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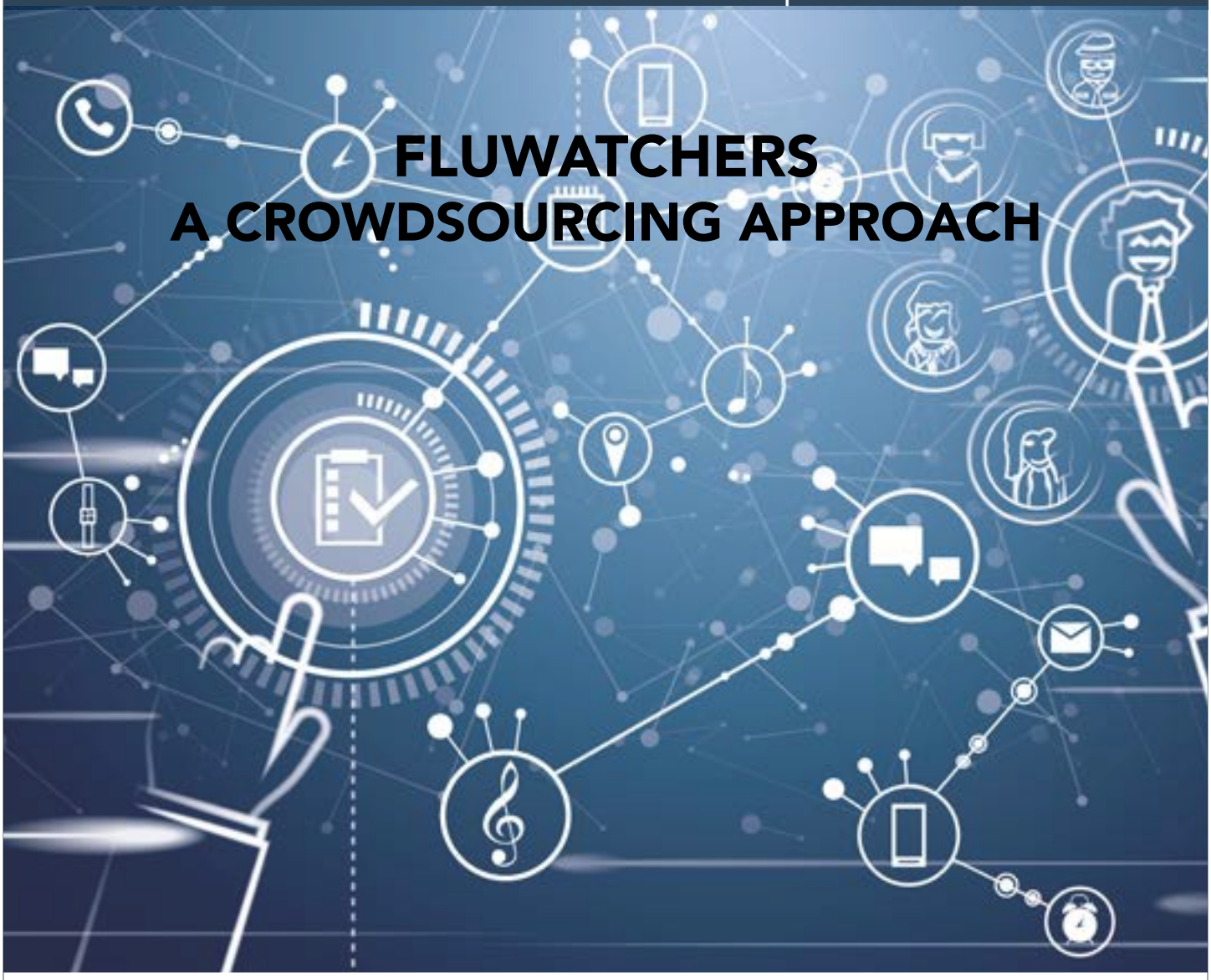

FLUWATCHERS
A CROWDSOURCING APPROACH

GUEST EDITOR: LIZA LEE

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

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FLUWATCHERS: A CROWDSOURCING APPROACH

TABLE OF CONTENTS

ERRATUM

The list of co-authors has been updated for the article published in July/August 2021 Vol. 47 No. 7/8 (Ontario COVID-19 Science Advisory Table and the Drugs & Biologics Clinical Practice Guidelines Working Group. Ivermectin treatment for Strongyloides infection in patients with COVID-19. Can Commun Dis Rep 2021;47(7/8):316–21. https://doi.org/10.14745/ccdr.v47i78a04)

COMMENTARY

Crowdsourced disease surveillance success story: The FluWatchers program

Liza Lee[1]*, Shamir Mukhi[2], Christina Bancej[1]

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Introduction

Syndromic surveillance is a core surveillance capacity for pandemic preparedness and for the detection of emerging respiratory pathogens or unexpected events related to previously circulating viruses (1). Syndromic surveillance related to illnesses such as severe acute respiratory illness and influenza-like illness (ILI) must be adaptable and ready for escalation in any pandemic (2).

Crowdsourced data collection is the process of "building a dataset with the help of a large group of people" (3). Whether you call it crowdsourcing, citizen science or participatory disease surveillance, the process of having volunteers report health information or symptoms online for the purpose of influenza surveillance is not new. Crowdsourced ILI surveillance has been in practice since 2003 and has been implemented in many countries, including Canada, because of its flexibility, low-cost, timeliness and accuracy (4,5). Its use in mitigating the current coronavirus disease 2019 (COVID-19) pandemic has also been reported and assessed (6).

About FluWatchers

Since 2015, FluWatchers, the program and its current 12,000+ participants, has been contributing to the Public Health Agency of Canada's (PHAC) weekly ILI surveillance dataset and helping with the early detection of ILI activity across Canada.

FluWatchers is a participatory (crowdsourced) syndromic surveillance system that relies on Canadian volunteers to report symptoms of cough or fever to PHAC on a weekly basis. Traditional influenza surveillance systems only capture the tip of the iceberg of cases. For case information to be captured by traditional means, an individual needs to feel sick enough to seek medical care, they need to be tested, and a virus must be detected and/or isolated. FluWatchers provides a more comprehensive insight on the true burden and effects of influenza each season in the community. Traditional surveillance systems, such as laboratory surveillance, may not capture such insight because not everyone who is sick will see a doctor and, traditionally, even fewer will be tested (5). FluWatchers has been providing PHAC with reliable data on ILI activity in the community that complement the data obtained from traditional influenza surveillance sources.

The FluWatchers questionnaire is administered by and the data are managed on the Canadian Network for Public Health Intelligence (CNPHI), an established scientific public health informatics and biosurveillance platform developed and managed within PHAC's National Microbiology Laboratory. The CNPHI infrastructure provides a secure, reliable and robust technical environment for the FluWatchers program.

Volunteer participants receive a reporting link each Monday. The weekly anonymous questionnaire asks whether the participant experienced a cough or fever in the previous week and captures their vaccination status. That is it! Two quick health-related questions, 15 seconds of a participant's day and an impactful contribution to public health is made.

Pivot to COVID-19 surveillance

FluWatchers primarily collects data on symptoms, specifically cough and fever since they are typical symptoms of influenza (7). Collecting syndromic data, rather than reports of a particular disease allows the flexibility for expanded monitoring for emerging symptoms, syndromes, illnesses and self-reported diagnoses as was done with COVID-19, without sacrificing the surveillance of another disease such as influenza.

FluWatchers was able to quickly pivot to track COVID-19 in the community when the pandemic was declared. In April 2020, the FluWatchers questionnaire was quickly adapted with minimal

changes to track COVID-19 in the community (while retaining the ability to track influenza-like illness).

The World Health Organization refers to surveillance system flexibility as the ability of a surveillance system to be adapted to meet changing needs including, but not limited to, the removal or inclusion of other diseases, modification of the reporting frequency and shifting data requirements (8). The FluWatchers program was able to include surveillance of COVID-19 by capturing information on symptoms, testing results and vaccine uptake for COVID-19 into its questionnaire. It changed its algorithm to flag a symptomatic participant from those reporting cough and fever to those reporting cough and/or fever. It also shifted to year-round surveillance from its previous reporting frame of October through May. Additionally, participation also increased from roughly 3,000 weekly participants to a high of almost 13,000 weekly participants with no negative impact on system performance. None of these inclusions required extensive changes to the existing system and as we learned more about the disease, we were able to quickly implement changes to the questionnaire. As additional work continues within the scientific community to develop appropriately sensitive and specific case definitions for COVID-19-like illness, relevant to the phases of the pandemic, FluWatchers maintains the flexibility to evolve alongside the evidence (9–13).

FluWatchers' contribution to public health

The FluWatchers program is one of two syndromic ILI surveillance programs in the national influenza surveillance system, FluWatch (14). Data collected by FluWatchers are analyzed each week and included in the FluWatch report. Data from FluWatchers are primarily used for "signal detection"—looking at the data for high or unusual influenza activity, as well as marking the start, peak and end of seasonal respiratory epidemics. The data are also published in real-time so that Canadians can see where activity is concentrated as quickly as public health officials. Access to the data is also provided on open data via Open Maps.

Since the COVID-19 pandemic, FluWatchers' data have been included in the Canada COVID-19 Weekly Epidemiology Report and have also been incorporated into COVIDTrends, a tool that provides summary data about COVID-19 in a particular area. The FluWatchers' volunteer base was recognized as a valuable source of engaged and reliable volunteers. Early in the vaccine roll-out, a time when vaccine effectiveness and safety research studies needed to be completed in a rapid fashion, the FluWatchers program was used as a means of recruiting its volunteers as participants in these studies.

Like all surveillance data, the FluWatchers' data come with their own set of limitations and biases, some of which have been amplified in the COVID-19 era (5,10). There are ways to overcome or limit the effects of these biases and limitations and it really all comes down to recruiting a more diverse array of participants (such as by geography, gender, age and race) (5,15,16).

What is next?

There is a solid foundation for using participatory surveillance for established and emerging disease surveillance in Canada; however, we need to build up the volunteer base prior to the circulation of the next emerging infectious disease so that when it does occur, experts can be focused on the data and not recruiting participants.

Participatory surveillance can be leveraged as governments are moving towards social innovation and open policy-making and design. FluWatchers encourages a two-way engagement between the government and its citizens, and this program can strengthen this relationship and build trust.

The number of FluWatchers participants grew over 300% from April 2020 to April 2021 (from approximately 3,000 to 12,000+ participants). We are still not at the point where we have enough participants to reliably pick up rare signals of unusual, increased activity. There are hundreds of communities across Canada where there are only a handful of participants, and this can hamper our efforts to use FluWatchers as an elite early warning program. The more participants in an area; the more accurate the data.

If you have not already, sign-up to be a FluWatcher, spread the word to your friends, family and neighbours. In comparison, Australia's FluTracking program has over 50,000 weekly participants (17). There is nothing stopping us from reaching or exceeding that number. Let's make Canada the leader for participatory disease surveillance!

Authors' statement

LL — Writing, review, editing
SM — Review, editing
CB — Review, editing

Competing interests

None.

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FluWatchers: Evaluation of a crowdsourced influenza-like illness surveillance application for Canadian influenza seasons 2015–2016 to 2018–2019

Liza Lee[1]*, Mireille Desroches[1], Shamir Mukhi[2], Christina Bancej[1]

Abstract

Background: Sentinel influenza-like illness (ILI) surveillance is an essential component of a comprehensive influenza surveillance program. Community-based ILI surveillance systems that rely solely on sentinel healthcare practices omit important segments of the population, including those who do not seek medical care. Participatory surveillance, which relies on community participation in surveillance, may address some limitations of traditional ILI systems.

Objective: We aimed to evaluate FluWatchers, a crowdsourced ILI application developed to complement and complete ILI surveillance in Canada.

Methods: Using established frameworks for surveillance evaluations, we assessed the acceptability, reliability, accuracy and usefulness of the FluWatchers system 2015–2016, through 2018–2019. Evaluation indicators were compared against national surveillance indicators of ILI and of laboratory confirmed respiratory virus infections.

Results: The acceptability of FluWatchers was demonstrated by growth of 50%–100% in season-over-season participation, and a consistent season-over-season retention of 80%. Reliability was greater for FluWatchers than for our traditional ILI system, although both systems had week-over-week fluctuations in the number of participants responding. FluWatchers' ILI rates had moderate correlation with weekly influenza laboratory detection rates and other winter seasonal respiratory virus detections including respiratory syncytial virus and seasonal coronaviruses. Finally, FluWatchers has demonstrated its usefulness as a source of core FluWatch surveillance information and has the potential to fill data gaps in current programs for influenza surveillance and control.

Conclusion: FluWatchers is an example of an innovative digital participatory surveillance program that was created to address limitations of traditional ILI surveillance in Canada. It fulfills the surveillance system evaluation criteria of acceptability, reliability, accuracy and usefulness.

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Keywords: influenza, seasonal, digital participatory surveillance, crowdsourced, Canada, FluWatchers, syndromic, influenza-like illness (ILI)

Introduction

FluWatch is Canada's national seasonal influenza surveillance program and consists of a network of laboratories, hospitals, physician offices, provincial and territorial ministries of health and Canadians (1). FluWatch consists of seven surveillance components (geographical spread, laboratory confirmed detections, syndromic influenza-like illness (ILI) surveillance, outbreak surveillance, severe outcome surveillance, strain characterization and antiviral resistance testing and vaccine

monitoring) that work together to allow FluWatch to meet three main program objectives (detect, inform and enable).

The World Health Organization (WHO) defines the global standards for the collection, reporting and analysis of seasonal influenza surveillance data and provides a framework for influenza surveillance for member states (2). While the WHO does not mandate the exact surveillance components that every surveillance system must contain, it does recommend the inclusion of community-based surveillance of ILI as part of a comprehensive influenza surveillance system (2).

Developed in 1996, the Sentinel Practitioner ILI Reporting System (SPIR) is the primary source for ILI surveillance data for the Public Health Agency of Canada's (PHAC) FluWatch program (1). The SPIR consists of outpatient influenza data submitted by primary care practitioners or registered nurses. There are, however, three major limitations to SPIR: it is reliant on voluntary reporting from a convenience sample of volunteer sentinel physicians or registered nurses; only data from individuals who seek medical attention are captured; and data submission is highly manual and interrupts practitioner workflow.

A growing trend is the use of hybrid surveillance systems that use digital surveillance to complement traditional surveillance (3). One popular digital surveillance trend is participatory surveillance or crowdsourced surveillance. Participatory surveillance systems rely on volunteer members of the community to regularly share and report health information via the internet for disease surveillance (3,4). Relying on volunteers address various limitations of traditional ILI surveillance systems, such as reporting delays, low participation and exclusion of individuals who do not seek medical care.

The need to address the limitations of SPIR and the advantages presented by participatory surveillance prompted the FluWatch program to create FluWatchers, an online participatory syndromic surveillance platform to help improve and complement ILI surveillance in Canada.

The FluWatchers system was developed on the Canadian Network for Public Health Intelligence (CNPHI) platform, an established PHAC initiative developed and managed by the National Microbiology Laboratory (5). The CNPHI is a purpose-built scientific public health informatics and biosurveillance platform (6). Its infrastructure provides a secure, reliable and robust technical environment to facilitate and promote multi-jurisdictional collaboration, supporting the cross-domain and cross-discipline exchange of information, ideas and intelligence. The CNPHI was a natural choice to help develop the FluWatchers program, administer the weekly questionnaire and manage the data.

FluWatchers' participants complete a brief, weekly symptom-based report via an anonymous online questionnaire that asks whether the participant, and/or registered household members, have had a cough and/or fever in the past week and their influenza immunization status. Data on other symptoms, absenteeism and healthcare utilization are also collected from individuals reporting cough and fever. The weekly questionnaire is typically administered from October through May.

The objective of the present study is to present a formal evaluation of the FluWatchers program against four surveillance metrics that were adapted from the Centers for Disease Control and Prevention's Framework for Evaluating Public Health Surveillance Systems for Early Detection of Outbreaks (7):

- Acceptability—Are Canadians willing to participate in FluWatchers?
- Reliability—Are participants providing data consistently?
- Accuracy—How well does the FluWatchers data track influenza patterns in Canada?
- Usefulness—Is FluWatchers adding value to the FluWatch program?

Methods

Data

FluWatch Sentinel Practitioner Influenza-like Illness Reporting System

The SPIR program consists of sentinel practitioners who report the total number of patient visits and the number of patient visits presenting with ILI on a weekly basis. Influenza-like illness is defined as a sudden onset of fever and cough and with one or more of the following: sore throat, joint pain, muscle aches, fatigue, which could be due to the influenza virus (1).

The weekly percentage of visits for ILI is defined as the number of patient visits to healthcare providers presenting with ILI symptoms in a given week divided by the total number of weekly patient visits to healthcare providers as a whole for that same week.

Respiratory Virus Detection Surveillance System

The Respiratory Virus Detection Surveillance System (RVDSS) is FluWatch's primary source for laboratory-based data on influenza and other seasonal respiratory viruses (adenovirus, coronavirus, enterovirus/rhinovirus, human metapneumovirus [hMPV], parainfluenza and respiratory syncytial virus [RSV]) (8). The RVDSS collects weekly data from provincial, regional and some hospital labs across Canada. Laboratories report on the number of tests performed and the number of tests positive for influenza and other respiratory viruses.

The weekly percentage of tests positive for influenza and all other respiratory viruses were used for this analysis. The weekly percentage of tests positive is defined as the number of positive tests for a given virus in a given week divided by the number of tests performed for a given virus for that same week.

FluWatchers

FluWatchers data consist of self-reported weekly episodes of cough and/or fever. For any participant reporting cough and fever, data on other symptoms experienced, absenteeism and healthcare utilization are collected. For the FluWatchers program, ILI is defined as a report of fever and cough.

The weekly percentage of FluWatchers reporting ILI is defined as the number of reports of cough and fever in a given week divided by the total number reports received by participants for that same week.

Measures

The four evaluation components were assessed as outlined in **Table 1**.

Analysis

Table 1: Evaluation framework, indicators and calculations used to evaluate the FluWatchers surveillance program

Evaluation component	Indicator	Estimation method/ calculation
Acceptability	Participation rate	Median number of weekly participants for a given season Average weekly response rate
	Retention rate	Number of baseline participants who participated in the subsequent season
Reliability	Proportion of registrants who report in a given week	Percentage of weeks within ±5%, ±10% or ±15% of the median number of weekly participants
Accuracy	Association between FluWatchers data compared with ILI and laboratory data	Pearson correlation for FluWatchers data and the weekly percentage of tests for influenza, other respiratory viruses and the SPIR data
Usefulness	Contribution to detection of cases and the program's impact and value-added applications	Qualitative assessment of other applications and the additional data variables

Abbreviations: ILI, influenza-like illness; SPIR, Sentinel Practitioner Influenza-like Illness Reporting

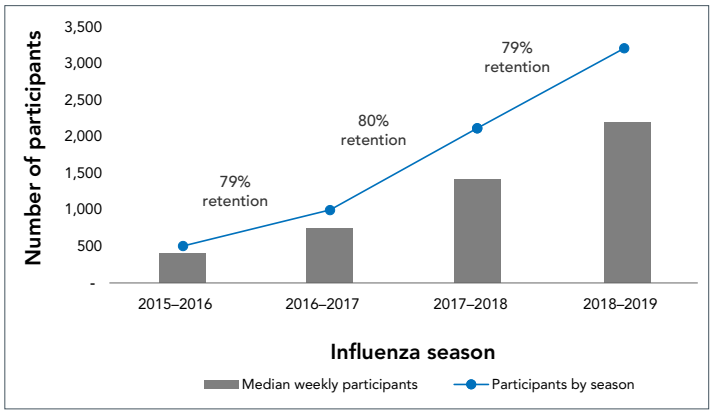
Analyses used data from epidemiological weeks 44 to 18 in the pilot 2015–2016 season, weeks 41 to 18 in 2016–2017 and weeks 40 to 18 in 2017–2018 and 2018–2019 to correspond to the weeks when the FluWatchers surveillance program was active. Analyses were performed in SAS 9.4 and Excel 2016.

Results

Acceptability

The number of FluWatchers participants increased from a weekly median of 500 participants in season 2015–2016 to just over 3,200 participants in season 2018–2019 (**Figure 1**). This represents a percent increase of 98% (from seasons 2015–2016 to 2016–2017), 112% (from 2016–2017 to 2017–2018) and 52% (from 2017–2018 to 2018–2019).

Figure 1: Number of FluWatcher participants and the median number of weekly participants by season, Canada, influenza seasons 2015–2016 to 2018–2019



There was a high retention rate among participants, with 79%–80% of participants continuing their participation to the following season: approximately 60% of participants who started in the 2015–2016 season were still participating in the 2018–2019 season.

The median number of participants also increased from 398 in 2015–2016 to 2,188 in 2018–2019. The average weekly response rate was 78% in 2015–2016, 78% in 2016–2017, 74% in 2017–2018 and 74% in 2018–2019.

Reliability

Across four seasons, FluWatchers was consistently more reliable than SPIR (i.e. the denominator was more consistent week to week). The percentage of weeks where the denominator (number of weekly FluWatcher participants) was found to be within ±5% of a season median ranged from 55%–64% (**Table 2**). This range is higher than the denominator (weekly number of patients seen) reported by SPIR sentinels, where only 26%–41% of reporting weeks were within ±5% of a respective season median. The percentage of weeks where the denominator was within ±10% or ±15% of a respective season median was always higher in the FluWatchers data. In the season 2018–2019 (**Figure 2**), the percentage of weeks where the denominator was found to be within ±5% of a season median was 65% in the FluWatchers data compared with 26% in the SPIR data. The percentage of weeks where the denominator was found to be within ±15% of the season median improved to 100% in the FluWatchers data and 65% in the SPIR data.

Accuracy

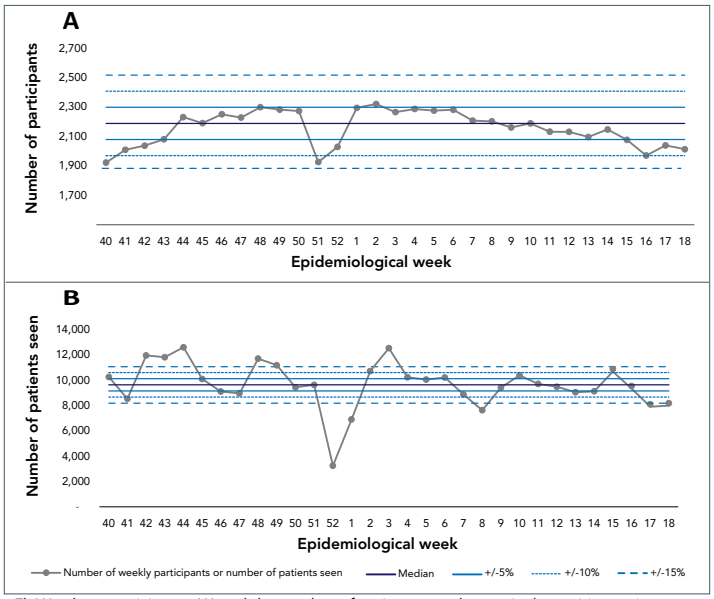
Across four seasons, when the weekly FluWatchers ILI rates were compared with the positivity rate of influenza from national surveillance system, there was a significant and strong correlation between the two datasets (**Figure 3**).

Table 2: Percentage of reporting weeks within ±5%, ±10% or ±15% of the median by program by season, Canada, influenza seasons 2015–2016 to 2018–2019

Season	Program	Percentage of reporting weeks within given percentage of the median		
		±5%	±10%	±15%
2015–2016	FluWatchers	55.6%	77.8%	85.2%
	SPIR	40.7%	59.3%	77.8%
2016–2017	FluWatchers	60.0%	86.7%	93.3%
	SPIR	36.7%	66.7%	80.0%
2017–2018	FluWatchers	61.3%	93.5%	96.8%
	SPIR	29.0%	64.5%	83.9%
2018–2019	FluWatchers	64.5%	93.5%	100.0%
	SPIR	25.8%	54.8%	64.5%

Abbreviation: SPIR, Sentinel Practitioner Influenza-like Illness Reporting System

Figure 2: Number of FluWatchers participants[a] and the number of patients seen by sentinel practitioners in Sentinel Practitioner Influenza-like Illness Reporting system, Canada, season 2018–2019



[a] FluWatchers participants (A) and the number of patients seen by sentinel practitioners in Sentinel Practitioner Influenza-like Illness Reporting System (B) within ± 5%, ±10% or ±15% of the median

Furthermore, when comparing the FluWatchers data to the positivity rate of other respiratory viruses across four seasons, there was either a weak or a negative correlation with adenovirus, enterovirus/rhinovirus, hMPV and parainfluenza (**Table 3**). There was a moderate to strong correlation between the FluWatchers data and seasonal coronavirus and RSV in all seasons except the 2015–2016 season.

Figure 3: Percentage of FluWatchers reporting cough and fever and national influenza positivity rate, Canada, seasons 2015–2016 to 2018–2019

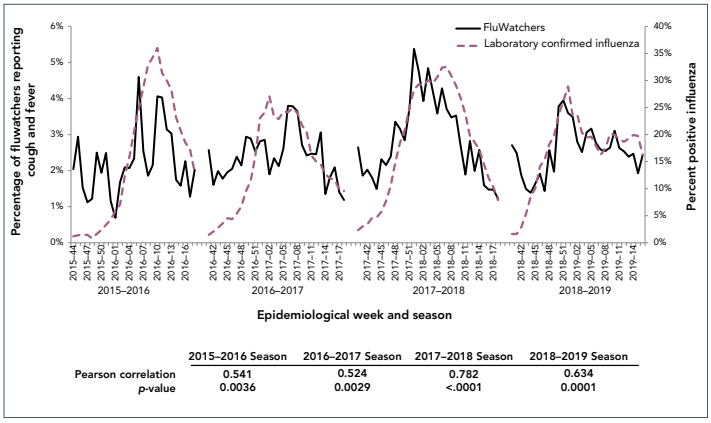


Table 3: Pearson correlation between FluWatchers reporting cough and fever and percentage of positive tests for other respiratory virus, Canada, seasons 2015–2016 to 2018–2019

Correlation with a given virus	Season			
	2015–2016	2016–2017	2017–2018	2018–2019
RSV	0.171	0.651*	0.555*	0.598*
Parainfluenza	-0.451*	-0.459*	-0.323	-0.179
Adenovirus	-0.515*	-0.252	-0.666*	-0.374*
hMPV	0.257	-0.135	-0.010	0.126
Rhinovirus/enterovirus	-0.403*	-0.521*	-0.609*	-0.296
Coronavirus	0.278	0.501*	0.738*	0.499*

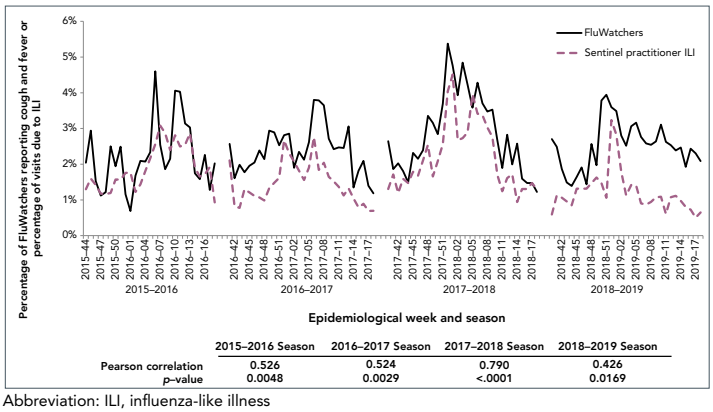
Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus
* Statistically significant *p*-value of <0.05

Weekly FluWatchers ILI rates were also compared to SPIR's weekly percentage of visits for ILI. The Pearson correlation coefficient varied across the four seasons ranging from moderate to strong (**Figure 4**). As a validation measure, the weekly percentage of visits for ILI was compared with the percentage of tests positive for influenza. During the four seasons, the correlation was variable between SPIR ILI and laboratory data, with a Pearson correlation coefficient (r) of 0.858, 0.685, 0.738 and 0.501 in seasons 2015–2016, 2016–2017, 2017–2018 and 2018–2019, respectively, all with statistically significant *p* values.

Usefulness

The FluWatchers program provided other data that had not previously been collected by PHAC or was not available weekly. These data include healthcare utilization, laboratory testing, vaccination status, absenteeism and demographic information such as age, gender, regular contact with patients and location (first three characters of a postal code—forward sortation area). Additionally, the FluWatchers program collected surveillance data from individuals who did not seek medical care or get tested.

Figure 4: Percentage of FluWatchers reporting cough and fever and percentage of visits due to influenza-like illnesses reported by sentinels, Canada, seasons 2015–2016 to 2018–2019



	2015–2016 Season	2016–2017 Season	2017–2018 Season	2018–2019 Season
Pearson correlation	0.526	0.524	0.790	0.426
p–value	0.0048	0.0029	<.0001	0.0169

Abbreviation: ILI, influenza-like illness

A more detailed analysis on healthcare utilization, vaccination status and absenteeism within the FluWatchers population can be found in the publication by Desroches *et al.* in this issue (9).

Discussion

Our analyses show that the FluWatchers program fulfills the four surveillance evaluation areas assessed.

Acceptability—Canadians are willing to participate in FluWatchers, as reflected by an increase in uptake over the four seasons and a high retention rate. In its fourth year of surveillance, the number of participants was comparable to that seen in mature participatory ILI surveillance systems, some of which have been established as early as 2005 and in countries with populations larger than Canada (10,11). Some programs from countries with smaller populations than Canada, such as the Flutracking in Australia and the De Grote Griepmeting system in Belgium and the Netherlands, have between 15,000 and 50,000 registered users. The United States' Flu Near You has over 50,000 users from a national population of over 327 million (10,11). FluWatchers is still a small and relatively new program and has the potential to attract and retain more participants.

Reliability—FluWatcher participants have been consistently providing data. The percentage of weeks where the number of FluWatcher participants (denominator) was within either ±5%, ±10% or ±15% from the season median was always higher than that of the SPIR system. Influenza season in Canada often peaks around Christmas and New Years (late December, early January), when data providers such as practitioners and laboratories may be at reduced capacities. This affects the timing and the quality of data around peak influenza season. FluWatchers participation consistently dropped in late December and early January; however, the drop was not as drastic as that seen for SPIR participants. Receiving consistent and reliable data is important in surveillance to interpret trends.

Accuracy—The FluWatchers data appeared to track influenza in Canada with a moderate to strong positive correlation to our main influenza activity indicator, the percentage of laboratory tests positive for influenza. The timing of the peaks suggest that FluWatchers ILI data peaks before the influenza laboratory data. This is not unexpected because one of the aims of syndromic surveillance is to identify an increase illness activity before formal diagnoses are confirmed and reported to public health agencies (12). The observed moderate to strong positive correlation between the FluWatchers data and seasonal coronavirus and RSV in all seasons (except the 2015–2016 season) and the weak or negative correlation with adenovirus, enterovirus/rhinovirus, hMPV and parainfluenza is also not unexpected. Seasonal coronavirus and RSV often circulate at the same time as influenza in Canada, while viruses such as enterovirus/rhinovirus often circulate outside the FluWatchers surveillance season (8). The FluWatchers' ILI case definition of cough and fever could identify activity of other respiratory viruses such as RSV and seasonal coronavirus. Since FluWatchers collects data on other symptoms, the FluWatchers case definition for ILI could be tailored to be more specific to influenza.

Usefulness—FluWatchers added value to the FluWatch surveillance program by filling gaps in data that is either not collected by PHAC or not available in a timely manner. Traditional surveillance programs within FluWatch typically capture the "tip of the iceberg" of influenza cases in Canada since only reports of positive laboratory confirmed cases are collected. FluWatchers may give us a better idea about the burden of influenza in Canada by capturing cases who did not seek medical attention or get tested for influenza, and by providing data on absenteeism and healthcare utilization. Additionally, the FluWatchers data can be used to inform work on initiatives such as the WHO's Pandemic Influenza Severity Assessment (PISA) (13). For example, "impact" is one of PISA's three main indicators, where school and work absenteeism due to influenza is recommended as a measurement of how an influenza epidemic affects society. Currently, data on the impact indicator is not currently available for Canada, and FluWatchers could potentially fill this gap with the weekly absenteeism data it collects.

Strengths and limitations

FluWatchers does have its limitations. The FluWatchers population differs from the Canadian population as seen in the 2016 Canadian Census: FluWatchers participants, while coming from all provinces and territories, from urban and rural settings, and all age groups, genders and influenza vaccine acceptance, under-represent the tails of Canada's age distribution and over-represent females, urban-dwelling Canadians and those who

engage in health promoting behaviors as indicated by high influenza vaccine coverage (9). This is not unique to Canada as other participatory surveillance systems around the world experience the same limitations but are still able demonstrate similar trends as traditional ILI sources (3,4,14,15). Despite this limitation, the FluWatchers data demonstrated positive attributes of other participatory surveillance systems, such as accuracy and sensitivity and being able to measure burden of illness (4,15). While the data provided by FluWatchers was comprehensive, further exploration of the data must be done and biases need to be quantified before using the data for other purposes than that of surveillance for ILI. The FluWatchers program is still in its infancy and public health practitioners can work towards using these data for other purposes, such as estimating vaccination coverage and effectiveness, informing disease transmission models, and supplying information for cost-benefit analyses of public health measures such as vaccination, as has been done by similar programs in other countries (4).

Conclusion

FluWatchers is an example of an effective and innovative surveillance program that was created to address limitations of traditional ILI surveillance in Canada. Currently, FluWatchers ILI rates are a formal indicator under syndromic surveillance and have been incorporated into Canada's weekly FluWatch report.

Authors' statement

LL — Writing, review, editing
MD — Review, editing
SM — Review, editing
CB — Review, editing

Competing interests

None.

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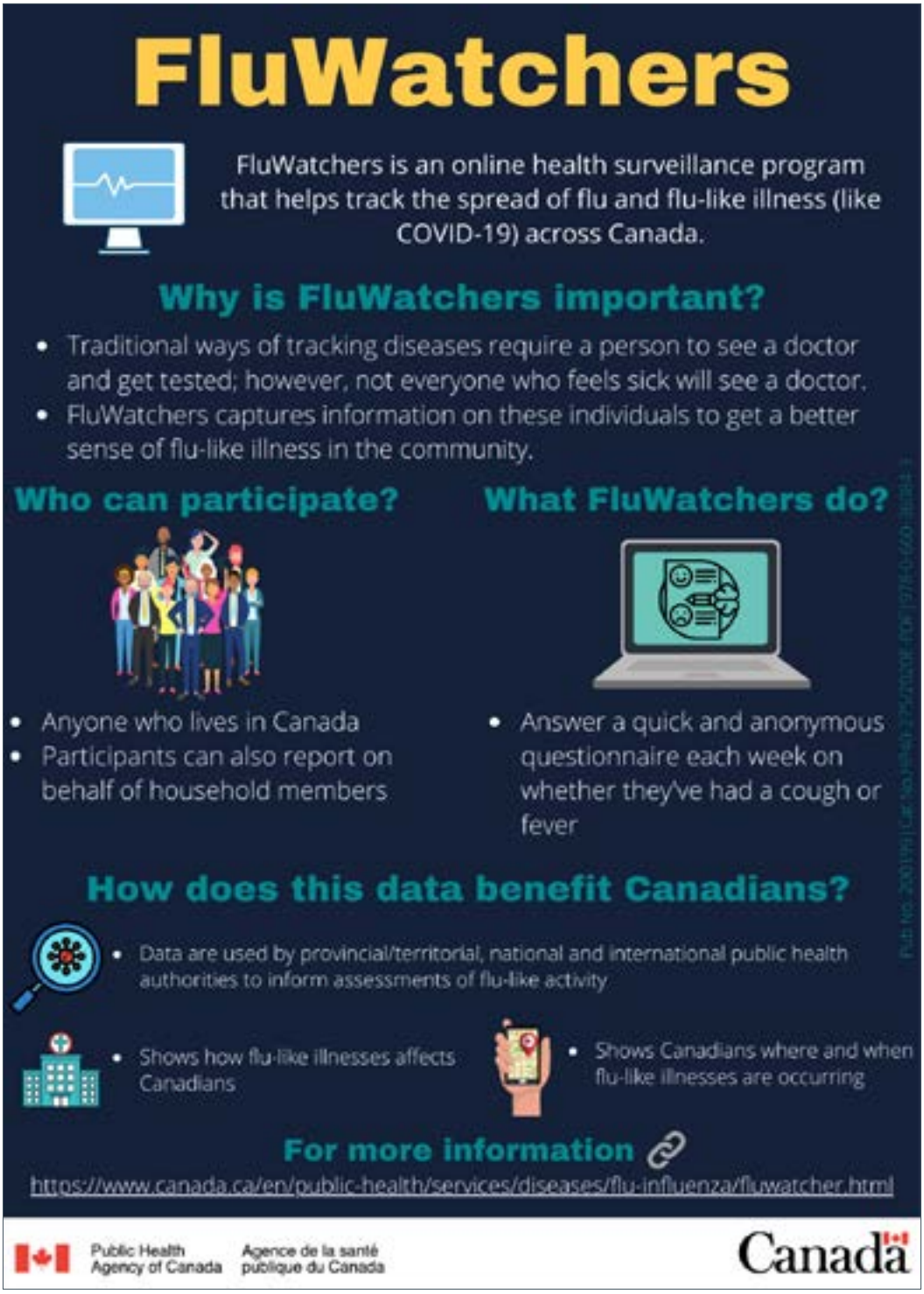

Representativeness of the FluWatchers Participatory Disease Surveillance Program 2015–2016 to 2018–2019: How do participants compare with the Canadian population?

Mireille Desroches[1]*, Liza Lee[1], Shamir Mukhi[2], Christina Bancej[1]

Abstract

Background: FluWatch is Canada's national surveillance system that monitors the spread of influenza. Its syndromic surveillance component monitors the spread of influenza-like illness (ILI) in near-real time for signals of unusual or increased activity. Syndromic surveillance data are collected from two main sources: the Sentinel Practitioner ILI Reporting System and FluWatchers.

We evaluated the representativeness of the most recent participant population to understand changes in representativeness since 2015, to identify demographic and geographic gaps and correlates/determinants of participation to characterize a typical participant.

Methods: In this serial cross-sectional study, characteristics of participants during four consecutive influenza seasons (2015–2016, 2016–2017, 2017–2018 and 2018–2019) were compared with the 2016 Canadian Census and the 2015–2016, 2016–2017, 2017–2018 and 2018–2019 National Seasonal Influenza Vaccination Coverage Surveys. Associations between demographic factors and the level of user participation were also analyzed among the 2018–2019 FluWatchers population.

Results: Infants (0–4 years) and older adults (65 years and older) were under-represented in FluWatchers across all four influenza seasons. Female and urban participants were significantly over-represented. Vaccination coverage remained significantly higher among the FluWatchers populations from the past four influenza seasons across all age groups. Level of participation among FluWatchers was associated with age and vaccination status, but not with sex or geography. Over its four years of implementation, the FluWatchers participant population became more representative of the Canadian population with respect to age and geography (urban/rural and provincial/territorial).

Conclusion: FluWatchers participants under-represent the tails of Canada's age distribution and over-represent those who engage in health promoting behaviours as indicated by high influenza vaccine coverage, consistent with typical volunteer-based survey response biases. Representativeness would likely improve with targeted recruitment of under-represented groups, such as males, older adults and Canadians living in rural areas.

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Keywords: influenza-like illness, syndromic surveillance, respiratory illness, Canada, online disease monitoring, digital epidemiology, crowdsourcing, participatory surveillance, public health

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Introduction

FluWatch is Canada's national surveillance system that monitors the spread of influenza. It is made up of seven components that, together, monitor the geographic spread of influenza and influenza-like illness (ILI), laboratory-confirmed detections, outbreaks, severe outcomes, strain characterization, antiviral resistance, and vaccine coverage and effectiveness (1). The FluWatch syndromic surveillance component relies on data from two main sources: the Sentinel Practitioner ILI Reporting system (SPIR), where primary care practitioners report the proportion of patients presenting with ILI each week (2); and FluWatchers, a program where Canadian volunteers are prompted to report whether they have had a cough and/or fever each week (1). Traditional, clinical-based syndromic surveillance data sources, such as SPIR, only capture cases of ILI among individuals who seek medical care (3). FluWatchers was developed as a complement to SPIR by aiming to track community ILI activity and to capture the spread of ILI among individuals who do not seek medical care.

The FluWatchers program, developed on the Canadian Network for Public Health Intelligence platform, was launched in 2015 as a pilot project. Recruitment focused primarily on the public health workforce where prospective participants were more amenable to participating in surveillance methods research. The number of participants has steadily increased each year, from 505 participants in the 2015–2016 influenza season, to 3,210 participants in the 2018–2019 influenza season. However, recruitment activities have been limited, resulting in a sample of Canadians that is both a convenience and purposive sample.

Like other online syndromic surveillance tools, FluWatchers has the potential to reach a very wide population by leveraging other data sources such as internet searches and social media (4). FluWatchers has shown to correlate well with influenza activity in Canada (5). Additionally, the use of participatory data for syndromic surveillance has been validated and other similar online tools have been shown to correlate well with traditional, clinical-based ILI syndromic surveillance for example, InfluenzaNet (Europe), FluTracking (Australia), GrippeNet (France) and Flu Near You (United States and Canada) (6–9).

Crowdsourced online syndromic surveillance tools, such as FluWatchers, monitor disease indicators in near real-time to serve as "early detection—early warning" systems to detect outbreaks before formal diagnoses are made (10). Reliable and timely indicator estimates of the spread of influenza are crucial for the early detection of unusual or increased influenza activity and for pandemic preparedness. To work effectively, it is imperative that FluWatchers participants be sufficient in quantity, diversity and geographical and population representativeness.

The objective of this study is to evaluate the representativeness of the most recent FluWatchers participant population against the Canadian population, to understand changes in representativeness since its pilot in 2015 and to characterize a typical FluWatcher to identify gaps and biases.

Methods

Sources of data and study populations

Any Canadian resident can sign up to participate in the FluWatchers program through the online FluWatchers registration (11). At the time of registration with a valid email address, participants provide their year of birth, gender (male, female or gender diverse) and forward sortation area code (FSA; first three characters of the postal code), report whether they have regular contact with patients, and have the option to add any household members to report on their behalf. Each weekly questionnaire, sent in the form of an email notification, asks the participant if they have experienced cough and/or fever in the previous week, and whether they have received their annual influenza vaccination. When ILI symptoms are reported (cough and fever reported in the same week), participants are prompted to answer more questions enabling collection of additional information on absenteeism and health-seeking behaviours. All data are anonymous and are collected from epidemiological week 40 to 18 each season (October through May). National estimates on age, sex and geographical distribution were obtained from the 2016 Canadian Census (12). National estimates on vaccination coverage were obtained from the 2015–2016, 2016–2017, 2017–2018 and 2018–2019 Seasonal Influenza Vaccination Coverage Surveys (13–16).

For this study, FluWatchers participants were defined as those who submitted at least one questionnaire over the respective influenza seasons (2015–2016, 2016–2017, 2017–2018 or 2018–2019), and who had complete year of birth, gender/sex (male or female) and FSA information. Participants who submitted reports with gender "gender diverse" (n<5) were excluded from this study as this information is not available from the 2016 Canadian Census (17), and thus could not be compared between the two populations. There were no other inclusion/exclusion criteria.

For most measures, data from the 2018–2019 influenza season were used, as they best represent the current participant population.

Measures

The characteristics and representativeness of FluWatchers participants' age, sex and geography were assessed against the Canadian Census estimates as follows:

- Age-distribution: infants (0–4 years), children (5–19 years), young adults (20–44 years), adults (45–64 years) and older adults (65 years and older)

- Sex distribution: male or female
- Geographic distribution: urban or rural, as determined using the second digit of the FSA (with second digit 0 indicated a wide-area rural region, and 1–9 indicated urban areas (18))
- Mean response rate per 100,000 population by province/territory: derived using the weekly average number of responses in a given province/territory as the numerator and Canadian Census estimates by province/territory as the denominator

The FluWatchers participants vaccination coverage were assessed against the Canadian 2015–2016, 2016–2017, 2017–2018 and 2018–2019 Seasonal Influenza Vaccination Coverage Surveys as follows:

- Age-specific influenza vaccination coverage: 18 years and older, 18–64 years, and 65 years and older (13–16)

Influenza vaccine coverage among children younger than 18 years could not be compared as no national survey estimates exist that provide coverage estimates in the pediatric population.

The levels of participation among the 2018–2019 FluWatchers population were defined as follows:

- Low level of participation: participants who completed fewer than 12 surveys over a whole influenza season
- Medium level of participation: participants who completed between 12 and 25 surveys over a whole influenza season
- High level of participation: participants who completed more than 25 surveys over a whole influenza season

Statistical analysis

For age, sex and urban/rural distributions, FluWatchers participants were compared to the 2016 Census population. For vaccination coverage, FluWatchers participants were compared to the Canadian 2015–2016, 2016–2017, 2017–2018 and 2018–2019 Seasonal Influenza Vaccination Coverage Survey populations, using Pearson chi-square tests. Similarly, the distribution of the FluWatchers population by province/territory was compared to Census estimates using a Fisher's exact test.

The sex-stratified age distribution of FluWatchers participants from the 2018–2019 influenza season was summarized and compared with the 2016 Canadian Census population, with male:female ratios and 95% confidence intervals.

Associations between demographic factors and the level of participation among participants from the 2018–2019 influenza season were analyzed using multiple logistic regression. Participants younger than 18 years of age were excluded from this analysis and could not be classified as high, medium or low-level participants as their participation likely depends on that of a household member submitting reports on their behalf. Age group, sex, geography and vaccination status were treated as independent variables in the model. Participants were classified into three categories of participation: high; medium; and low, according to the number of surveys completed over the influenza season. The cut off numbers used to define the level of participation were determined empirically by assessing a histogram of the number of surveys completed. The adult age group was used as the reference for odds ratio estimation as it comprised the largest number of participants. Females and the "not vaccinated" groups were used as the references for sex and vaccination status odds ratio estimates for the same reason.

All analyses were performed using SAS-EG 7.1.

Results

Representativeness of FluWatchers participants from the 2018–2019 influenza season

Over the 2018–2019 influenza season, a total of 3,210 FluWatchers participants met the inclusion criteria with a collective total of 66,808 questionnaires submitted.

The mean age of participants was 41.2 ± 18.6 years and the median age was 43 years (IQR=24) comparable to the 2016 Census population (mean [SD]: 41.0 ± 22.8 years) (**Table 1**). The adult age group had the highest proportion of participants (37.2%), and the infant age group had the smallest proportion of participants (2.2%). Each relevant age group was represented among the FluWatchers population; however, FluWatchers' age distribution significantly differed from that of the 2016 Census population ($p<0.0001$) (Table 1). Overall, adults were over-represented while infants and older adults were significantly under-represented ($p<0.0001$).

Of those 3,210 participants, 2,071 were female (64.5%) and 1,139 were male (35.5%). Females were significantly over-represented compared to the 2016 Census population (50.9%, $p<0.0001$). Similarly, FluWatchers participants' geographical distribution significantly differed from that of the 2016 Census population ($p<0.0001$). The majority (n=2,873; 89.5%), of FluWatchers participants had FSA codes for urban areas, while only 337 participants (10.5%) had FSA codes for rural regions. Thus, participants residing in urban areas were significantly over-represented relative to the Canadian population ($p<0.0001$).

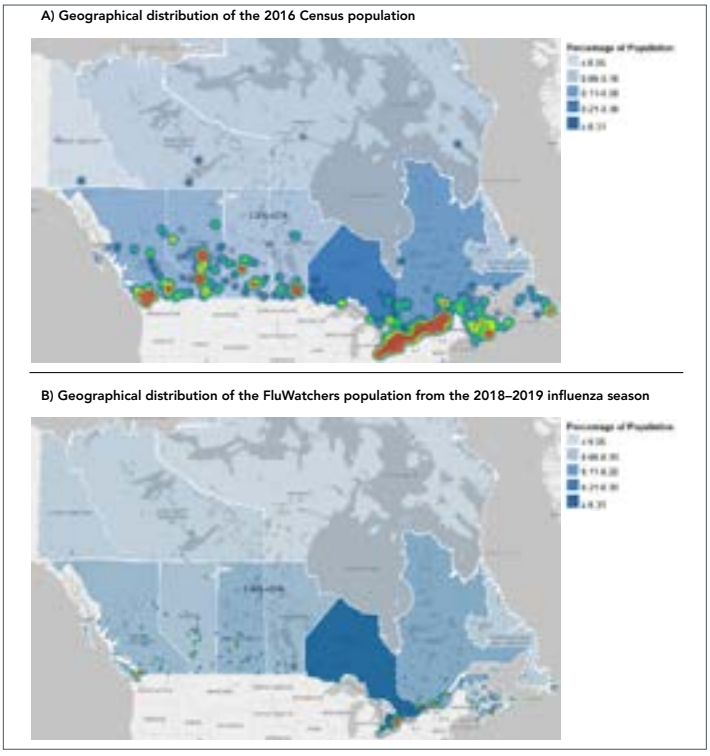
The distribution of the FluWatchers participants was compared geographically to the 2016 Census population distribution (**Figure 1**). Ontario and Saskatchewan were the most over-represented, while Québec and Alberta were the most underrepresented provinces. The average weekly response rate per province/territory was highest in the Yukon Territory (31.1 weekly submissions per 100,000 population) followed by Prince Edward Island, Saskatchewan, Manitoba, Nova Scotia, Northwest Territories, Ontario, New Brunswick, Newfoundland,

Table 1: Summary of FluWatchers participants from the 2015–2016 to 2018–2019 influenza seasons compared with the 2016 Canadian Census population

Characteristic	FluWatchers				2016 Canadian Census (n=35,151,730)
	2015–2016 (n=505)	2016–2017 (n=998)	2017–2018 (n=2,114)	2018–2019 (n=3,210)	
Mean ± SD	38.5 ± 18.1	38.8 ± 17.8	40.6 ± 17.5	41.2 ± 18.6	41.0 ± 22.8
Median	42	42	43	43.0	41.2
IQR	31	25	23	24	37
Age, year (%)					
Infants (0–4)	0.0	1.2	1.2	2.2	5.4
Children (5–19)	24.0	20.7	17.4	16.7	17.0
Young adults (20–44)	34.9	36.9	36.8	37.0	32.4
Adults (45–64)	36.6	37.7	39.5	37.2	28.3
Older adults (65 and older)	4.6	3.5	5.6	6.9	16.9
Sex (%)					
Male	42.2	40.1	37.0	35.5	49.1
Female	57.8	59.9	63.0	64.5	50.9
Geography (%)					
Urban	96.0	92.1	90.9	89.5	83.3
Rural	4.0	7.9	9.1	10.5	16.7

Abbreviations: IQR, interquartile range; SD, standard deviation

Figure 1: Comparison of the geographical distribution of the 2016 Canadian Census population and the geographical distribution of the FluWatchers population from the 2018–2019 influenza season



Population density by province/territory is displayed in blue, ranging from dark blue to light blue. Heat map colors represent population distribution in each respective map, ranging from green to red, where cool colors (green to yellow) represent lower density and warm colors (orange to red) represent higher density

Québec, British Columbia, Alberta and Nunavut (17.9, 16.5, 13.7, 10.5, 8.6, 7.6, 5.7, 3.9, 3.8, 3.7, 2.3, 0.1 weekly submissions per 100,000 population, respectively). There was a difference between the geographical distribution of all registered FluWatchers compared with provincial/territorial average weekly response rates. For example, Ontario is one of the most over-represented provinces in terms of its proportion of registered participants but ranks among the lowest of the provinces and territories in terms of average weekly response rate per 100,000 population. Overall, the geographical distribution of the FluWatchers population is not representative of the 2016 Census population and significantly differed from the average weekly response rates ($p<0.0001$).

When comparing the sex-stratified age distribution of the FluWatchers population compared with that of the 2016 Census population (**Table 2**), the male to female sex ratios were almost equal in the children and older adult categories. The young adults' and adults' sex ratios differed most from those of the 2016 Census population, as there were 71% and 67% more women than men, respectively.

Among 2018–2019 FluWatchers participants, 65.9% of adult female participants received their seasonal influenza vaccination compared to 46.8% among adult female Canadians in the same year. Similarly, 59.4% of male FluWatchers received their seasonal influenza vaccination compared to only 36.6% among male Canadians in the same year. Vaccination coverage was significantly different between males and females from

Table 2: Summary of FluWatchers participants sex-stratified age distribution from the 2018–2019 influenza season compared with the 2016 Canadian Census population

Characteristics	2018–2019 FluWatchers population (n=3,210)			2016 Census population (n=35,151,730)		
	Males n=1,139	Females n=2,071	Sex ratio (M:F)	Males n=17,264,200	Females n=17,887,540	Sex ratio (M:F)
Infants (0–4)						
Number	n=31	n=40	0.78	n=973,030	n=925,760	1.05
%	2.7	1.9		4.4	5.2	
95% CI	2.7–2.8	1.9–2.0		4.3–4.4	5.1–5.2	
Children (5–19)						
Number	n=273	n=264	1.03	n=3,059,100	n=2,907,830	1.05
%	23.9	12.7		13.7	16.3	
95% CI	23.9–24.0	12.7–12.8		13.6–13.7	16.2–16.3	
Young adults (20–44)						
Number	n=341	n=847	0.40	n=5,660,330	n=5,741,250	0.99
%	29.94	40.9		25.3	32.1	
95% CI	29.9–30.0	40.8–40.9		25.3–25.4	32.0–32.1	
Adults (45–64)						
Number	n=394	n=799	0.49	n=4,876,590	n=5,072,215	0.96
%	34.6	38.6		44.5	28.4	
95% CI	34.5–34.6	38.5–38.6		44.5–44.8	28.3–28.4	
Older adults (65 and older)						
Number	n=100	n=121	0.83	n=2,695,150	n=3,240,485	0.83
%	8.8	5.8		12.1	18.1	
95% CI	8.7–8.8	5.8–5.9		12.0–12.1	18.1–18.2	

Abbreviations: CI, confidence interval; F, female; M, male

both populations, although they show a similar trend in that vaccination coverage is higher among females in both populations. Vaccination coverage across all three adult age groups (**Table 3**) was consistently higher among the FluWatchers population over the four influenza seasons.

Comparisons of FluWatchers participants characteristics and representativeness from the 2015–2016 to 2018–2019 influenza seasons

All other descriptive statistics summarized in Table 1 were similar over the four influenza seasons.

Associations between demographic factors and the level of user participation

Table 4 presents a summary of the adjusted odds ratios of being a FluWatcher participant with a high level of participation. Of the 2,650 participants from the 2018–2019 influenza season aged 18 years or older, 1,288 (49%) were classified under the high level of participation, 767 (29%) under the medium level of participation and 595 (22%) under the low level of participation. Age group and vaccination status were statistically significant correlates of level of participation.

The odds of a FluWatcher participating at the high level increased with increasing age category. Those who received their annual influenza vaccination were 1.35-fold more likely to be a high-participation FluWatchers participant. Sex was not correlated with high participation in the full model ($p>0.05$). A descriptive analysis of the level of participation variable by sex revealed the proportions of males and females among each level of participation were nearly the same, although actual counts significantly differed. A typical FluWatcher was a high level of participation user in the 45–64 years of age group, female, vaccinated and residing in an urban area.

Table 3: Summary of FluWatchers participants vaccination coverage[a] from the 2015–2016 to 2018–2019 influenza seasons compared with the Seasonal Influenza Vaccination Coverage Survey results from the 2015–2016 to 2018–2019 surveys

Age group	2015–2016		2016–2017		2017–2018		2018–2019	
	FluWatchers (n=505)	SIVCS (n=2,000)	FluWatchers (n=998)	SIVCS (n=2,024)	FluWatchers (n=2,114)	SIVCS (n=2,850)	FluWatchers (n=3,210)	SIVCS (n=3,726)
All adults[b]	67.8	34.3	57.0	35.8	58.5	38.3	63.7	41.8
18–64	67.7	27.9	56.7	28.5	57.5	29.7	61.8	34.3
65 and older	69.6	64.6	62.9	69.5	73.6	70.7	85.1	69.9

Abbreviation: SIVCS, Seasonal Influenza Vaccination Coverage Survey
[a] Vaccination coverage by age group, year and percentage
[b] 18 years of age and older

Table 4: Summary table of adjusted odds ratios of being a high level of participation FluWatchers participant in the 2018–2019 influenza season

Variable	Reference group	Percentage at high level of participation (%)	Adjusted odds ratio	95% CI	*p*-value
Age group (years)					
25 and younger	45–64	0.5	0.79	0.57–1.09	0.0154
26–44	45–64	37.8	0.75	0.65–0.88	0.0003
45–64	N/A	50.8	1.0[a]	N/A	N/A
65 and older	45–64	10.9	1.34	1.01–1.78	0.0453
Sex					
Sex: male	Female	69.2	0.87	0.74–1.02	0.0710
Vaccination status					
Vaccination status: not vaccinated	Vaccinated	72.5	0.81	0.61–0.83	0.0003

Abbreviations: CI, confidence interval; N/A, not applicable
[a] Reference group

Discussion

Since its inception in the 2015–2016 influenza season, FluWatchers has recruited participants from all provinces and territories and across all age groups, participants who identify as male, female and gender diverse, individuals residing in rural and urban settings and those who did/did not receive the seasonal influenza vaccine. Overall, the FluWatchers population has improved in its representativeness of the Canadian population along measures such as age, rural/urban and provincial/territorial participation. However, over-representativeness has increased among females and persons reporting receipt of annual influenza vaccination. Though FluWatchers has shown to correlate well with influenza activity in Canada thus far, overall, the FluWatchers population is not representative of the 2016 Census population by age, sex and geography.

The infant and older adult age groups remain under-represented; however, these groups have seen the most improvement in representativeness. The geographical representativeness has improved as well; however, Ontario and Saskatchewan are over-represented, and Québec and Alberta are underrepresented in the FluWatchers population. The provincial and territorial average weekly response rates per 100,000 population were not higher in provinces with more participants. As the influenza season in Canada often begins in the west and makes its way east, under-representation in the westernmost provinces limits FluWatchers as an early detection—early warning system. Additionally, there are gaps in participation particularly among the northern provinces/territories with too few participants from the territories to permit estimation of key surveillance parameters or statistical analysis. Overall, the geographic distribution of all registered FluWatchers and the geographic distribution using average weekly response rates lack in their representativeness of the 2016 Census population. The vast majority (90%) of FluWatchers participants are clustered around large urban areas (e.g. greater metropolitan areas in Ontario).

The FluWatchers population remains female-dominant (64.5%). Given the increase in reporting patterns among females over the past four influenza seasons, underlying factors like methods of recruitment, program advertising and high employment rates of women in the public health sector may be driving this

participation bias. This trend is consistent with findings from other studies on similar participatory surveillance programs that show women are more interested in health-related topics and show more active online information-seeking behaviour (19). Participants of InfluenzaNet, FluTracking and Flu Near You surveillance systems were more likely to be female than in their respective target general populations (6,20,21). These findings are also consistent with survey response and non-response studies that show women, affluent and younger individuals are more likely to participate in survey-based programs than men, less affluent and older individuals (22).

Level of vaccination coverage

The FluWatchers population vaccination coverage has remained steady over the years. A high proportion of FluWatchers participants report receiving their annual influenza vaccinations, which differs from influenza vaccination behaviours of the general Canadian population (63.7% among all adults aged 18 years or older in the 2018–2019 influenza season compared to only 41.8% in the 2016 Census population, $p<0.0001$).

Level of participation

A higher level of participation among FluWatchers participants was associated with age and vaccination status. Geography did not correlate with the level of participation. Sex was also not a useful predictor of the level of participation. While there is significant over-representation of females among the FluWatchers population, the distribution of males and females among the high, medium and low levels of participation were nearly the same. A similar study on Flu Near You participants found odds ratios comparing participation habits among males and females were also close to one and InfluenzaNet found that there were no significant differences between males and females on the level of participation (6,23). Approximately 25% (n=761) of FluWatchers participants submitted all 31 reports over the 2018–2019 influenza season, and over 1,200 classified as high-level users. The average FluWatcher participant is a high-level user.

Limitations

One of the limitations of this study is that data on socioeconomic status and chronic diseases are not collected by the FluWatchers program, and thus could not be analyzed or compared with the general Canadian population. Additionally, Canadians living in non-household dwellings (e.g. long-term care facilities, correctional facilities, etc.) likely face different barriers to participating in the FluWatchers program versus the Canadian Census, due to different data collection methods (12). Similar studies on programs such as GrippeNet and Flu Near You, with similar participant population distributions (age, sex and vaccination status), showed that the majority of participants had at least a high school diploma, paid employment, access to their own car (did not rely on public transport), were not smokers and had a healthy body mass index (6,8). There is a strong likelihood that FluWatchers participants will exhibit the same characteristics.

As the FluWatchers population is a convenience and purposive sample, the extent to which the results can be generalized to the general Canadian population is related to the extent to which FluWatchers participants reflect their respective group (a typical FluWatchers participant is a vaccinated female adult living in an urban area). Additionally, it is not currently possible to assess the magnitude of selection bias in the sample. More research is needed to better understand the bias among the FluWatchers population and how it affects the interpretation of the surveillance data and its future use of the data for non-surveillance purposes. Furthermore, by quantifying the bias, we will be able to make better recommendations for future recruitment goals.

Conclusion

With targeted recruitment of under-represented groups (males and older adults) and under-represented geographical areas (western and northern Canada), the FluWatchers population has the potential to become more representative of the Canadian population, as demonstrated by its improvements over the last four influenza seasons. With these strategic efforts, it has the potential to become a more robust and complementary surveillance system that will benefit the Canadian population and will improve the accuracy of the early detection—early warning system that influenza syndromic surveillance strives to achieve.

Authors' statement

MD — Participated in data acquisition, analyzed and interpreted the data, and drafted the manuscript
LL — Participated in data acquisition, reviewed and edited the manuscript
CB — Reviewed and edited the manuscript
SM — Reviewed and edited the manuscript

Competing interests

None.

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Fifteen seconds of your time each week can make a difference in public health. For more information on the program and sign-up information, visit the following site: https://www.canada.ca/en/public-health/services/diseases/flu-influenza/fluwatcher.html.

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Summary of the National Advisory Committee on Immunization (NACI) Seasonal Influenza Vaccine Statement for 2021–2022

Angela Sinilaite[1], Kelsey Young[1], Robyn Harrison[2,3] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Several influenza vaccines are authorized in Canada and the evidence on influenza immunization is continually evolving. The National Advisory Committee on Immunization (NACI) provides recommendations regarding the use of seasonal influenza vaccines annually to the Public Health Agency of Canada (PHAC).

Objective: To summarize NACI recommendations regarding the use of seasonal influenza vaccines for 2021–2022 and to highlight new recommendations.

Methods: Annual influenza vaccine recommendations are developed by NACI's Influenza Working Group for consideration and approval by NACI. The development of the recommendations is based on the NACI evidence-based process.

Results: The following new recommendations were made: 1) Influvac® Tetra may be considered as an option among the standard dose quadrivalent inactivated influenza vaccines (IIV4-SD) offered to adults and children three years of age and older; 2) Fluzone High Dose Quadrivalent (IIV4-HD) may be considered an option for individuals 65 years of age and older who are currently recommended to receive Fluzone® High Dose (trivalent); and 3) Flucelvax® Quad may be considered amongst the quadrivalent influenza vaccines offered to adults and children nine years of age and older for annual influenza immunization. Guidance for use of influenza immunizations during the coronavirus disease 2019 pandemic is also highlighted.

Conclusion: NACI continues to recommend that an age-appropriate influenza vaccine should be offered annually to anyone six months of age 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.

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Keywords: National Advisory Committee on Immunization, NACI, influenza, influenza vaccine, guidance

Introduction

Seasonal influenza is an infectious viral illness that occurs globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children (1). Epidemics of seasonal influenza occur annually in Canada, generally in the late fall and winter months; however, the burden of influenza illness can vary from year to year. Current information on influenza activity globally can be found on the World Health Organization's FluNet website (2) and nationally on the Public Health Agency of Canada's (PHAC) FluWatch website (3).

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 development of the annual influenza vaccine recommendations, which 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 on a variety of issues, which can include the following: the burden of influenza illness and the target populations for vaccination, efficacy, effectiveness, immunogenicity and safety of influenza vaccines, vaccine schedules, and other aspects of influenza immunization. Issues related to ethics, equity, feasibility and acceptability are also systematically examined by NACI for comprehensive development of vaccine guidance (4).

The objective of this article is to provide a concise summary of NACI's recommendations and supporting information for the 2021–2022 influenza season, including conclusions from reviews of evidence on 1) a new, biosimilar, egg-based, quadrivalent inactivated influenza vaccine (Influvac® Tetra; IIV4-SD), 2) a new quadrivalent, egg-based high dose inactivated influenza vaccine (Fluzone® High Dose Quadrivalent; IIV4-HD), and 3) a mammalian cell culture-based influenza vaccine (Flucelvax® Quad; IIV4-cc). 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 2021–2022* (the Statement) (5) and related publications.

Influenza vaccine abbreviations

Updated abbreviations used by NACI to describe the defining features of various types of influenza vaccines are presented in **Table 1**.

Table 1: National Advisory Committee on Immunization (NACI) 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
Live attenuated influenza vaccine (LAIV)	Trivalent (LAIV3)	Unadjuvanted, Nasal spray, egg-based	LAIV3
	Quadrivalent (LAIV4)	Unadjuvanted, Nasal spray, egg-based	LAIV4

Abbreviations: 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; IM, intramuscular; 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

[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 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

Source: Table reproduced from *NACI Seasonal Influenza Vaccine Statement for 2021–2022* (5)

Methods

In the preparation of the 2020–2021 seasonal influenza vaccine recommendations, NACI's 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 (6). For a more detailed explanation of the strength of NACI recommendations and the grading of evidence refer to **Appendix Table A1**. 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 (4).

For the 2020–2021 influenza season, the IWG reviewed evidence regarding the use of two new vaccines: 1) Influvac Tetra, a new biosimilar, egg-based, quadrivalent inactivated influenza vaccine; and 2) Fluzone High Dose (HD) Quadrivalent an egg-based high dose quadrivalent inactivated influenza vaccine (IIV4). Influvac Tetra (IIV4-SD) was first authorized for use in Canada in adults in March 2019 and subsequently in children three years of age and older in February 2020. Fluzone High Dose (HD) Quadrivalent was first authorized for use in Canada in adults in June 2020. A trivalent formulation, Fluzone High-Dose, was previously authorized for use in adults 65 years of age and older in Canada, and recommended by NACI, but marketing of the vaccine was discontinued as of February 2021. Following the review and

analysis of available pre-licensure clinical trial data and Health Canada's Clinical Review Reports for these two vaccines, the IWG proposed new recommendations for vaccine use to NACI. NACI critically appraised the available evidence and approved the specific recommendations brought forward.

Recommendations and supporting evidence on the use of mammalian cell culture-based, inactivated seasonal influenza vaccine (Flucelvax Quad) from the *NACI Supplemental Statement – Mammalian Cell Culture-Based Influenza Vaccines* (7) were also incorporated into the *Statement on Seasonal Influenza Vaccine for 2021–2022*. Flucelvax Quad is the first and only available mammalian cell culture-based inactivated seasonal influenza vaccine in Canada; it was first authorized for use in adults and children nine years of age and older on November 22, 2019. The IWG oversaw the completion of a systematic review to inform the development of guidance on the use of Flucelvax Quad (IIV4-cc). Six electronic databases (EMBASE, MEDLINE, Scopus, ProQuest Public Health and ClinicalTrials.gov) were searched from inception until February 12, 2019, using a predefined search strategy to identify relevant literature on the efficacy, effectiveness, immunogenicity and safety in adults and children four years of age and older. Registered clinical trials and grey literature from international public health authorities and National Immunization Technical Advisory Groups were also considered. Additionally, hand-searching of the reference lists of included articles was performed by one reviewer to identify additional relevant publications. Two reviewers independently screened the titles and abstracts of records retrieved from the search and eligible full-text articles for inclusion. One reviewer extracted data from eligible studies and appraised the methodological quality of these studies using the criteria outlined by Harris *et al.* (8). A second reviewer independently validated the data extraction and quality assessment. A narrative synthesis of the extracted data was performed. NACI provided new recommendations based on assessment of the evidence.

Results

Use of seasonal influenza vaccine in the presence of the novel coronavirus disease 2019 (COVID-19)

In light of the ongoing coronavirus disease 2019 (COVID-19) pandemic, PHAC, in consultation with NACI and the Canadian Immunization Committee, has developed the following additional guidance on the delivery of influenza vaccination programs and administration of seasonal influenza vaccine to support provincial and territorial vaccine programs and primary care providers during the COVID-19 pandemic for 2021–2022:

- *Guidance for Influenza Vaccine delivery in the presence of COVID-19* (9)
- *Guidance on the use of seasonal influenza vaccine in the presence of COVID-19* (10)

This guidance is based on currently available scientific evidence and expert opinion. The content will be reviewed regularly, and updates will be made as necessary throughout the upcoming influenza season as the public health context evolves and new evidence and policy issues emerge.

New egg-based quadrivalent influenza vaccine

NACI concluded that Influvac Tetra is safe and has non-inferior immunogenicity to the trivalent Influvac formulation. Therefore, NACI recommended that **Influvac Tetra may be considered among the standard dose quadrivalent inactivated influenza vaccines (IIV4-SD) offered to adults and children three years of age and older (Discretionary NACI Recommendation).**

New egg-based high dose quadrivalent influenza vaccine

NACI concluded that Fluzone High Dose Quadrivalent is comparably safe and has non-inferior immunogenicity to the previously authorized trivalent Fluzone High Dose formulation. Therefore, NACI has issued the following discretionary individual-level recommendation on the use of Fluzone High Dose Quadrivalent (IIV4-HD): **For individuals 65 years of age and older whom are currently recommended to receive Fluzone High Dose (trivalent), NACI recommends that Fluzone High Dose Quadrivalent (IIV4-HD) may be considered as an option (Discretionary NACI Recommendation)**. Recommendations for public health programs remain unchanged at this time.

Inclusion of mammalian cell culture-based quadrivalent influenza vaccine

The peer-reviewed published evidence on the effectiveness, immunogenicity and safety of IIV4-cc manufactured using fully cell-derived viruses was sparse. The systematic review identified four observational studies (11–14) investigating the vaccine effectiveness of IIV4-cc compared with egg-based IIV and two peer-reviewed randomized controlled trials that assessed the immunogenicity and safety of IIV4-cc compared with different IIV3-cc formulations (produced using the same Madin-Darby Canine Kidney [MDCK] cell culture-based manufacturing process). There was evidence indicating that IIV4-cc may be more effective than egg-based IIV3 and IIV4 influenza vaccines against non-laboratory confirmed influenza-related outcomes, including influenza-related health care interactions and influenza-like-illness (ILI). Although some data suggest that IIV4-cc may be more effective against laboratory-confirmed influenza A(H3N2) virus infection than egg-based IIV, there was no consistent and statistically significant difference in effectiveness identified for adults or children vaccinated with IIV4-cc compared with egg-based IIV. Two studies that assessed the immunogenicity and safety of IIV4-cc compared with different IIV3-cc formulations (produced by Seqirus using the same MDCK cell culture-based manufacturing process) were identified in this review (15,16). There was also evidence indicating that IIV4-cc has a comparable

immunogenicity and safety profile to egg-based influenza vaccines already licensed in Canada and the trivalent formulation of this cell culture-based influenza vaccine that has been licensed in the United States and Europe, but for which licensure has never been sought in Canada (17–22).

Based on assessment of the available pre-licensure and post-market clinical trial and observational data, NACI concluded that IIV-cc is an effective, safe, well-tolerated and immunogenic alternative to conventional egg-based influenza vaccines for children and adults. Therefore, NACI has made the following recommendation, supplementing NACI's overarching recommendation for influenza vaccination, which is available in the *NACI Seasonal Influenza Vaccine Statement* (5):

NACI recommends that Flucelvax Quad may be considered among the IIV4 offered to adults and children nine years of age and older (Discretionary NACI Recommendation).

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

For complete details of this review, rationale, relevant considerations and additional information supporting this recommendation, refer to the *NACI Supplemental Statement: Mammalian Cell Culture-Based Influenza Vaccines* (7). Notably, Flucelvax Quad was recently authorized by Health Canada for use in adults and children two years of age and older. This updated authorized age indication supersedes theinformation for Flucelvax Quad found in relevant sections within the *NACI Statement on Seasonal Influenza Vaccine for 2021–2022* (5). Further details are available in the new product monograph for this vaccine (23).

Summary of National Advisory Committee on Immunization recommendations for the use of influenza vaccines for the 2021–2022 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 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 women
- 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

- Health care 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 child care 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 Canadian Immunization Guide for additional information about vaccination of people with chronic diseases (24)
Source: List reproduced from *NACI Seasonal Influenza Vaccine Statement for 2021–2022* (5)

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 (nine years of age and over) LAIV4	• An age appropriate IIV4-SD, LAIV4, or IIV4-cc (IIV4-cc only authorized for nine years of age and older) should be used in children without contraindications, including those with non-immune compromising 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. o There are currently no IIV4-cc vaccines licensed for children younger than nine years of age. • LAIV4 may be given to children with: o Stable, non-severe asthma o Cystic fibrosis who are not being treated with immunosuppressive drugs (e.g. prolonged systemic corticosteroids) o Stable HIV infection, if the child is currently being treated with HAART and has adequate immune function • LAIV should not be used in children for whom it is contraindicated for, such as those with: o Severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing) o Medically attended wheezing in the seven days prior to vaccination o Current receipt of aspirin or aspirin-containing therapy o Immune compromising conditions, with the exception of stable HIV infection, i.e. if the child is treated with HAART (for at least four months) and has adequate immune function • LAIV is contraindicated in pregnant adolescents. IIV4-SD or IIV4-cc[c] should be used instead. • If IIV4-SD, IIV4-cc[c], and LAIV4 are not available, IIV3-SD should be used.	
18–59 years	IIV3-SD[a] IIV4-SD IIV4-cc LAIV4	• Any of the available influenza vaccines should be used in adults without contraindications. o There is some evidence that IIV may provide better efficacy than LAIV in healthy adults • LAIV is not recommended for the following: o Pregnant women o Adults with any of the chronic health conditions identified in List 1, including immune compromising conditions o Healthcare workers	
60–64 years	IIV3-SD[a] IIV4-SD IIV4-cc	Any of the available influenza vaccines should be used in those without contraindications.	
65 years and older[d]	IIV3-SD[a] IIV3-Adj IIV3-HD[e] IIV4-SD IIV4-cc	**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. o 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 should be used. o 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: 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

[a] IIV3-SD formulations will not be available for use in Canada during the 2021-2022 influenza season

[b] Refer to Table 4 of the *NACI Seasonal Influenza Vaccine Statement for 2021–2022* for a summary of vaccine characteristics of LAIV compared with IIV in children 2–17 years of age

[c] IIV4-cc is currently authorized for use in adults and children nine years of age and older

[d] Refer to Table 5 of the *NACI Seasonal Influenza Vaccine Statement for 2021–2022* for a comparison of the vaccine characteristics of influenza vaccine types available for use in adults 65 years of age and older (5)

[e] IIV3-HD formulations will not be available for use in Canada during the 2021-2022 influenza season

Source: Table reproduced from the *NACI Seasonal Influenza Vaccine Statement for 2021–2022* (5)

Table 3: Recommended dose and route of administration, by age, for influenza vaccine types authorized for the 2021–2022 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)	IIV3-HD[e] (IM)	IIV4-HD[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	–	–	–	–	0.2 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	–	–	–	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	0.5 mL	–	–	–	–	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.7 mL	–	1

Abbreviations: IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent; IIV4-cc, quadrivalent mammalian cell-culture based inactivated influenza vaccine; IIV4-HD, high-dose quadrivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; IM, intramuscular; LAIV4, quadrivalent live attenuated influenza vaccine; –, not applicable

[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 (nine years and older)

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

[e] Fluzone® High-Dose (65 years and older) was previously authorized, but marketing of the vaccine has been discontinued as of February 2021

[f] Fluzone® High-Dose Quadrivalent (65 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 (25,26). 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* (27)

[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 younger 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 2021–2022* (5)

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. For the 2021–2022 influenza season, NACI newly recommends that Influvac Tetra and Flucelvax Quad may be considered as options among the quadrivalent inactivated influenza vaccines offered to adults and children for their annual vaccination. NACI also newly recommends that Fluzone High-Dose Quadrivalent may be considered as an option for adults 65 years of age and older.

In addition, people capable of transmitting to high-risk individuals, people who provide essential community services and people in direct contact during culling operations with poultry infected with avian influenza are particularly recommended to receive the influenza vaccine.

Authors' statement

AS — Writing, original draft, review, editing
KY — Review, editing
RH — Review, editing

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Competing interests

None.

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Appendix

Table A1: Ratings for strength of National Advisory Committee on Immunization (NACI) recommendations 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	

Burden of illness in infants and young children hospitalized for respiratory syncytial virus: A rapid review

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Abstract

Respiratory syncytial virus (RSV) infections are common among young children and represent a significant burden to patients, their families and the Canadian health system. Here we conduct a rapid review of the burden of RSV illness in children 24 months of age or younger. Four databases (Medline, Embase, Cochrane Database of Clinical Trials, ClinicalTrials.gov from 2014 to 2018), grey literature and reference lists were reviewed for studies on the following: children with or without a risk factor, without prophylaxis and with lab-confirmed RSV infection. Of 29 studies identified, 10 provided within-study comparisons and few examined clinical conditions besides prematurity. For infants of 33–36 weeks gestation (wGA) versus term infants, there was low-to-moderate certainty evidence for an increase in RSV-hospitalizations (n=599,535 infants; RR 2.05 [95% CI 1.89–2.22]; 1.3 more per 100 [1.1–1.5 more]) and hospital length of stay (n=7,597 infants; mean difference 1.00 day [95% CI 0.88–1.12]). There was low-to-moderate certainty evidence of little-to-no difference for infants born at 29–32 versus 33–36 wGA for hospitalization (n=12,812 infants; RR 1.20 [95% CI 0.92–1.56]). There was low certainty evidence of increased mechanical ventilation for hospitalized infants born at 29–32 versus 33–35 wGA (n=212 infants; RR 1.58, 95% CI 0.94–2.65). Among infants born at 32–35 wGA, hospitalization for RSV in infancy may be associated with increased wheeze and asthma-medication use across six-year follow-up (RR range 1.3–1.7). Children with versus without Down syndrome may have increased hospital length of stay (n=7,206 children; mean difference 3.00 days, 95% CI 1.95–4.05; low certainty). Evidence for other within-study comparisons was of very low certainty. In summary, prematurity is associated with greater risk for RSV-hospitalization and longer hospital length of stay, and Down syndrome may be associated with longer hospital stay for RSV. Respiratory syncytial virus-hospitalization in infancy may be associated with greater wheeze and asthma-medication use in early childhood. Lack of a comparison group was a major limitation for many studies.

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Keywords: respiratory syncytial virus, disease burden, hospitalization, systematic review

Introduction

Respiratory syncytial virus (RSV) infections are common among young children (1,2), presenting as bronchiolitis, pneumonia, or other respiratory morbidity (3). Hospitalization due to RSV is a significant burden for patients, families and the Canadian health system (4).

Increased risk for RSV-hospitalization has been associated with age younger than one year (3,5), prematurity (6), chronic lung disease (7), congenital heart disease (8), other chronic conditions including cystic fibrosis, immunodeficiency (9–12) and residence in Indigenous, northern or remote communities (13). These populations may also have higher rates of admission to intensive care units (ICU), requirements for respiratory support, and higher mortality attributable to RSV (9). RSV-hospitalization in the first two years of life has also been associated with wheezing in childhood (14–16).

While no active vaccines exist for RSV prophylaxis, the monoclonal antibody palivizumab (Synagis®, AstraZeneca) has demonstrated effectiveness in preventing RSV-hospitalization among some high risk populations (17,18). However, while efficacy of palivizumab (PVZ) in clinical trials appears to be high for children with some underlying clinical conditions, real-world evidence from observational studies is less certain (2), with wide variations in effectiveness. Due to the high numbers needed to treat in order to prevent hospitalization and the relatively high cost of PVZ, most jurisdictions use the intervention sparingly for select groups at highest risk of severe disease. Additionally, RSV vaccine development has been well under way, with some vaccine candidates undergoing phase 3 clinical trials (19). There is currently no global consensus on RSV risk groups and variable policies exist even within Canada.

The objective of this rapid review is to address the following question: What is the burden of RSV illness including long-term sequelae among children 24 months of age and younger without prophylaxis, and with or without risk factors for severe RSV disease, and for immunocompromised children younger than 18 years of age?

Findings from the review will help inform updated recommendations of Canada's National Advisory Committee on Immunization on the use of PVZ prophylaxis to prevent severe consequences of RSV infection. This evidence base will also be relevant for future deliberations on program design for anticipated RSV vaccines and newer monoclonal antibodies (19).

Methods

This review was guided by methods for reviews of interventions (20), overall prognosis (21), and risk of future event (prognosis) (22); a protocol was developed a priori (**Supplement 1**), and reviewed and approved by the National Advisory Committee on Immunization RSV Working Group. In light of the restricted literature search timeframe of interest to the review commissioners, we refer to the undertaken work as a rapid review.

Literature search

Searches were conducted on September 6, 2018, in Medline, Embase, Cochrane Database of Clinical Trials, ClinicalTrials.gov, and websites of international public health authorities (**Supplement 2**). Limits were applied for date of publication (January 1, 2014 to September 6, 2018) and language (English or French). The date limit was aimed at capturing outcomes just before and after significant changes in clinical practice stemming from the revised recommendations for PVZ prophylaxis by the American Academy of Pediatrics (23) as well as the Canadian Paediatric Society (2).

Study selection and eligibility criteria

Two reviewers independently screened titles and abstracts followed by full texts. Discrepancies were resolved by discussions.

Studies conducted in Organisation for Economic Co-operation and Development (OECD) countries, including observational studies and placebo groups of controlled trials were eligible for inclusion. Studies reporting on children 24 months of age and younger, with or without a risk factor of interest, or immunocompromised children 18 years of age and younger without PVZ prophylaxis and with lab-confirmed RSV infection were eligible. Children without RSV infection were eligible as a comparator group for long-term outcomes. Short-term outcomes included RSV-hospitalization, hospital length of stay, ICU admission and length of stay, oxygen support and duration, mechanical ventilation and duration, extracorporeal membrane oxygenation and duration, case fatality (death due to RSV), and complications from RSV infection (e.g. secondary infection). Long-term outcomes (minimum one-year follow-up) included self-reported, parent-reported or physician-diagnosed recurrent wheeze, atopic asthma, deterioration of pulmonary or cardiac function, and impaired growth or development. Detailed inclusion and exclusion criteria are in **Supplement 3**.

Data extraction, synthesis/analysis and risk of bias assessment

One reviewer extracted data with second-reviewer verification.

For dichotomous outcomes, we extracted the number of events and the number analysed in each eligible group, or relative measures (e.g. odds ratio) if crude events were not reported. For continuous outcomes, mean values for each time-point, and change scores, including standard deviations or measures of variability were extracted. Risk ratio (RR) with 95% confidence interval (CI) and mean difference (MD) were used for comparisons between groups.

Our primary interest was using data from studies that reported on two or more groups, either having different risk factors, or a risk group versus healthy term infants (within-study/direct comparisons). For similar comparisons reported by more than one study, data were pooled using the DerSimonian Laird random effects model inverse variance method with Mantel-Haenszel weighting. Risk differences were used when rare or zero events appeared in at least one study group. We also made comparisons between short-term outcomes in risk groups and healthy term infants reported by different studies (between-study/indirect comparisons). We used the double-arc sine transformation to pool single-group proportions across multiple studies. When no comparison was made, we report event proportions for the single group in these studies.

For outcomes where estimates were statistically significant, we calculated the absolute risk difference (24).

Analyses were performed using Excel, Review Manager (version 5.3) and STATA (version 14.2).

Two reviewers independently assessed the risk of bias for each study, using a modified tool based on the Quality Assessment Tool for Observational Cohort and Cross-sectional Studies and the Quality In Prognosis Studies (QUIPS) tool (**Supplement 4**). Disagreements were resolved via consensus or third-reviewer consultation.

Certainty of evidence

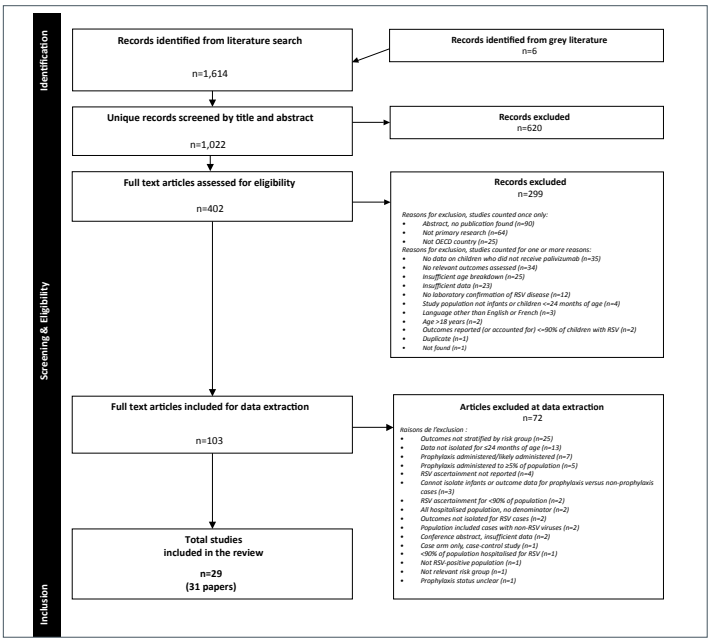
Two reviewers independently assessed the certainty of evidence for each outcome (as high, moderate, low, or very low) from within-study comparisons (direct evidence), with disagreements resolved through consensus. The approach followed principles of the Grading of Recommendations Assessment, Development and Evaluation working group and considerations for a body of evidence that examines risk of future events (prognosis) (**Supplement 5**) (21).

Results

Study selection and characteristics

Twenty-nine cohort studies were included (**Figure 1, Table 1**, and **Supplements 6 and 7**) (13,25–52); of these, 10 reported at least one within-study comparison (26–28,31,32,36,37,42,50,52). Twelve studies were conducted in the United States (25,26,33,34,36,38,42,45–47,49,50), three each, in Canada (13,29,48) and the Netherlands (30,43,52), two each, in Finland (27,28), France (35,37) and Japan (40,41) and one each in Chile (44), Denmark (31), Ireland (39), Spain (32) and multiple countries (51). Thirteen (13,25,26,29–32,37,43,45,46,51,52) studies had some form of industry funding. Three papers reported on the same study: primary publication by Ambrose *et al.* (25), with associated publications by Franklin *et al.* (53) and Simões *et al.* (54).

Figure 1: Flow diagram of study selection



Abbreviations: OECD, Organisation for Economic Co-operation and Development; RSV, respiratory syncytial virus

Table 1: Summary of included studies

Study design & setting (no. of studies)	Risk groups (no. of studies[a])	RSV infection (no. of studies)	Short-term outcomes (no. of studies[a])	Long-term outcomes and follow-up (no. of studies[a])	Risk of bias by outcome (no. of studies[a])
Study design: • Prospective cohort (n=15) • Retrospective cohort (n=12) • Retrospective follow-up of prospective cohort (n=1) • Retrospective cohort with non-concurrent control (n=1) Country: • United States (n=12) • Canada (n=3) • Netherlands (n=3) • Finland (n=2) • Japan (n=2) • France (n=2) • Chile (n=1) • Denmark (n=1) • Ireland (n=1) • Spain (n=1) • International, multi-site (n=1)	At-risk: • Premature (n=11) • CF (n=2) • CCLD (n=1) • chILD (n=1) • Down syndrome (n=1) • HS-CHD (n=1) • Remote geographic (n=2) • Leukemia (AML & ALL) (n=1) • Liver transplant recipient (n=1) • Sickle cell disease (n=1) Not-at-risk: • Healthy term infants (n=11)	Age at RSV: • First RSV season (n=1) • <6 mo at infection (n=1) • ≤6 mo at study enrolment or start of RSV season (n=4) • <10 mo at infection (n=1) • ≤12 mo at RSV season (n=1) • ≤12 mo at hospitalization (n=8) • ≤12 mo at end of insurance enrollment, study period or first year of life (n=1) • ≤24 mo at hospitalization (n=8) • <3 y of age (n=1) • <18 y of age (n=1) • <18 y, ≤24 mo post-transplantation (n=1) Birth cohort with FU to 6 y of age (n=1)	Incidence of RSV-hospitalization (n=23) Hospital LOS (n=16) ICU admission (n=13) ICU LOS (n=5) Oxygen therapy (n=6) Oxygen therapy duration (n=5) MV (n=15) MV duration (n=4) Case fatality (n=7)	Wheeze: • At 1 y FU (n=1) • Across 2–6 y of age (n=1) • At 6 y of age (n=1) Asthma: • Across 2–6 y of age (n=1) • At 7 y of age (n=1) • At 17–20 y of age (n=1) • At 28–31 y of age (n=1) Lung function: • At 6 y of age (n=1) • At 17–20 y of age (n=1) • At 28–31 y of age (n=1)	Incidence of RSV-hospitalization: • High (n=10) • Moderate (n=11) Short-term outcomes: • High (n=2) • Moderate (n=9) • Low (n=10) Long-term outcomes: • Moderate (n=5) • Low (n=1)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CCLD, congenital cystic lung disease; CF, cystic fibrosis; chILD, childhood interstitial lung disease; FU, follow-up; HS-CHD, hemodynamically significant congenital heart disease; ICU, intensive care unit; LOS, length of stay; mo, month(s); MV, mechanical ventilation; no., number; RSV, respiratory syncytial virus; y, year(s)

[a] Study may contribute to more than one risk group, outcome and/or follow-up duration

Eighteen studies (25,26,29,30,33–37,39–43,45,48,50,51) included children either not given or not considered for PVZ prophylaxis prior to RSV-hospitalization; four studies (13,32,46,47) reported prophylaxis among less than 5% of the applicable population with RSV, and seven studies (27,28,31,38,44,49,52) were considered by clinical judgement to not have included children who received prophylaxis. One study included some children who may have received prophylaxis (34).

We included three studies of children with RSV older than 24 months of age to capture evidence for immunocompromised populations: children three years old or younger with Down syndrome with or without known risk factors for RSV (50), and younger than 18 years old with liver transplantation (38) and sickle cell disease (49).

Studies of at-risk populations reporting short-term outcomes included the following: infants with premature birth (eleven studies) (25,26,30,32,36,37,42,43,47,48,51); cystic fibrosis (two studies) (29,39); one study each for congenital cystic lung disease (40), childhood interstitial lung disease (35), Down syndrome (50), sickle cell disease (49), acute leukemia (41) and prior liver transplant (38); and children residing in remote geographic locations (two studies) (13,46).

Seven studies reporting short-term outcomes included data on healthy term infants hospitalized for RSV (33,37,42,44,45,50,52).

Six studies reported on long-term outcomes: healthy term infants with versus without RSV in infancy (27,28,31,52), premature infants with versus without RSV-hospitalization in infancy (32), and premature versus term infants hospitalized for RSV in their first RSV season (37).

Risk of bias

Risk of bias ratings are in Table 1 and Supplements 4 and 6. Studies that reported incidence of RSV-hospitalization were at moderate-to-high risk of bias, mainly due to lack of blinding to childrens' risk status by healthcare providers that may have influenced admission to hospital. For other short-term outcomes, studies were mostly at moderate risk of bias (25,26,29,33,35,39,45–47). Two studies were at high risk of bias due to concerns in more than one domain (41,44). Nearly all reported long-term outcomes (27,28,32,37,52) were at moderate risk of bias, arising from lack of blinding for patient or parent-reported outcomes and/or potential selection biases.

Short-term outcomes from within-study comparisons

Table 2 summarizes evidence for short-term outcomes from within-study comparisons. Here we do not report further on findings having very low certainty of evidence.

Different degrees of prematurity: One study found little-to-no difference in RSV-hospitalization during their first RSV season for infants born at 29–32 compared with 33–36 weeks' gestation (wGA) (36). This study found little-to-no difference for hospital stay of less than one day versus one day or more between infants born at 29–32 or 33–36 wGA (36).

Another study of infants born at 29–32 versus 33–35 wGA who were hospitalized for RSV in the first year of life found little-to-no difference for ICU admission, but longer (although not statistically significant) ICU length of stay among the infants born at 29–32 wGA (26). There was a greater need for mechanical ventilation for hospitalized infants born at 29–32 wGA versus 33–35 wGA (26).

There were no studies of premature infants born before 29 wGA.

Premature versus term infants: One study found that being born late-premature (33–36 wGA) versus at term was associated with increased RSV-hospitalization in the first two years of life (42). The same study found slightly longer hospitalization for the preterm group (42).

Down syndrome: One study comparing children with Down syndrome without additional risk factors for RSV versus healthy children, all followed to three years of age, reported a higher hospitalization rate in those with Down syndrome (50). There was a discrepancy between the text and tables for RSV-hospitalization rates in these groups that could not be resolved due to unsuccessful attempts to contact the study authors (50). This study also found that RSV was associated with longer hospital length of stay among children with Down syndrome without other risk factors versus children without Down syndrome (50). For all cases of Down syndrome, including those with known risk factors for RSV, the authors conclude that Down syndrome is independently associated, after adjusting for known risk factors for RSV disease, with an increased risk for RSV-hospitalization (50). Of note, data on children younger than 24 months of age without risk factors were not isolated from those with additional risk factors, and therefore, were not used in our analysis.

Select short-term outcome comparisons: Other data

Supplement 8 contains single risk group data and pooled analyses (when appropriate). Data for between-study comparisons are in **Supplement 9**. Findings for select outcomes are reported below; data on other short-term outcomes are in Supplement 8.

Single group proportions for RSV-hospitalizations were 5.1% in the first six months of life and 3.3% in the first two years of life for infants 29 to younger than 33 wGA (36,37) and 32/33 to 35

Table 2: Summary of evidence for short-term outcomes among within-study population comparisons

Outcome	Comparator 1	Comparator 2	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
				Comparator 2 risk	Absolute risk difference[a]			
RSV-hospitalization								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–36 wGA	RC[36] (n=1); 12,812	4.2 per 100	NS	RR 1.20 (0.92, 1.56)	Moderate to low[b,c,d]	**Little to no difference** For RSV-hospitalization in their first RSV season among infants born premature at 29–32 wGA vs. 33–36 wGA
At-risk vs. not-at-risk population	Prematurity: 33–36 wGA	Term: ≥37 wGA	RC[42] (n=1); 599,535	1.2 per 100	1.3 more per 100 (1.1 to 1.5 more)	RR 2.05 (1.89, 2.22)	Moderate to low[b,c,d]	**Increase** RSV-hospitalization by age <24 months among infants born premature (33–36 wGA) vs. at term Among this group, infants born at 33–34 wGA had highest incidence density for RSV hospitalization at 6–12 months of age (adjusted hazard ratio [aHR] 1.74 [1.17–2.58], $p<0.05$) and 12–24 months of age (aHR 1.96 [1.26–3.05], $p<0.05$) compared to term infants
At-risk vs. not-at-risk population	Prematurity: <33 wGA	Term: 39–41 wGA	RFUPC[37] (n=1); 443	1.5 per 100	4.3 more per 100 (0.2 to 18 more)	RR 3.88 (1.13, 13.30)	Very low[b,c,e]	**Very uncertain** For RSV-hospitalization in their first RSV season among infants born at <33 wGA vs. at term
Hospital length of stay, mean days								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 212	MD 4.00 (1.54, 6.46)		N/A	Very low[b,c,e]	**Very uncertain** For hospital length of stay among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
At-risk vs. not-at-risk population	Prematurity: 33–36 wGA	Term: ≥37 wGA	RC[42] (n=1); 7,597	MD 1.00 (0.88, 1.12)		N/A	Moderate to low[b,c,d]	**Small increase** For hospital length of stay among infants born premature at 33–36 wGA vs. at term and hospitalized for RSV at <24 months
At-risk vs. not-at-risk population	Down syndrome	No Down syndrome	RC[50] (n=1); 7,206	MD 3.00 (1.95, 4.05)		N/A	Low[b,c]	**Small increase** For hospital length of stay for RSV among infants with vs. without Down syndrome and hospitalized for RSV at <3 years
Hospital length of stay, <1 day vs. ≥1 day								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–36 wGA	RC[36] (n=1); 542	13.9 per 100	NS	<1 day: RR 0.86 (0.41, 1.78)	Low[c,e]	**Little to no difference** For hospital length of stay <1 day among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized in their first RSV season
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–36 wGA	RC[36] (n=1); 542	86.1 per 100	NS	≥1 day: RR 1.02 (0.93, 1.13)	Low[c,e]	**Little to no difference** For hospital length of stay ≥1 day among infants born premature at 29–32 wGA vs. 33–36 wGA and hospitalized in their first RSV season

Table 2: Summary of evidence for short-term outcomes among within-study population comparisons (*continued*)

Outcome	Comparator 1	Comparator 2	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
				Comparator 2 risk	Absolute risk difference[a]			
ICU admission, among RSV-hospitalized population								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 212	50.4 per 100	NS	RR 1.03 (0.79, 1.34)	Low to very low[b,c,d,e]	**Little to no difference/very uncertain** For ICU admission among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
ICU length of stay, mean days								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 169	MD 2.00 (-0.28, 4.28)		N/A	Low to very low[b,c,d,e]	**Small increase/very uncertain** For ICU length of stay among infants born premature at 29–32 wGA or at 33–35 wGA and hospitalized for RSV at <12 months
Mechanical ventilation, among RSV-hospitalized population								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 212	17.1 per 100	NS	RR 1.58 (0.94, 2.65)	Low[c,e]	**Small increase** For mechanical ventilation among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
Mechanical ventilation, among ICU population								
At-risk population	Prematurity: 29–32 wGA		PC[26] (n=1); 108	33.9 per 100	NS	RR 1.54 (0.99, 2.40)	Very low[c,e,f]	**Very uncertain** For mechanical ventilation therapy among infants born premature at 29–32 wGA vs. 33–35 wGA and admitted to ICU for RSV at <12 months
Mechanical ventilation therapy duration, mean days								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 45	MD 2.00 (-1.21, 5.21)		N/A	Very low[c,e,f]	**Very uncertain** For duration of mechanical ventilation therapy among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
Case fatality, among RSV-hospitalized population								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 212	0 per 100	NS	RR 4.13 (0.17, 100.30)	Very low[c,e,f]	**Very uncertain** for death due to RSV among infants born premature at 29–32 wGA vs. 33–35 wGA and hospitalized for RSV at <12 months
Case fatality, among ICU population								
At-risk population	Prematurity: 29–32 wGA	Prematurity: 33–35 wGA	PC[26] (n=1); 108	0 per 100	NS	RR 4.02 (0.17, 96.53)	Very low[c,e,f]	**Very uncertain** For death due to RSV among infants born premature at 29–32 wGA vs. 33–35 wGA and admitted to ICU for RSV at <12 months

Abbreviations: CI, confidence interval; ICU, intensive care unit; MD, mean difference; N/A, not applicable; no., number; NS, not significant (results failed to show a difference between groups); PC, prospective cohort; RC, retrospective cohort; RFUPC, retrospective follow-up of prospective cohort; RR, relative risk; RSV, respiratory syncytial virus; vs., versus; wGA, weeks' gestational age

[a] Absolute risk reductions were calculated when findings were statistically significant; NS denotes when findings were not statistically significant

Certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Starting at high for observational studies (for prognosis evidence) each outcome is rated as high, moderate, low or very low based on downgrading (if any) for one or more of the following domains:

[b] Study limitations, including selective outcome reporting

[c] Inconsistency

[d] Half decrement (-0.5) due to small concern for this domain

[e] Imprecision

[f] Two decrements (-2) due to very serious concerns for this domain

wGA (25,30,32,36,42,43,48,51), respectively; 5.3% two years post-transplantation, 8.3% in the first two years of life, 12.3% in the first two years of life and 30.0% in the first or second RSV season for liver transplant (38), congenital cystic lung disease (40), cystic fibrosis (29,39) and childhood interstitial lung disease (35), respectively. The 95% confidence intervals for the latter three conditions were very wide. The pooled proportion for healthy term infants was 1.2% in the first two years of life (37,42,45,52).

Case fatality rate attributable to RSV for those hospitalized were 1.1 % (n=89), 2.5% (n=80), 4.4% (n=135) and 40.0% (n=10) for infants of 29–32 wGA (26), children residing in remote geographic area (46), children with liver transplant (38) and with leukemia (41), respectively. Most studies reported no attributable deaths. Many studies of clinical conditions contained very small sample sizes.

Complications

One study reported on complications associated with RSV-hospitalization (**Supplement 10**).

Long-term outcome comparisons from within-study comparisons

Tables 3 to 5 summarize evidence for long-term outcomes from within-study comparisons. No study reported on growth or impaired development. Here we do not report on findings having very low certainty evidence.

Table 3: Summary of evidence for wheeze associated with RSV infection among within-study population comparisons

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Simple wheeze; parent and/or physician-reported									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	During 6th y	PC[32] (n=1); 434	14 per 100	NS	RR 1.16 (0.70, 1.93)	Low[b,c]	**Little to no difference** For parent/physician-reported simple wheeze (episodes <3 within 12 months) during the 6th year among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	Across 2–6 y	PC[32] (n=1); 474	49 per 100	18 more per 100 (7–30 more)	RR 1.36 (1.15, 1.60)	Low[b,c]	**Small increase** For parent/physician-reported simple wheeze (episodes <3 within 12 months) from 2–6 years among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. not-at-risk with RSV-H	Prematurity: <33 wGA & RSV-H	Term: 39–41 wGA & RSV-H	1 y	RFUPC[37] (n=1); 17	67 per 100	NS	RR 0.54 (0.18, 1.55)	Very low[b,c,d]	**Very uncertain** For parent and physician-reported simple wheeze (episodes <3 in 12 months) within one year among premature (<33 wGA) vs. term infants with hospitalization in their first RSV season
Recurrent wheeze; parent and/or physician-reported									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	During 6th y	PC[32] (n=1); 434	10 per 100	NS	RR 1.28 (0.71, 2.32)	Low[b,c]	**Little to no difference** For parent/physician-reported recurrent wheeze (≥3 episodes within 12 months) during the 6th year among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	Across 2–6 y	PC[32] (n=1); 422	27 per 100	19 more per 100 (7–35 more)	RR 1.70 (1.27, 2.29)	Low[b,c]	**Small increase** For parent/physician-reported recurrent wheeze (≥3 episodes within 12 months) from 2–6 years among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. not-at-risk with RSV-H	Prematurity: <33 wGA & RSV-H	Term: 39–41 wGA & RSV-H	1 y	RFUPC[37] (n=1); 17	0 per 100	NS	RR 0.80 (0.04, 16.14)	Very low[b,c,d]	**Very uncertain** For parent and physician-reported recurrent wheeze ≥3 episodes in 12 months) within one year among premature (<33 wGA) vs. term infants with hospitalization in their first RSV season

Table 3: Summary of evidence for wheeze associated with RSV infection among within-study population comparisons (*continued*)

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Severe wheeze; parent or physician-reported									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	During 6th y	PC[34] (n=1); 434	9 per 100	NS	RR 0.91 (0.44, 1.88)	Low[b,c]	**Little to no difference** For parent/physician-reported severe wheeze (≥1 hospitalization or ≥3 medical attendances or medication for three consecutive months or five cumulative months) during the 6th year among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H <12 months of age	Prematurity: 32–35 wGA, No RSV-H <12 months of age	Across 2–6 y	PC[34] (n=1); 427	24 per 100	14 more per 100 (3–29 more)	RR 1.59 (1.13, 2.24)	Low[b,c]	**Small increase** For parent/physician-reported severe wheeze (≥1 hospitalization or ≥3 medical attendances or medication for three consecutive months or five cumulative months) from 2–6 years among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
At-risk with RSV-H vs. not-at-risk with RSV-H	Prematurity: <33 wGA & RSV-H	Term: 39–41 wGA & RSV-H	1 y	RFUPC[37] (n=1); 17	0 per 100	NS	RD 0.00 (-0.34, 0.34)	Very low[b,c,d]	**Very uncertain** For physician-reported severe wheeze (hospitalization for wheeze in 12 months) within one year among premature (<33 wGA) vs. term infants with hospitalization in their first RSV season
Wheeze duration (days per month post-RSV); parent-reported									
Not-at-risk population	RSV-positive, hospitalized	RSV-positive, non-hospitalized	1 y	PC[52] (n=1); 90	MD 0.70 (-0.94, 2.34)		N/A	Very low[b,c,d]	**Very uncertain** For parent-reported days with wheeze at one year among hospitalized vs. non-hospitalized healthy term infants positive for RSV at <12 months

Abbreviations: CI, confidence interval; FU, follow-up; MD, mean difference; N/A, not applicable; no., number; NS, not significant; PC, prospective cohort; RD, risk difference; RFUPC, retrospective follow-up of prospective cohort; RR, risk ratio; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; vs., versus; wGA: weeks' gestational age; y, year(s)

[a] Absolute risk reductions were calculated when findings were statistically significant; NS denotes when findings were not statistically significant

Certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Starting at high for observational studies (for prognosis evidence) each outcome is rated as high, moderate, low or very low based on downgrading (if any) for one or more of the following domains:

[b] Inconsistency

[c] Imprecision

[d] Two decrements (-2) due to very serious concerns for this domain

Table 4: Summary of evidence for asthma associated with RSV infection among within-study population comparisons

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Asthma; physician-diagnosed									
Not-at-risk population	RSV infection in first year of life	Infection with a respiratory pathogen other than RSV in first year of life	7 y	PC[31] (n=1); 329	12 per 100	15 more per 100 (4–35 more)	RR 2.33 (1.35, 4.05) Adjusted for total number of respiratory episodes: OR 1.26 (0.54, 2.91), *p*=0.59	Very low[b,c,d,e]	**Very uncertain** For physician-diagnosed asthma at seven years of age among healthy infants with RSV vs. a different respiratory pathogen in the first year of life
Not-at-risk population	RSV-H	No RSV-H	28–31 y	PC[28] (n=1); 129	13 per 100	NS	RR 1.82 (0.84, 3.94)	Very low[b,c,e]	**Very uncertain** For physician-diagnosed asthma at 28–31 years of age among term infants with vs. without hospitalization for RSV at age <24 months
Asthma; self-reported									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 203	15 per 100	19 more per 100 (0.1–60 more)	RR 2.28 (1.01, 5.12)	Low[b,e]	**Small increase** For self-reported asthma in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Asthma medication (bronchodilator)									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H	Prematurity: 32–35 wGA, No RSV-H	Across 2–6 y	PC[32] (n=1); 487	17 per 100	8 more per 100 (4–13 more)	RR 1.48 (1.23, 1.77)	Low[c,e]	**Small increase** Parent-reported bronchodilator use from 2–6 years of age among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months
Not-at-risk population	RSV-H	No RSV-H	28–31 y	PC[28] (n=1); 129	14 per 100	16 more per 100 (1–47 more)	RR 2.17 (1.08, 4.34)	Very low[b,c,e]	**Very uncertain** For self-reported bronchodilator use in adulthood (28–31 years of age) among term infants with vs. without hospitalization for RSV at age <24 months
Asthma medication (inhaled CS)									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H	Prematurity: 32–35 wGA, No RSV-H	Across 2–6 y	PC[32] (n=1); 487	16 per 100	10 more per 100 (2–22 more)	RR 1.65 (1.13, 2.40)	Low[c,e]	**Small increase** Parent-reported ICS use from 2–6 years of age among infants born premature (32–35 wGA) with hospitalization for RSV at <12 months
Not-at-risk population	RSV-H	No RSV-H	28–31 y	PC[28] (n=1); 129	11 per 100	NS	RR 1.56 (0.62, 3.89)	Very low[b,c,e]	**Very uncertain** For self-reported ICS use in adulthood (28–31 years of age) among term infants with vs. without hospitalization for RSV at age <24 months

Table 4: Summary of evidence for asthma associated with RSV infection among within-study population comparisons (*continued*)

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Asthma medication (leukotriene antagonist)									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H	Prematurity: 32–35 wGA, No RSV-H	Across 2–6 y	PC[32] (n=1); 487	6 per 100	10 more per 100 (3–22 more)	RR 2.52 (1.43, 4.42)	Low[c,e]	**Increased** Parent-reported leukotriene antagonist use from 2–6 years of age among infants born premature (32–35 wGA) with vs. without hospitalization for RSV at <12 months

Abbreviations: CI, confidence interval; CS, corticosteroid(s); FU, follow-up; ICS, inhaled corticosteroid(s); no., number; NS, not significant; OR, odds ratio; PC, prospective cohort; RR, risk ratio; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; vs.: versus; wGA, weeks' gestational age; y, year(s)

[a] Absolute risk reductions were calculated when findings were statistically significant; NS denotes when findings were not statistically significant

Certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Starting at high for observational studies (for prognosis evidence) each outcome is rated as high, moderate, low or very low based on downgrading (if any) for one or more of the following domains:

[b] Study limitations, including selective outcome reporting

[c] Inconsistency

[d] Indirectness

[e] Imprecision

[f] Half decrement (-0.5) due to small concern for this domain

Table 5: Summary of evidence for lung function associated with RSV infection among within-study population comparisons

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Lung function: FEV_1 Z-score ranking [-2,-1]									
At-risk with RSV-H vs. at-risk without RSV-H	Prematurity: 32–35 wGA, RSV-H	Prematurity: 32–35 wGA, No RSV-H	During 6th y	PC[32] (n=1); 243	21 per 100	NS	RR 0.83 (0.45, 1.53)	Low[b,c]	**Little to no difference** For forced expiratory volume in one second (Z-score rank of [-2, -1], considered extreme range) during the 6th year of age among children hospitalized with RSV at <12 months
Lung function (FEV_1 pre-BD, mean % of predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD -7.63 (-11.35, -3.91)		N/A	Low[c,d]	**Small decrease** For forced expiratory volume in one second (mean % of predicted, pre-bronchodilation test) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (FEV_1, change in mean % predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD 0.81 (-0.67, 2.30)		N/A	Low[c,d]	**Little to no difference** For forced expiratory volume in one second (change in mean % predicted, pre vs. post-bronchodilation test) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (FVC pre-BD, mean % of predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD -4.74 (-7.80, -1.67)		N/A	Low[c,d]	**Small decrease** For forced vital capacity (mean % of predicted, pre-bronchodilation test) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months

Table 5: Summary of evidence for lung function associated with RSV infection among within-study population comparisons (*continued*)

Outcome	Comparator 1	Comparator 2	FU	Study design (no. of studies); Sample size	Absolute difference (95% CI)		Relative risk (95% CI)	Certainty of evidence	Conclusion
					Comparator 2 risk	Absolute risk difference[a]			
Lung function (FVC, change in mean % predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y	PC[27] (n=1); 74	MD 0.60 (-0.67, 1.87)		N/A	Very low[c,d,e]	**Very uncertain** For forced vital capacity (change in mean % predicted, pre vs. post-bronchodilation test) in adulthood (17–20 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD -3.20 (-9.07, 2.67)		N/A	Very low[b,c,d]	**Very uncertain** For FEV_1/FVC (mean % of predicted, pre-bronchodilation test) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (FEV_1/FVC, change in mean % predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y	PC[27] (n=1); 74	MD -0.20 (-2.71, 2.31)		N/A	Very low[b,c,e]	**Very uncertain** For FEV_1/FVC (change in mean % predicted, pre vs. post-bronchodilation test) in adulthood (17–20 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (FENO, mean ppb)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y; 28–31 y	PC[27,28] (n=2); 202	MD -1.00 (-14.49, 12.49)		N/A	Low[c,d]	**Little to no difference** For fractional exhaled nitric oxide (mean ppb) in adulthood (17–31 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (MEF50 pre-BD, mean % of predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y	PC[27] (n=1); 74	MD -4.00 (-14.95, 6.95)		N/A	Very low[b,c,d,e]	**Very uncertain** For maximum expiratory flow after 50% of expired FVC (change in mean % predicted, pre-bronchodilation test) in adulthood (17–20 years of age) among infants with vs. without hospitalization for RSV at age <24 months
Lung function (MEF50, change in mean % predicted)									
Not-at-risk population	RSV-H	No RSV-H	17–20 y	PC[27] (n=1); 74	MD 3.70 (-5.42, 12.82)		N/A	Very low[b,c,d,e]	**Very uncertain** For maximum expiratory flow after 50% of expired FVC (change in mean % predicted, pre vs. post-bronchodilation test) in adulthood (17–20 years of age) among infants with vs. without hospitalization for RSV at age <24 months

Abbreviations: BD, bronchodilator; CI, confidence interval; FENO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; FU, follow-up; FVC, forced vital capacity; MD, mean difference; MEF50, maximum expiratory flow after 50% of expired FVC; N/A, not applicable; no., number; NS, not significant; PC, prospective cohort; ppb, parts per billion; RR, risk ratio; RSV, respiratory syncytial virus; RSV-H, respiratory syncytial virus hospitalization; vs., versus; wGA, weeks' gestational age; y, year(s)

[a] Absolute risk reductions were calculated when findings were statistically significant; NS denotes when findings were not statistically significant

Certainty of evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Starting at high for observational studies (for prognosis evidence) each outcome is rated as high, moderate, low or very low based on downgrading (if any) for one or more of the following domains:

[b] Indirectness

[c] Imprecision

[d] Study limitations, including selective outcome reporting

[e] Two decrements (-2) due to very serious concerns for this domain

Prematurity: One study enrolled premature (32–35 wGA) infants with or without hospitalization for RSV infection before 12 months of age to examine several long-term outcomes (32). Data were collected through telephone calls every four months and annual visits until the 6th year of life. The authors analysed data both across the five years and only within the 6th year. All findings offered low certainty evidence.

Across years two through six, associations were found between RSV-hospitalization and increased risk for parent or physician-reported simple wheeze, recurrent wheeze, severe wheeze and any/all wheeze (32). When examining the 6th year only, there was little-to-no difference in parent or physician-reported simple wheeze, recurrent wheeze, severe wheeze and any/all wheeze (32). This study also compared groups for parent-reported asthma-associated medication use across years two through six. There were associations with increased risk from RSV-hospitalization for use of bronchodilators, inhaled corticosteroids, oral corticosteroids and leukotriene antagonists (32). Through lung function testing using spirometry, there was little-to-no difference in severe respiratory morbidity at six years of age between groups (32).

RSV without risk factors: Pooled data from two studies of children with versus without RSV-hospitalization at younger than 24 months of age found low certainty of an increase in self-reported asthma in adulthood (27,28). Of note, there was no difference in physician-diagnosed asthma (considered more reliable than patient-reported asthma) (28), but certainty of evidence was very low for this outcome. An association was also found between RSV and lower pre-bronchodilation mean percent of predicted forced expiratory volume in one second (FEV_1), but there was little-to-no difference in change in FEV_1 from pre to post-bronchodilation (27,28). The RSV was associated with lower predicted forced vital capacity, but not fractional exhaled nitric oxide (27,28).

Long-term outcome comparisons: Other data

Supplement 11 contains single group data and pooled analyses (when appropriate). We did not conduct analyses for between-study comparator groups, since single studies that contributed to each long-term outcome were represented among within-study comparisons.

Discussion

Summary of findings and limitations

Few studies contributed data for within-study comparisons of outcomes of interest. There was moderate-to-low certainty that RSV is associated with a small increase in hospitalization and length of stay among moderate-to-late preterm (33–36 wGA) compared with term infants. There was moderate-to-low certainty evidence for no significant differences in hospitalizations between infants born at 29–32 wGA versus 33–36 wGA. Low certainty of evidence was found for a slight increase in mechanical ventilation among those born at 29–32 wGA versus 33–35 wGA and hospitalized for RSV prior to 12 months of age. Low certainty evidence was found for increased hospital length of stay among children younger than three years of age with versus without Down syndrome. There was low certainty evidence for increased wheezing and asthma medication use from two to six years of age among RSV-hospitalized versus non-hospitalized premature (32–35 wGA) infants, although there was little-to-no difference for these outcomes in the 6th year of follow-up. Low certainty evidence was found for decreased lung function measurements before bronchodilation but changes in measurements after bronchodilation did not differ between groups. Very low certainty evidence was found for other long-term outcomes comparing different risk groups.

Single studies contributed data for most outcomes, where populations with rare conditions (e.g. cystic fibrosis) often represent small/under-powered sample sizes, precluding investigation of heterogeneity among studies for important population and RSV characteristics, or consistency in findings. The paucity of studies on clinical conditions other than prematurity is a limitation of the evidence base. We also did not find studies of premature infants born before 29–30 weeks gestation, or of children with chronic lung disease of prematurity or congenital heart disease, groups for whom prophylaxis is now recommended in the United States and in Canada (2,23).

Retrospective study designs utilizing older data (i.e. pre-2014) were included, and may reflect different practices (e.g. prophylaxis, RSV-testing, standard of care) over time and across countries and settings. Detection of RSV infection may be impacted by variation in testing methods, including types of tests and indications for testing, and seasonal and geographic variability. Among tested individuals, the proportion of patients with viral or bacterial co-infections may be an important confounder in etiology of outcome severity. Lack of blinding of healthcare providers to risk status may influence rates of hospitalization and possibly other care parameters, particularly among children with known RSV risk factors.

Comparison with other reviews

A series of systematic reviews of publications from 1995 to 2015 found that RSV-hospitalization is associated with significant morbidity among children younger than 18 years old in Western countries (Canada, United States, Europe), particularly for young children with prematurity, chronic lung disease of prematurity and congenital heart disease (6–9). Whereas the current work focused on children younger than two years of age with a single risk factor, these reviews also included studies of children up to 18 years of age. Our review scope searched comparatively more recent publications (2014–2018) and covered a broader geographic area by including high-income (OECD) countries.

Future research

Based on current evidence, there is a need for studies to focus on the burden of RSV disease among children with underlying chronic conditions, for some of which data on risk are contradictory or non-existing. Assessments of current RSV surveillance activities in Canada have identified data gaps for particular populations, including children with underlying medical conditions and those living in Indigenous, northern or remote communities (19). Gaps will need to be filled in preparation for monitoring of RSV vaccine effectiveness in the future.

Conclusion

Prematurity is associated with increased risk for RSV-hospitalization in infancy and increased hospital length of stay, and may be associated with increased wheeze and asthma-medication use at up to six years of age. Down syndrome may be associated with longer hospital length of stay. We are very uncertain about evidence from other within-study comparisons. Very few studies included a comparison group.

Authors' statement

AW — Conceptualization, methodology, analysis, writing–original draft, review and editing
JP — Conceptualization, methodology, analysis, writing–review and editing
DLM — Conceptualization, methodology, analysis, writing–review and editing
SG — Analysis, writing–review and editing
BV — Analysis, writing–review and editing
MPD — Conceptualization, methodology, analysis
AS — Conceptualization, methodology, analysis, writing–review and editing
MT — Conceptualization, methodology, writing–review and editing
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Competing interests

AW, JP, SG, BV, MPD and LH report grants from the Public Health Agency of Canada during the conduct of the study.

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Supplemental material

These documents can be accessed on the Supplemental material file.
Supplement 1: Methods
Supplement 2: Search strategy
Supplement 3: Inclusion/exclusion criteria
Supplement 4: Methodological quality assessments
Supplement 5: Certainty of evidence assessments
Supplement 6: Characteristics of included studies
Supplement 7: Outcomes of included studies
Supplement 8: Single group proportions for short-term outcomes
Supplement 9: Summary of evidence for short-term outcomes—between-study
Supplement 10: Complications
Supplement 11: Single group proportions for long-term outcomes

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