system, Panorama, from the 2020–2021 school year, spanning various phases of the pandemic (including the Alpha variant wave), to better understand the risk of in-school transmission of COVID-19 in Saskatchewan schools.

Results: The majority (over 80%) of school-associated COVID-19 infections were acquired outside the school setting. This finding suggests that the non-pharmaceutical measures in place (including masking, distancing, enhanced hygiene, and cohorting) worked to limit viral spread in schools.

Conclusion: Implementation of such control measures may play an essential role in allowing children and youth to safely maintain in-person learning during the pandemic.

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Keywords: COVID-19, SARS-CoV-2, school, COVID-19 transmission, Saskatchewan

Introduction

Since the start of the coronavirus disease 2019 (COVID-19) pandemic in North America, the question of whether schools can safely operate in-person has been the focus of much debate. Schools were frequently included in widespread shutdowns to limit viral transmission and exponential growth, despite a lack of evidence related to their role in transmission. Stakeholders, including parents, educators, public health professionals, and the media, have presented many differing viewpoints on the risks/benefits of in-person learning during the pandemic. The issue remains at the forefront during the third school year affected by COVID-19.

Prior to start of the 2020–2021 school year, there was little real-world evidence related to in-person learning and the risk of COVID-19 transmission. Evidence has been emerging since that time, however, and we now have a better understanding of COVID-19 transmission dynamics in schools in a variety of geographic settings (1–10). Several of these studies have found that with appropriate mitigation measures in place (such as cohorting, distancing, or masking), the risk of in-school transmission was relatively low. A study of 17 rural Wisconsin schools found that of COVID-19 cases identified among students, only 3.7% were acquired in the school setting (2). One report

of a large outbreak in a Jerusalem high school concluded that crowded classrooms, the suspension of masking requirements (due to a heatwave), and continuous air conditioning were factors that substantially increased transmission. However, attack rates among students and staff were still relatively low at 13.2% and 16.6% (4). Data from British Columbia found a similar proportion of overall school-associated cases were likely acquired in school (13.0%) (8). Another British Columbia study reported that in-person schooling was not associated with an increased risk of COVID-19 acquisition among school staff (1), and other Canadian and United States studies have reported relatively low risk associated with in-person schooling as well (6,9). Here we present the characteristics of cases and risk of transmission of COVID-19 in preschools, elementary, and high schools in Saskatchewan, a jurisdiction that largely maintained in-person learning throughout the 2020–2021 school year.

Methods

We analyzed population-level data from the 2020–2021 school year in Saskatchewan, spanning various phases of the pandemic (including the Alpha variant wave), to better understand the risk of in-school transmission of COVID-19 in Saskatchewan schools.

Routinely collected case-based surveillance data from Saskatchewan's electronic integrated public health system, Panorama, were used for the analysis. Data on all laboratory-confirmed COVID-19 cases were entered in Panorama, and standardized data collection worksheets are used for case and contact investigations. These surveillance data were used to better understand the epidemiology of COVID-19, including case volumes over time, demographics and case type (e.g. staff versus student), and most likely exposure sources for cases.

The study period for the 2020–2021 school year was from September 2, 2020 (start of school year) to July 12, 2021 (approximately two weeks post the end of the school year). Data were extracted on July 13, 2021, and analyzed using IBM SPSS Statistics 22.0 and Microsoft Excel 2016. This analysis represents a synthesis of province-wide data from the full 2020–2021 school year; similar analyses were conducted throughout the school year at the local and provincial level and were used to inform decisions around maintaining in-person learning.

"School-associated" cases were identified using risk factor variables routinely collected during case investigations that indicate whether a person was a teacher, a preschool attendee, a school attendee (e.g. K–12) or other school staff. We included only those school-associated cases that had a most likely source (MLS) of exposure flagged in Panorama, which is also routinely collected during case interviews, as determined by trained case investigators, who are typically public health nursing staff. The determination is based on a thorough retrospective investigation, taking into account the incubation period of the organism, period of communicability, and all potential exposure settings during the relevant time period for acquisition. Ultimately the investigator makes the determination of which reported exposure is the most likely source of infection.

Results

From September 3, 2020, through July 12, 2021, a total of 5,952 school-associated cases occurred in Saskatchewan. Among these, 4,980 (83.7%) had MLS data available; this analysis is based on those 4,980 cases. Of these cases, the largest proportion occurred among children aged 5–13 years (n=2,336, 46.9%), followed by youth aged 14–19 years (n=1,470, 29.5%). Other age groups made up substantially smaller proportions of the overall caseload (**Table 1**).

Table 1: School-associated COVID-19 cases, by age group, Saskatchewan, September 3, 2020–July 10, 2021 (N=4,980)

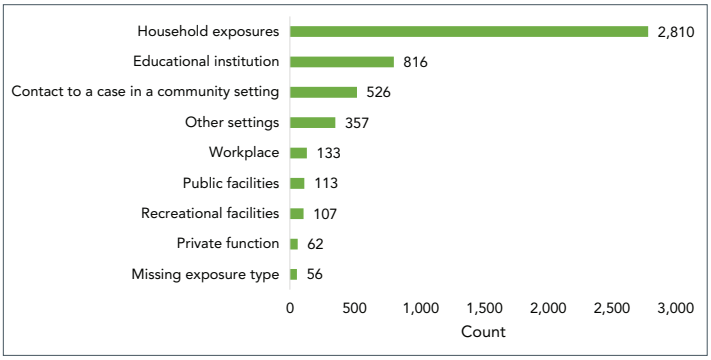
Age group (years)	n	%
0–4	199	4.0%
5–13	2,336	46.9%
14–19	1,470	29.5%
20–44	586	11.8%
45–64	368	7.4%
65+	21	0.4%
Total	4,980	100%

By category, the majority of cases (n=3,853, 77.4%) were among elementary/high school students, with smaller proportions comprising teachers (n=491, 9.9%), other school staff (n=420, 8.4%), and preschool students (n=216, 4.3%). Teachers had the highest proportion of in-school exposures (n=112, 22.8%), followed by elementary/high school students (n=614, 15.9%), other school staff (n=65, 15.5%), and preschool students (n=25, 11.6%) (**Table 2**). Throughout the academic year, 816 (16.4%) school-associated cases were found to have acquired their infection in the school, with household exposure (n=2,810, 56.4%) being responsible for the majority of infections (**Figure 1**).

Table 2: In-school acquisition by case type, school-associated COVID-19 cases, Saskatchewan, September 3, 2020–July 10, 2021 (N=4,980)

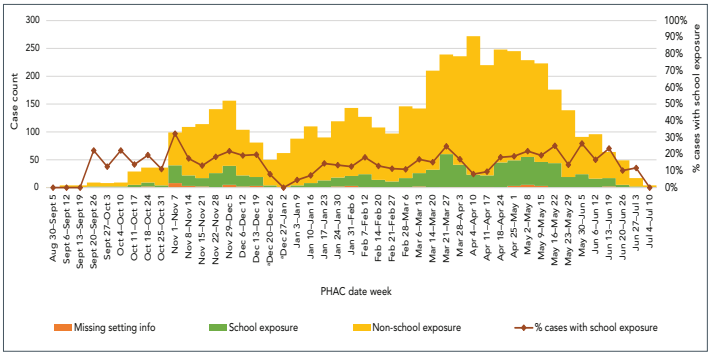
Case type	Total cases		Total school acquired within case type category	
	n	%	n	%
Elementary/High school student	3,853	77.4%	614	15.9%
Teacher	491	9.9%	112	22.8%
Other school staff	420	8.4%	65	15.5%
Preschool student	216	4.3%	25	11.6%
Total	4,980	100%	816	16.4%

Figure 1: School-associated COVID-19 cases, by exposure setting, Saskatchewan, September 3, 2020–July 10, 2021 (N=4,980)



The epidemic curve of school-associated COVID-19 cases during the 2020–2021 school year (**Figure 2**) illustrates that while the volume of school-associated cases (height of the bars) varied throughout the time period, the proportion of infections acquired in school (green portion of the bars, also shown as a percent by the red line) remained relatively stable throughout the period. Of note, the Alpha variant was first identified in Saskatchewan in February 2021, and led to a subsequent surge in infections by mid-March. This surge was clearly reflected among school-associated cases on the epidemic curve, beginning the week of March 14–20; however, the overall proportion of cases attributed to in-school exposure remained relatively steady throughout this surge in cases.

Figure 2: Epidemic curve, school-associated COVID-19 cases, by week and exposure setting, September 3, 2020–July 10, 2021 (N=4,980)[a]



Abbreviation: PHAC, Public Health Agency of Canada
[a] Schools were closed for Christmas break from December 20, 2021 through December 31, 2021

Discussion

Unlike many North American jurisdictions, schools in Saskatchewan began the 2020–2021 school year offering in-person learning; students and parents were also provided with an alternative option to choose online learning if desired. While there was some regional variation throughout the school year, for the most part, Saskatchewan maintained in-person learning for all grades from K–12 for the duration of the academic year. Temporary exceptions did occur based on local epidemiology; for example, rural versus urban areas and northern versus central/southern areas may have had different protocols at different times. Additionally, individual schools in the province had the option to temporarily move to online learning, based on local epidemiology, when needed. The Saskatchewan Ministry of Education provided school divisions four "Levels" of learning based on local risk assessment/epidemiology: Level 1 indicated "normal" return to school, Level 2 required continuous mask use by all students and staff, Level 3 included cohorting and hybrid (mixed online/in person) learning modules (to allow for smaller class sizes), and Level 4 indicated mandatory online learning school-wide. Most schools in Saskatchewan operated at Level 2 or Level 3 for the majority of the academic year, with some temporarily (10–14 days) moving to Level 4 following the declaration of a school outbreak or based on other local risk assessments. It was more common for larger schools and upper grades to operate at Level 3 compared with elementary grades (11).

Overall, with temporary regional variation as mentioned, the non-pharmaceutical interventions (NPIs) in place included non-medical masking for students and staff, enhanced environmental cleaning and personal hygiene, physical distancing where possible, the suspension of youth recreational sports, symptom screening and stay home policies, universal access to testing, and cohorting of students in some schools. Contact tracing of each school-associated case was guided by a risk assessment matrix (12,13), which led to identification and exclusion/quarantine of close contacts in the school setting.

The majority (over 80%) of school-associated COVID-19 cases during the study period were found to have been acquired outside the school setting. This suggests that the non-pharmaceutical measures in place (including masking, distancing, enhanced hygiene and cohorting) worked to limit viral spread in schools.

Limitations

There are several limitations to this analysis. First, this study included only cases that were tested and subsequently diagnosed. Asymptomatic school-associated cases that were not tested would not be included in Panorama, which relies on a positive laboratory result to confirm a case. Second, inadvertent inclusion of post-secondary students may have occurred in situations where incorrect risk factors were chosen. It is also possible that students from congregate living settings (boarding schools) were also inadvertently included, which would overestimate total school-associated cases, and likely in-school exposures as well. Third, the true burden of in-school acquisition may also have been underestimated given many schools temporarily moved to Level 4 learning (online) following the declaration of a school-associated outbreak or other risk assessment; however, we would argue this is further evidence

that the measures taken in schools to limit and control viral transmission, including temporary shifts to online learning when required, worked. Further, our findings demonstrate these "school-associated" index cases, which may have triggered Level 4 learning, usually did not acquire their infection in school, but in households, social gatherings, and other outside-school activities. Fourth, is also important to note this study period occurred prior to the emergence and widespread circulation of the Delta and Omicron variants. Because these variants are more transmissible, findings may not be generalizable to the context of the pandemic in the later part of 2021 and into 2022. Fifth, we were also unable to assess the impact of ventilation on limiting disease spread. Lastly, only cases with MLS information were included in the analysis. Completeness of data varied by geographic area and over time; however, over the time period and across the province, 83.7% of cases had MLS information available.

Conclusion

Our finding that the proportion of school-associated COVID-19 cases attributed to in-school exposure was low and remained stable throughout the school year despite an overall surge in cases in spring 2021, is consistent with data from other jurisdictions (1,2,4,6,8,10). These studies imply that the NPIs in place in school settings likely contributed to limiting disease transmission. Compared with many community settings, Saskatchewan schools were a relatively controlled environment during the 2020–2021 school year. As we move into the immunization era, with a safe and effective pharmaceutical intervention available, we expect that immunization of age-eligible individuals in schools will contribute to reducing transmission. Even in this new era, however, given high background community transmission rates, the potential for breakthrough infections, and variable vaccination coverage rates among children and youth, NPIs remain important interventions in schools. While it is possible the arrival of new variants and the faster rate of viral spread will change the epidemiological picture, our findings contribute to the larger body of evidence that to date suggests in-person learning is not a substantial contributor to COVID-19 transmission when appropriate NPIs are in place.

Authors' statement

MT — Writing–original draft, writing–review & editing, data analysis, conceptualization, visualization, interpretation
LM — Writing–review & editing, conceptualization, visualization, interpretation
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The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

None.

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