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RESPONDING TO NEW CLUSTERS OF COVID-19

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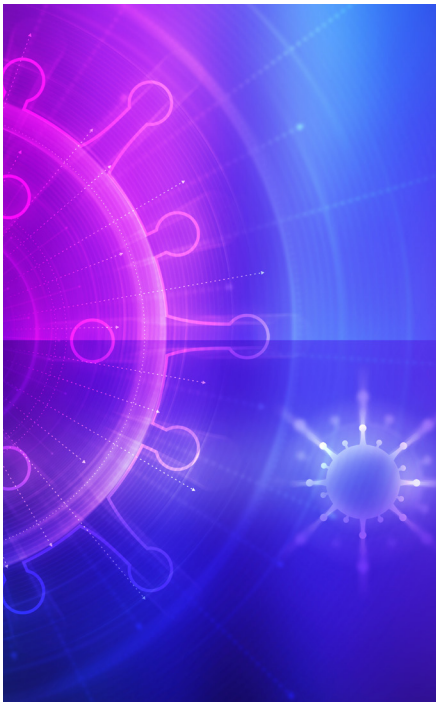

RESPONDING TO NEW CLUSTERS OF COVID-19

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Population surveillance approach to detect and respond to new clusters of COVID-19

Erin E Rees[1]*, Rachel Rodin[2], Nicholas H Ogden[1]

Abstract

Background: To maintain control of the coronavirus disease 2019 (COVID-19) epidemic as lockdowns are lifted, it will be crucial to enhance alternative public health measures. For surveillance, it will be necessary to detect a high proportion of any new cases quickly so that they can be isolated, and people who have been exposed to them traced and quarantined. Here we introduce a mathematical approach that can be used to determine how many samples need to be collected per unit area and unit time to detect new clusters of COVID-19 cases at a stage early enough to control an outbreak.

Methods: We present a sample size determination method that uses a relative weighted approach. Given the contribution of COVID-19 test results from sub-populations to detect the disease at a threshold prevalence level to control the outbreak to 1) determine if the expected number of weekly samples provided from current healthcare-based surveillance for respiratory virus infections may provide a sample size that is already adequate to detect new clusters of COVID-19 and, if not, 2) to determine how many additional weekly samples were needed from volunteer sampling.

Results: In a demonstration of our method at the weekly and Canadian provincial and territorial (P/T) levels, we found that only the more populous P/T have sufficient testing numbers from healthcare visits for respiratory illness to detect COVID-19 at our target prevalence level—assumed to be high enough to identify and control new clusters. Furthermore, detection of COVID-19 is most efficient (fewer samples required) when surveillance focuses on healthcare symptomatic testing demand. In the volunteer populations: the higher the contact rates; the higher the expected prevalence level; and the fewer the samples were needed to detect COVID-19 at a predetermined threshold level.

Conclusion: This study introduces a targeted surveillance strategy, combining both passive and active surveillance samples, to determine how many samples to collect per unit area and unit time to detect new clusters of COVID-19 cases. The goal of this strategy is to allow for early enough detection to control an outbreak.

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Introduction

As with many countries around the world, Canada has implemented lockdowns to control the transmission of the virus that causes the coronavirus disease 2019 (COVID-19): severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Common lockdowns include travel restrictions and closure of social gathering locations such as restaurants, bars and other indoor entertainment venues. The decision to lift, reduce or stop lockdown measures is multi-criterial with social, economic and health considerations and decisions about the extent and timing of the lockdowns controlled at the federal, municipal and provincial and territorial (P/T) levels. At the most simplistic level, lockdowns can be relaxed at a defined prevalence level; a strategy used by Germany during their process of lifting lockdowns after the first wave of COVID-19 cases (1). To maintain control of the epidemic as lockdowns are lifted, it is crucial to enhance alternative public health measures (contact tracing, quarantining). Specifically, we need to detect a high proportion of new cases quickly so that they can be isolated, and people

who have been exposed to or been in contact with these cases must be traced and quarantined. If there is insufficient capacity to test and trace, then resurgence of the epidemic that may overwhelm healthcare capacity is likely (2,3).

The ability to detect disease in a population depends on the type of surveillance strategy and the required number of samples to test. In large populations (i.e. greater than 1,000) a standard approach assumes random sampling from individuals that have equal risk of testing positive for the disease (4). However, if information is known about characteristics contributing to the probability of testing positive, then a targeted approach can be used to optimize sample size determination by weighing samples in their ability to detect given their characteristics (5).

In Canada there are currently two main strategies for collecting samples in COVID-19 surveillance: 1) healthcare visits and hospital admissions for respiratory illness (health care symptomatic testing demand); and 2) at-risk populations such as essential workers concerned that they may have been exposed to infection (6–8). However, these methods may not yield a sample size sufficiently large enough to detect new clusters of transmission at a time early enough (i.e. when infection prevalence in the community is low) to ensure that there is sufficient public health capacity to trace and quarantine contacts to control transmission. To achieve a sufficient sample size, a sampling strategy that tests volunteers may be required. This would likely capture more asymptomatic cases than when sampling those seeking health care; nevertheless, the value of including the volunteer population sampling would be twofold: first, to improve early warning by testing more broadly in the community and thus increase the probability of detecting new clusters; and second, to trigger a public health response at a determined level of prevalence in the population at which control of the outbreak is possible without the need to re-implement widespread lockdowns.

Targeted surveillance strategies can be used to efficiently sample from a population, which contains sub-populations having different probabilities of being infected, when the goal is early detection of disease at a given prevalence level (9,10). This approach requires weighing samples given their probability of detection and thus requires information on characteristics that relate to probability of a positive test result. This information includes factors affecting exposure and information on the frequency of these factors within the population, such as the proportion of people in each exposure category (11).

The probability of a positive test result may also include factors that are inherent to data from passive surveillance (12). The two main strategies for collecting COVID-19 samples in Canada are passive in the sense that people tested have decided to visit a health centre because they have developed symptoms or are at-risk individuals concerned about exposure. In contrast, a volunteer testing strategy is active surveillance in the sense of seeking out people to test. Other studies discuss strategies for accounting for under-ascertainment bias when not all diseased individuals present for health care, in the context of incorporating both passive and active surveillance data (12–14).

At the onset of an emerging disease, there may be insufficient information to account for challenges to using data from passive surveillance. The goal of this intervention study is to introduce a targeted surveillance strategy, combining both passive and active surveillance samples, and that uses minimal information for determining how many samples to collect per unit area and unit time to detect new clusters of COVID-19 cases—at a stage early enough to allow case isolation, contact tracing and contact quarantine—to control an outbreak.

Methods

To determine the need for volunteer sampling, the first step is to determine if the expected number of samples obtained from healthcare-based surveillance for respiratory virus infections provide a sample size that is already adequate to detect new clusters of COVID-19 at the desired threshold prevalence of infection in the general population for the time frame of interest. If the sample size is found to be inadequate, the second step is to determine how many additional weekly samples are needed from volunteers to detect new clusters of COVID-19 at the desired threshold prevalence in the general population.

We used a relative weighted approach, in which the expected prevalence level in a particular section of the population defines the weight that sample would have in detecting COVID-19 at p_0. The approach assumes random sampling from within the sampling group. Every sample receives weight points given the expected prevalence in their population group. Sample collection continues until enough points have been reached to detect COVID-19 at p_0. We demonstrated our method at the P/T and weekly levels, though this approach can be adjusted to other regional units or time frames.

Step 1: Determine if enough samples are obtained from symptomatic patients in healthcare settings

Pre-COVID-19 in Canada, testing for respiratory viruses was targeted to inpatients, as well as institutional and outbreak settings, where it would have the most impact on clinical care (15). However, COVID-19 testing is now recommended for all symptomatic individuals in Canada (16). Here, data on pre-COVID-19 healthcare visits for people with symptoms of respiratory infections are used to determine the expected number of weekly healthcare visits at which testing for COVID-19 could take place.

For pre-COVID-19 pandemic healthcare visit data, we needed to choose a recent time period during which there was no other pandemic underway. During the H1N1 influenza pandemic in

2009–2010, there were obviously more healthcare visits for viral infection symptoms than in most years. We assumed that if COVID-19 is being controlled at an acceptable level of risk, that the expected number of visits will conform to healthcare visits in years other those in which the H1N1 influenza pandemic occurred. Therefore, we used the mean annual number of reported visits for the non-pandemic time period of 2016 to 2018 as the mean annual expected healthcare visits for Canada (n=13,310,000) (**Table 1**; *Canadian Institute for Health Information, unpublished analysis for Public Health Agency of Canada, 2020*). The expected number of weekly healthcare visits per P/T, E, can then be calculated as a function of the population size of the P/T and time unit:

Equation 1:

$$E = \frac{P/T\ population\ size}{Canadian\ populaton\ size} \times \frac{Canadian\ annual\ number\ of\ visits}{52\ weeks}$$

Table 1: Estimated annual number of ambulatory care visits and admissions for respiratory illness during a non-pandemic time period, Canada, 2016–2018

Type of visit	Number of visits
Hospital admissions	220,000[a]
Emergency department visits	1,900,000[a]
Primary healthcare visits	11,000,000[a]
Number of residents in long-term care homes[b]	190,000
TOTAL	13,310,000

[a] Canadian Institute for Health Information (CIHI). Annual number, average of FY 2016–2018
[b] Canadian Institute for Health Information, 2020; refers to publicly funded/subsidized long-term care homes

To determine if E is sufficient to detect COVID-19 as early as possible at an acceptable level of risk it is necessary to define the threshold prevalence level, p_0, in the general population to detect and control the eruption of new cases. For reference, Germany used a level at $p_0 = 0.05\%$ during their process of lifting lockdown (1). This level corresponds to a 7-day period prevalence of 50/100,000. Here we investigate a more cautious value of $p_0 = 0.025\%$ to correspond to a 7-day period prevalence of 25/100,000.

Healthcare visits for people with symptoms of respiratory infections are expected to have a higher probability of infection than asymptomatic people. We assume a 0.64% prevalence in the healthcare visits population to be a realistic value that can occur when COVID-19 is acceptably controlled and there is a relaxation of public health measures. This value is in the lower range of weekly mean percent positivity reported in the Canadian Network for Public Health Intelligence (CNPHI) System for Analysis of Laboratory Tests (SALT) for the month of May 2020, completing the spring period when maximal public health measures were in place in Canada. Then the weight of contribution of samples from sample group i, here being the healthcare visits population, with a prevalence of p, to detect COVID-19 at p_0, during the time frame of interest t, is:

Equation 2:

$$w(i, t) = p(i, t)/p_0$$

This weight is then used to translate weekly number of healthcare visits E into the number of weight points that go towards detecting COVID-19:

Equation 3:

$$wp(i, t) = \frac{E}{w(i, t)}$$

The result, $wp(healthcare, t)$, is then compared with the number of samples needed to detect at least one positive case of COVID-19, $d(i, t)$, in the healthcare visits population using a standard sample size calculation (4):

Equation 4:

$$d(i, t) = \frac{-\ln(1 - \alpha)}{p \times f}$$

for an $\alpha = 0.95$ being the confidence of detecting at least one positive case of COVID-19 at a minimum detection threshold $p = p(healthcare, t)$, and $f = 0.79$ being the test sensitivity for samples from symptomatic people (17). Sample size will increase with increasing levels of α. Typical values range from 0.95 to 0.99, and as more information becomes available, it may become evident that higher levels are needed to detect community transmission early enough to control the outbreak. If $wp(i, t) < d(healthcare, t)$, then more samples from members of the public not visiting healthcare are needed to detect at least one positive case of COVID-19 at p_0.

Step 2: Determine how many additional weekly samples are needed from volunteers

If there are not enough healthcare visit samples, a second step is used to calculate how many additional samples are needed from the general population for early detection during the time frame of interest t. Equation 4 is used again, but this time from the perspective of using volunteer sampling to detect COVID-19 at p_0, meaning that in Equation 4, $p = p_0$. Furthermore, volunteers are mostly asymptomatic, so we define a lower test sensitivity $f = 0.70$ for asymptomatic people (18,19). The result, $d(volunteer, t)$ is then used to calculate the number of additional tests needed from volunteers given sampling effort from the healthcare visits, E, as:

Equation 5:

$$a(t) = d(volunteer, t) - E$$

To optimize sample collection from volunteers, we apply the relative weighted approach to target sampling by probability of testing positive. Selection of volunteer groups depends on knowledge of and data availability for characteristics

influencing the probability for testing positive to COVID-19. In demonstration of our method, we defined volunteer groups by level of contact rates according to occupation data (*unpublished data from the Centre for Labour Market Information, Statistics Canada at the request of the Public Health Agency of Canada. 2020*), though other data characteristics could also be used (e.g. travel history, age group). The premise is that targeting sampling to higher risk groups reduces the overall sample size needed to detect COVID-19. Here we create three plausible volunteer populations whose expected infection prevalence differ according to the number of contacts (low, medium and high numbers of contacts) they have with other people (co-workers or other members of the public) each day according to their occupation. For this example, we use a prevalence for the medium contact of 0.04%. This is the mean prevalence observed in Alberta for asymptomatic people who were not close contacts or part of outbreak investigations during a period from February 14 to July 5, 2020 (*unpublished data from Government of Alberta, 2020*). We assume the low and high contact group prevalence levels are then twice and half, respectively, of the medium contact group.

The prevalence from sample group i is used to calculate their weight of contribution, $w(i, t)$, towards detecting COVID-19 at p_0 using Equation 2. Then, the number of tests needed from each volunteer population, in addition to E, needed to detect at least one positive case of COVID-19 at p_0 given $w(i, t)$ is calculated as:

Equation 6:

$$v(i, t) = \frac{\alpha(t)}{w(i, t)}$$

The value of $v(i, t)$ is the total number of samples to test if sampling exclusively from that group. The final consideration is to calculate the optimum number of sample-tests needed from all volunteer sample groups given the probability of sampling from their populations. Data from the March 2020 Labour Force Survey (20) and the O*Net occupational database (*unpublished data from the Centre for Labour Market Information, Statistics Canada at the request of the Public Health Agency of Canada. 2020*) define the proportion of Canadians having jobs with low, medium and high contact rates, $proportion(i)$, as 0.112, 0.392, and 0.494, respectively. Thus, the probability of a sample-test coming from volunteer sampling group i, in a P/T at t, given they are not part of E is:

Equation 7:

$$\Pr(i,t) = \lambda \times proportion(i)$$

where λ is the probability of not being in the healthcare visits population: 1 – *E/P/T population size*. Therefore, the total number of sample-tests needed from all volunteer populations in a P/T at t to detect at least one positive cases of COVID-19 at p_0 is:

Equation 8:

$$Z(t) = \sum_{i}^{J} v(i, t) \times \Pr(i, t)$$

Where i is the volunteer sampling group and J is the total number of sampling groups.

This method depends on population size given the calculation of E. To assess the sensitivity of population size we also show results for $Z(t)$ when $p_0 = 0.05\%$ to compare the proportion of population that must be surveyed when $p_0 = 0.05\%$ and $p_0 = 0.025\%$.

Results

Here we present results for sample size determined at the provincial level and weekly levels. For all P/T, we assumed the same prevalence levels for the sampling groups. Considering only the weight of contribution to detect COVID-19 at p_0 given assumed prevalence of the sampling groups, samples from the healthcare visits population are at least eight times to result in a positive COVID-19 test result (i.e. 25.6/3.20) (**Table 2**).

Table 2: Prevalence levels and weights of the volunteer sample groups in comparison with the healthcare visits population with low, *l*, medium, *m*, and high, *h*, contact rates

Sample groups, i	Prevalence, $p(i, t)$	Weight, $w(i, t)$
Healthcare visits	0.64	25.6
Volunteers with high contact rates	0.08	3.20
Volunteers with medium contact rates	0.04	1.60
p_0	0.025	1.0
Volunteers with low contact rates	0.02	0.80

As is inherent with the calculation, P/T with higher populations will have a higher number of expected healthcare visits, E. Given the high weight of contribution from this population to detect COVID-19 at p_0, larger populations will require fewer additional, if any, samples for early detection. If the goal is to detect COVID-19 at p_0 at the P/T level during the time frame of interest t, then only British Columbia, Alberta, Ontario and Québec would have a sufficient number of healthcare visit samples (**Table 3**). This assumes visits for respiratory illness at the assumed prevalence levels when maximal public health measures were in place from mid-March until just before the period of their relaxation in May 2020.

In step 2, it can be seen that low contact rate sample groups require model samples for early detection (**Table 4**). In calculation of the optimum number of additional samples

Table 3: Identification of province and territories that are short of samples by healthcare visits population[a,b]

Province/territory	E[c]	$wp(healthcare, t)$	$d(healthcare, t)$
BC	34,522	1,349	593
AB	29,809	1,164	
SK[d]	7,982	312	
MB[d]	9,304	363	
ON	99,371	3,882	
QC	57,668	2,253	
NB[d]	5,268	206	
NS[d]	6,602	258	
PE[d]	1,068	42	
NL[d]	3,522	138	
YK[d]	277	11	
NT[d]	303	12	
NV[d]	264	10	

Abbreviations: AB, Alberta; BC, British Columbia; MB, Manitoba; NB, New Brunswick; NL, Newfoundland and Labrador; NS, Nova Scotia; NT, Northwest Territories; NV, Nunavut; PE, Prince Edward Island; ON, Ontario; QC, Québec; SK, Saskatchewan; YK, Yukon

[a] Identification of province and territories that are short of samples by healthcare visits population as based on the number of expected healthcare visits, E, translated into weight points, $wp(healthcare, t)$, and compared to the number of weighted samples, $d(healthcare, t)$, needed to detect COVID-19 in the healthcare visits population at p_0

[b] Values are rounded up

[c] Expected number of samples from healthcare visits at the provincial/territorial level, E, and this number translated into weight points towards detecting COVID-19, $wp(healthcare, t)$

[d] Identification of province and territories that are short of samples by healthcare visits population

Table 4: Number of samples needed to detect COVID-19[a,b]

Province/territory	$d_{volunteer}(t)$	$n_{volunteer}(t)$	Low contacts	Medium contacts	High contacts
SK	17,118	9,137	11,421	5,711	2,855
MB		7,814	9,767	4,884	2,442
NB		11,850	14,812	7,406	3,703
NS		10,516	13,145	6,573	3,286
PE		16,050	20,063	10,031	5,016
NL		13,597	16,996	8,498	4,249
YK		16,841	21,051	10,526	5,263
NT		16,815	21,019	10,509	5,255
NV		16,854	21,068	10,534	5,267

Abbreviations: MB, Manitoba; NB, New Brunswick; NL, Newfoundland and Labrador; NS, Nova Scotia; NT, Northwest Territories; NV, Nunavut; PE, Prince Edward Island; SK, Saskatchewan; YK, Yukon

[a] Number of samples needed to detect COVID-19 at P_0 for asymptomatic test sensitivity, $d_{volunteer}(t)$; number of tests needed in addition to the healthcare visits samples from all volunteer sample groups, $n_{volunteer}(t)$, and if sampling exclusively from each group, $g_{volunteer}(sample\ group, t)$, with low, medium and high contacts at work

[b] Values are rounded up

needed to detect COVID-19 at p_0, when augmenting with volunteer samples, $Z(t)$, the low number of E compared with the total population of the P/T results in $\Pr(i, t)$ being very similar to the proportion of people with occupations with low, medium and high contact rates (**Table 5**). The less populous P/T require more volunteer samples for early detection because their E is

Table 5: Optimum number of additional samples needed to detect COVID-19

P/T	i	Population size	E	λ	$Proportion\ (i)$	$\Pr(i, t)$	$wp(i, t)$	$Z(t)$	% P/T	$Z(t)$ at $p_0 = 0.05\%$	% P/T at $p_0 = 0.05\%$
SK	L	1,181,666	7,982	0.99	0.112	0.111	11,420	4,867	0.41	307	0.26
	M			0.99	0.392	0.386	5,710				
	H			0.99	0.494	0.490	2,855				
MB	L	1,377,517	9,304	0.99	0.112	0.111	9,766	4,162	0.30	N/A	N/A
	M			0.99	0.392	0.386	4,883				
	H			0.99	0.494	0.490	2,441				
NB	L	779,993	5,268	0.99	0.112	0.111	14,812	6,312	0.81	1,753	0.23
	M			0.99	0.392	0.386	7,406				
	H			0.99	0.494	0.490	3,703				
NS	L	977,457	6,602	0.99	0.112	0.111	13,144	5,602	0.57	1,042	0.11
	M			0.99	0.392	0.386	6,572				
	H			0.99	0.494	0.490	3,286				
PE	L	158,158	1,068	0.99	0.112	0.111	20,063	8,550	5.41	3,991	2.52
	M			0.99	0.392	0.386	10,031				
	H			0.99	0.494	0.490	5,016				
NL	L	515,828	3,522	0.99	0.112	0.111	17,042	7,263	1.41	2,703	0.52
	M			0.99	0.392	0.386	8,521				
	H			0.99	0.494	0.490	4,261				

Table 5: Optimum number of additional samples needed to detect COVID-19 (*continued*)

P/T	i	Population size	E	λ	*Proportion* (i)	$\Pr(i, t)$	$wp(i, t)$	$Z(t)$	% P/T	$Z(t)$ at $p_0 = 0.05\%$	% P/T at $p_0 = 0.05\%$
YK	L	41,078	277	0.99	0.112	0.111	21,051	8,972	21.8	4,412	10.7
	M			0.99	0.392	0.386	10,526				
	H			0.99	0.494	0.490	5,263				
NT	L	44,904	303	0.99	0.112	0.111	21,019	8,958	20.0	4,398	9.80
	M			0.99	0.392	0.386	10,509				
	H			0.99	0.494	0.490	5,255				
NV	L	39,097	264	0.99	0.112	0.111	21,068	8,979	23.0	4,419	11.3
	M			0.99	0.392	0.386	10,534				
	H			0.99	0.494	0.490	5,267				

Abbreviations: H, high; L, low; M, medium; MB, Manitoba; N/A; not applicable; NB, New Brunswick; NL, Newfoundland and Labrador; NS, Nova Scotia; NT, Northwest Territories; NV, Nunavut; PE, Prince Edward Island; P/T, province/territory; SK, Saskatchewan; YK, Yukon
Note: At p_0 when augmenting with volunteer samples from sample group i, $Z(t)$, and the underlying values for the calculation, including λ, the probability of not being in the expected healthcare visits population, E. Also shown is the percentage of the provincial population that would need to participate in volunteer testing at temporal unit t

lower, and hence the percentage of the population that needs to volunteer is higher. When p_0 is increased from 0.25% to 0.50%, Manitoba has a sufficient number of E for early detection and the percentage of the population requiring volunteer sampling in the other P/T is reduced by half (Table 5).

Discussion

We present a relative weighted approach for calculating the number of sample-tests required to detect at least one case of COVID-19 at a threshold level for early detection and control of new outbreaks. This approach combines expected numbers of tests from healthcare visits, with additional sampling from the general population. From the sampling groups, the probability of detecting COVID-19 is highest from the healthcare visits population. When insufficient samples are available from this group, sampling the general population using a relative weighted approach can provide the additional samples required.

Our approach is more feasible for large populations because they have higher testing rates from the healthcare visits population. If additional samples are needed, then the proportion of the population required as volunteers is more achievable than with smaller populations. For example, in our demonstration of sample size determination using P/T as the surveillance population, we find that British Columbia, Alberta, Ontario and Québec already have sufficient sample sizes from the healthcare visits population at the weekly level. Augmenting samples from volunteers requires testing 0.3 to 0.81% of the population for Saskatchewan, Manitoba, New Brunswick and Nova Scotia. However, for Prince Edward Island, Newfoundland and Labrador, Yukon, Northwest Territories and Nunavut, more than 1%–23% of the population must be tested. It is unlikely that level of compliance and/or ability to travel to testing sites would be achieved. This range reduces to 0.5%–11.3% of the population if assuming $p_0 = 0.05\%$ instead of $p_0 = 0.025\%$, as was done for Germany following their first wave of COVID-19 infections.

Strengths and limitations

We did not consider test specificity in our approach. Polymerase chain reaction (PCR) tests for SARS-CoV-2 infection show excellent specificity of at least 98% but are more variable for test sensitivity (21,22). Even at 98%, large sample sizes can result in considerable numbers of false positives; for example, 160 false positive test results would be expected from testing 8,000 people. False positive test results can have significant consequences if the person with a false positive result undergoes unnecessary treatment for COVID that endangers the health of that person. Whereas a false positive result for a healthy person will only mean self-isolation for a while, and that would have limited impact on the health of that person.

The value of our approach is guiding surveillance efforts at the onset of an emerging disease when little is known about factors affecting the probability of a sample testing positive for the disease. At the onset of disease emergence, surveillance systems are developing their capacity to test and collect information that is pertinent for understanding transmission risk. Collecting information about high risk factors, such as travel history, lag behind socio-demographic information such as sex and age group. Furthermore, the association of socio-demographic information with the test result may not yet have been determined. When information for high risk factors becomes available, approaches that harness this type of information into a relative weighted approach can refine estimates of sample size determination, as shown by Jennelle *et al.* (10). This approach includes accounting for changes in the transmission risk over time as the disease risk grows, peaks and wanes. This also includes accounting for the passive nature of surveillance systems that result in violating the assumption that sampling is non-random.

For example, barriers to access healthcare or testing centres in relation to gender, age, occupation or ethnicity. Consequently, overrepresentation of people with a certain socio-demographic profiles may skew the accuracy of prevalence values for the sampling groups. At present, sampling to collect nasopharyngeal swabs from patients visiting primary health care is rarely done, so less invasive sampling methods, such as mouth rinse tests, would facilitate reaching target sample sizes.

At the emergence of a novel disease there is likely insufficient information to accurately define the probability of a positive test result, which can then be used to inform sample size determination for early detection. Here we present a method to estimate sample sizes for early detection using limited information, as we show with prevalence levels (both estimated and assumed) from multiple sampling groups. Weighing the contribution of a sample from a given sampling group to result in a positive test result enables a more efficient sampling strategy for early detection, helping to target surveillance efforts and resources. Ideally, prevalence levels are updated, when possible, to reduce the error in the sample size estimates as the prevalence levels in sampling groups change over time and space. More specifically, P/Ts can cover large areas, where cities may be separated by hundreds of kilometers and, thus, may be only weakly connected in terms of drivers of infection. There may be multiple epidemiological units within a P/T, meaning that community transmission patterns are more similar within a unit than among neighbouring units. Hence, prevalence levels in the sampling groups can differ among the units over space and time. Metrics resulting from surveillance, such as sample size determination, are ideally performed at the spatial level of the epidemiological unit (12). The method presented here can be adapted to the level of an epidemiological unit. This approach would ensure that sample size determination for early detection is reflective of the sampling efforts (i.e. E) and prevalence levels for the sampling groups that are unique to the unit during the time frame of interest.

Conclusion

This intervention study introduces a targeted surveillance strategy, combining both passive and active surveillance samples, to determine how many samples to collect per unit area and unit time to detect new clusters of COVID-19 cases. The goal of this strategy is to allow for early enough detection to control an outbreak.

Authors' statement

EER — Conception, formal analysis, writing–original draft, writing–review and editing
RR — Conception, revising of writing, critical review
NHO — Conception, revising of writing, critical review

Competing interest

None.

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Trends in HIV pre-exposure prophylaxis use in eight Canadian provinces, 2014–2018

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Abstract

Introduction: Canada has endorsed the Joint United National Programme on HIV and AIDS global targets to end the acquired immunodeficiency syndrome (AIDS) epidemic, including reducing new human immunodeficiency virus (HIV) infections to zero, by 2030. Given the effectiveness of pre-exposure prophylaxis (PrEP) to prevent new infections, it is important to measure and report on PrEP utilization to help inform planning for HIV prevention programs and policies.

Methods: Annual estimates of persons using PrEP in Canada were generated for 2014–2018 from IQVIA's geographical prescription monitor dataset. An algorithm was used to distinguish users of tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) for PrEP versus treatment or post-exposure prophylaxis. We provide the estimated number of people using PrEP in eight Canadian provinces by sex, age group, prescriber specialty and payment type.

Results: The estimated number of PrEP users increased dramatically over the five-year study period, showing a 21-fold increase from 460 in 2014 to 9,657 in 2018. Estimated PrEP prevalence was 416 users per million persons across the eight provinces in 2018. Almost all PrEP users were male. Use increased in both sexes, but increase was greater for males (23-fold) than females (five-fold). Use increased across all provinces, although there were jurisdictional differences in the prevalence of use, age distribution and prescriber types.

Conclusion: The PrEP use in Canada increased from 2014 to 2018, demonstrating increased awareness and uptake of its use for preventing HIV transmission. However, there was uneven uptake by age, sex and geography. Since new HIV infections continue to occur in Canada, it will be important to further refine the use of PrEP, as populations at higher risk of HIV infection need to be offered PrEP as part of comprehensive sexual healthcare.

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Keywords: HIV, Canada, pre-exposure prophylaxis, prevention

Introduction

The government of Canada has endorsed the Joint United National Programme on HIV and AIDS (UNAIDS) global targets to end the AIDS epidemic (1–3), including reducing new human immunodeficiency virus (HIV) infections to zero, by 2030. Given the effectiveness of pre-exposure prophylaxis (PrEP) to prevent new infections, and the goal of increasing access to combination prevention for key populations, it is important to measure and report on its uptake in Canada. Increasing our understanding of trends in PrEP utilization will help to inform planning for HIV prevention programs and policies.

The estimated number of new HIV infections in Canada has decreased from about 4,000 per year in the mid-1980s to an estimated 2,165 in 2016 (4). This decrease is likely due, in part, to the introduction of effective antiretroviral treatment, which can suppress viral load and thereby decrease HIV transmission (5,6). The estimated number of new HIV infections in Canada decreased until 2011, but has been stable or has increased slightly since then (4), despite the availability of antiretroviral therapy as well as behavioural interventions. Pre-exposure prophylaxis is one of the highly effective strategies to reduce the risk of acquiring an HIV infection, and has the potential to contribute to decreasing HIV incidence in Canada. In

2016, Health Canada approved the drug combination tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for use as PrEP; and in July 2017, lower cost generic versions became available in Canada.

Because PrEP use is not included in national HIV surveillance in Canada, one feasible method to estimate uptake is through the analysis of administrative prescription data. The Public Health Agency of Canada purchased and analysed data from the IQVIA longitudinal prescriptions database to estimate the number of persons prescribed PrEP ("PrEP users") from eight Canadian provinces, and to describe their basic demographic characteristics.

Methods

Data source

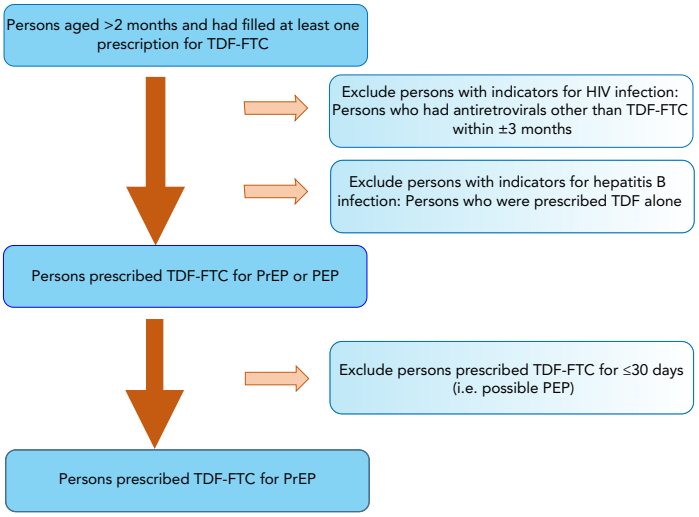
Data on antiretroviral drug prescriptions dispensed between January 1, 2014 and December 31, 2018, were extracted by IQVIA from their geographical prescription monitor dataset. The IQVIA database includes Canadian aggregate dispensed prescription data projected from a sample of approximately 6,000 pharmacies in the eight available provinces, representing close to 60% of all retail pharmacies in Canada. Patient counts are then projected from this sample of pharmacies. While dispensation data provided to IQVIA is de-identified, it is linkable by IQVIA for the same person using anonymous identifiers, allowing for counts of unique individuals. The database includes antiretroviral drugs dispensed and de-identified, individual-level information on patient demographics (sex, age group), the physician specialty and payer type (private insurance, public insurance or out of pocket).

Missing data on PrEP users are possible within this dataset, since only prescriptions that were acquired from a community pharmacy are included. Dispensations from hospital pharmacies, those provided at no cost, and those purchased online are not included.

Algorithm to identify pre-exposure prophylaxis users

Specific diagnostic or procedural codes for PrEP use are not available within the IQVIA database; therefore, an algorithm was used to estimate the annual number of PrEP users (**Figure 1**). This algorithm discerned whether TDF/FTC was prescribed for PrEP, HIV treatment, hepatitis B treatment or HIV post-exposure prophylaxis (PEP), and was adapted from a validated United States Centers for Disease Control algorithm (7–9) and modified to fit the Canadian context. Briefly, in a given year, we selected persons older than two months of age who had one or more TDF-FTC prescription. Since TDF-FTC is also used to treat HIV or hepatitis B infections and as HIV PEP, we applied several exclusion criteria. First, we excluded persons who were prescribed antiretrovirals other than TDF-FTC within ±3 months (persons on HIV treatment). Second, we excluded persons who were prescribed with TDF alone (for hepatitis B treatment). Third, we excluded persons who were prescribed TDF-FTC for fewer than 30 days (PEP users). In any given year, persons prescribed TDF-FTC who were not excluded with our algorithm were considered PrEP users.

Figure 1: Algorithm to assign pre-exposure prophylaxis treatment indication



Abbreviations: HIV, human immunodeficiency virus; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; TDF-FTC, tenofovir disoproxil fumarate/emtricitabine

For the entire analysis, all ages were taken into account when IQVIA extracted the data and estimated the number of projected patients by indication. However, the results for patients younger than 15 years of age were omitted in the age and sex analysis due to small counts.

Analysis

Pre-exposure prophylaxis use estimates by sex, age group, payer type and physician specialty are descriptive. The prevalence of persons who used PrEP among all persons 15 years of age and older per million for each year were also estimated. Cochran Armitage trend tests were conducted to determine whether the proportion of PrEP uptake changed significantly over time. Analyses were performed using SAS Version 9.4 (SAS Institute).

Results

In 2018, a total of 9,657 people were estimated to be on PrEP in eight Canadian provinces (Saskatchewan (SK), Manitoba (MB), Ontario (ON), Québec (QC), New Brunswick (NB), Nova Scotia (NS), Prince Edward Island (PE) and Newfoundland and Labrador (NL)). The estimated number of PrEP users increased dramatically over the five-year study period (**Table 1**), showing a 21-fold increase from 460 in 2014 to 9,657 in 2018. Almost all (98%) PrEP users were male during the five-year time period and the number of users increased in both sexes, but

increases were greater for males (23-fold) than females (five-fold) (Table 1).

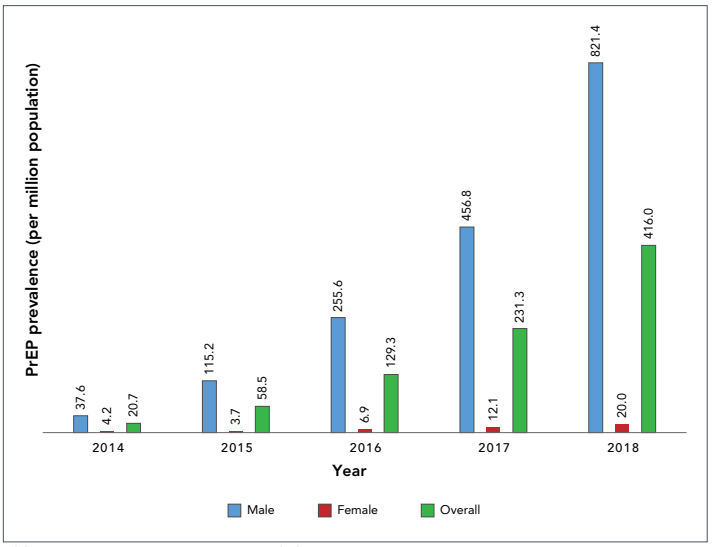
Table 1: Annual estimated number of individuals prescribed pre-exposure prophylaxis[a], by sex and age group, in eight provinces in Canada, 2014–2018

Estimated PrEP users	Number (%) by year									
	2014		2015		2016		2017		2018	
Sex	#	%	#	%	#	%	#	%	#	%
Male	411	89.5	1,267	96.8	2,842	97.3	5,147	97.3	9,401	97.6
Female	48	10.5	42	3.2	79	2.7	141	2.7	235	2.4
Total	460	100.0	1,309	100.0	2,922	100.0	5,291	100.0	9,657	100.0
All estimated PrEP users										
Age group (years)	#	%	#	%	#	%	#	%	#	%
15–17	0	0.0	3	0.2	3	0.1	6	0.1	19	0.2
18–24	15	3.3	30	2.3	91	3.1	234	4.4	860	8.9
25–35	99	21.5	351	26.8	913	31.2	1,815	34.3	3,527	36.5
36–45	136	29.6	430	32.8	920	31.5	1,626	30.7	2,604	27.0
46–55	120	26.1	316	24.1	637	21.8	985	18.6	1,683	17.4
56–64	30	12.6	90	9.2	196	9.2	332	9.0	435	7.5
65+	32	7.0	53	4.0	90	3.1	148	2.8	237	2.5
Male PrEP users										
Age group (years)	#	%	#	%	#	%	#	%	#	%
15–17	0	0.0	3	0.2	3	0.1	6	0.1	17	0.2
18–24	12	2.9	27	2.1	88	3.1	225	4.4	807	8.6
25–35	81	19.7	338	26.7	881	31.0	1,755	34.1	3,433	36.5
36–45	124	30.2	415	32.8	898	31.6	1,586	30.8	2,552	27.1
46–55	112	27.3	310	24.5	624	22.0	966	18.8	1,650	17.6
56–64	53	12.9	121	9.6	259	9.1	462	9.0	707	7.5
65+	29	7.1	53	4.2	89	3.1	147	2.9	235	2.5
Female PrEP users										
Age group (years)	#	%	#	%	#	%	#	%	#	%
15–17	0	0.0	0	0.0	0	0.0	0	0.0	2	0.9
18–24	3	6.3	3	7.1	3	3.8	9	6.4	51	21.7
25–35	17	35.4	13	31.0	32	40.5	57	40.4	82	34.9
36–45	12	25.0	15	35.7	21	26.6	40	28.4	50	21.3
46–55	8	16.7	6	14.3	13	16.5	19	13.5	30	12.8
56–64	5	10.4	5	11.9	9	11.4	15	10.6	18	7.7
65+	3	6.3	0	0.0	1	1.3	1	0.7	2	0.9

Abbreviation: PrEP, pre-exposure prophylaxis
[a] Data obtained from IQVIA longitudinal prescription database

The prevalence of persons prescribed PrEP among those 15 years of age or older increased significantly, from 20.7 per million in 2014 to 416.0 per million in 2018 ($P_{trend} < 0.001$) (**Figure 2**). When stratified by sex, PrEP prevalence among the male population increased significantly over time ($P_{trend} < 0.001$) with a very large increase in 2018 to 821.4 persons prescribed PrEP per million. The PrEP prevalence among the female population also showed an increasing trend, from 4.2 per million in 2014 to 20.0 per million in 2018 ($P_{trend} < 0.001$); however, the overall uptake among females was much lower than that in the male population (Figure 2).

Figure 2: Estimated prevalence (per million) of persons prescribed pre-exposure prophylaxis[a], by sex and overall, in eight provinces in Canada[b], 2014–2018



Abbreviation: PrEP, pre-exposure prophylaxis
[a] Data obtained from IQVIA longitudinal prescription database
[b] Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Québec and Saskatchewan

The estimated number of male PrEP users increased across all age groups between 2014 and 2018, while the relative increase in male PrEP users was greatest in the 18–24 year age category (67-fold) (Table 1). Males aged 36–45 years comprised the greatest proportion of PrEP users from 2014 to 2016; however, in 2017 and 2018, there was a shift to the younger age category with males aged 25–35 years making up the highest proportion of PrEP users (Table 1).

The estimated number of female PrEP users also increased across all age groups between 2015 and 2018, with the exception of the 65+ age group (Table 1). The relative increase in female PrEP users was greatest in the 18–24 years of age category (17-fold increase). The 25–35 years of age category consistently made up the greatest proportion of female PrEP users except for 2015, when females aged 36–45 years accounted for the greatest proportion (Table 1). These percentages were based on relatively small numbers; therefore, these trends should be interpreted with caution.

Pre-exposure prophylaxis was most frequently prescribed by primary care providers (family and general practitioners), and this trend was consistent over the five-year period. In 2018, the majority of the estimated PrEP users were prescribed TDF/FTC by primary care providers (75.5%), followed by infectious disease specialists (11.9%), internal medicine specialists (4.7%) and others (3.8%) (**Table 2**). From 2014 to 2018, the estimated proportion of users whose PrEP was prescribed by infectious disease and internal medicine physicians decreased by 30% while the estimated proportion prescribed by primary care providers increased by 10 % (Table 2).

Table 2: Annual estimated number of individuals prescribed pre-exposure prophylaxis[a], by prescriber specialty, payment type[b] and selected provinces[c] in Canada, 2014–2018

Estimated PrEP users	Number (%) by year									
	2014		2015		2016		2017		2018	
Prescriber specialty	#	%	#	%	#	%	#	%	#	%
Primary care provider	275	68.9	896	79.6	2,037	78.9	3,616	78.8	6,107	75.5
Infectious diseases	68	17.0	125	11.1	294	11.4	589	12.8	965	11.9
Internal medicine	28	7.0	43	3.8	73	2.8	113	2.5	381	4.7
Public health and preventive medicine	0	0.0	7	0.6	40	1.5	49	1.1	196	2.4
Medical microbiology	8	2.0	16	1.4	59	2.3	88	1.9	130	1.6
Others	20	5.0	39	3.5	78	3.0	131	2.9	308	3.8
Payer type	#	%	#	%	#	%	#	%	#	%
Out of pocket	19	4.1	45	3.4	89	3.0	191	3.6	258	2.7
Private insurance	282	61.3	899	68.8	2,068	70.6	3,874	73.2	6,612	68.4
Public insurance	159	34.6	362	27.7	771	26.3	1,226	23.2	2,793	28.9
Province										
Manitoba	8		9		16		43		129	
New Brunswick	0		0		60		100		136	
Newfoundland and Labrador	0		1		4		12		37	
Nova Scotia	0		5		98		178		281	
Ontario	239		579		1,397		2,715		5,684	
Prince Edward Island	0		0		0		0		12	
Québec	192		696		1,316		2,182		3,244	
Saskatchewan	0		0		11		44		342	

Abbreviation: PrEP, pre-exposure prophylaxis
[a] Data obtained from IQVIA longitudinal prescription database
[b] Payer type—eight provinces (Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario, Prince Edward Island, Québec and Saskatchewan)
[c] Prescriber specialty—five provinces (New Brunswick, Nova Scotia, Ontario, Québec and Saskatchewan)

On average, more than two-thirds of the estimated PrEP users covered the cost of the prescription through private health insurance, and this trend was consistent over time (Table 2). The estimated number of PrEP prescriptions covered by private and public insurance increased from 2015 to 2018 by 23-fold and 18-fold, respectively (Table 2). Approximately 3%–4% of PrEP prescriptions were paid "out of pocket" by the individual. However, no follow-up was done for these individuals whose expenses could then have been reimbursed by private or public health insurance (Table 2).

Annual PrEP use increased in every province (Table 2); however, there was variation within the increasing trend of people on PrEP between the eight provinces. Annual PrEP prevalence for each province by year, showed that 2018 PrEP prevalence was highest in ON, QC and SK, at 471, 446 and 355 per million persons, respectively (**Table 3**). Consistently, more than 85% (range 87%–100%) of PrEP users were males across all provinces (data not shown).

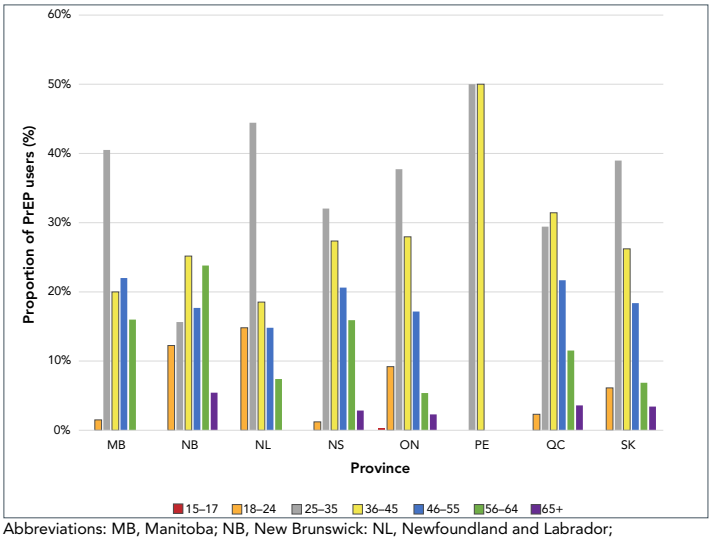
Table 3: Annual estimated pre-exposure prophylaxis[a] prevalence (per million) in eight provinces in Canada, 2014–2018

Annual estimated PrEP prevalence (by province)	Number (per million) by year				
	2014	2015	2016	2017	2018
Manitoba	7.7	9.5	15.0	44.4	107.5
New Brunswick	0.0	0.0	92.0	151.0	204.7
Newfoundland and Labrador	0.0	2.2	8.8	26.4	81.7
Nova Scotia	0.0	5.0	107.6	193.7	292.5
Ontario	21.0	50.4	120.1	229.6	471.5
Prince Edward Island	0.0	0.0	0.0	0.0	26.5
Québec	30.4	102.2	192.0	308.6	445.9
Saskatchewan	0.0	0.0	13.1	69.0	354.9

Abbreviation: PrEP, pre-exposure prophylaxis
[a] Data obtained from IQVIA longitudinal prescription database

In five of the provinces (NL, NS, ON, PE and SK), the age group with the highest proportion of PrEP use was 25–35 years, followed by 36–45 years (**Figure 3**). The age of PrEP users differed for MB, with those aged 46–55 years being the second highest proportion of users. In NB, PrEP users were older, with the highest proportion of PrEP users among those aged 36–45 years, followed by 56–64 years. In QC, the highest proportion was among people aged 36–45 years followed by 25–35 years.

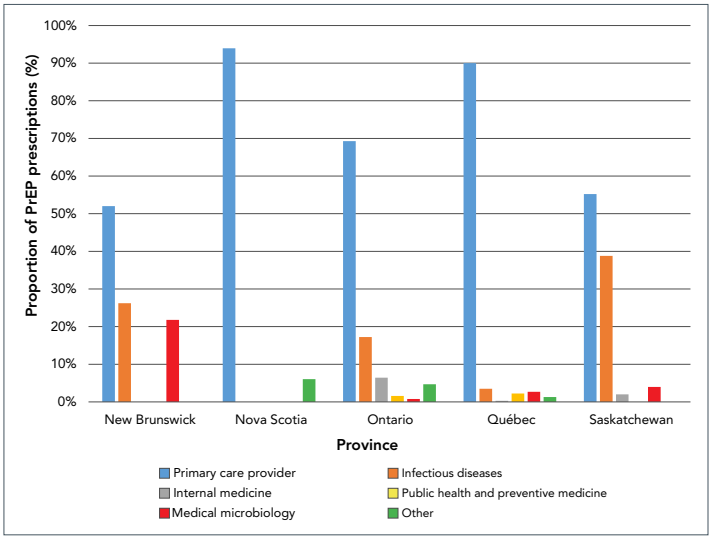
Figure 3: Estimated proportion of individuals prescribed pre-exposure prophylaxis[a] by age group, 2014–2018



Abbreviations: MB, Manitoba; NB, New Brunswick: NL, Newfoundland and Labrador; NS, Nova Scotia; ON, Ontario; PE, Prince Edward Island; PrEP, pre-exposure prophylaxis; QC, Québec; SK, Saskatchewan
[a] Data obtained from IQVIA longitudinal prescription database

Information on prescription by physician speciality was available for five of the eight provinces (**Figure 4**). Primary care providers prescribed PrEP most frequently in all provinces, followed by infectious disease specialists in all provinces but NS. In contrast, infectious disease specialists in SK prescribed almost 40% of PrEP prescriptions (Figure 4). For some provinces, there was a large amount of data missing for prescriber specialty; therefore, these data should be interpreted with caution. Over the 5-year period, the most common payer type was private insurance in the majority of provinces, ranging between 58% and 100%, with the exception of SK, where public insurance covered more than 80% of PrEP prescriptions between 2014 and 2018 (data not shown).

Figure 4: Estimated proportion of individuals prescribed pre-exposure prophylaxis[a] by physician specialty, 2014–2018



Abbreviation: PrEP, pre-exposure prophylaxis
[a] Data obtained from IQVIA longitudinal prescription database

Discussion

In the current analysis, we found an increasing trend in the estimated number of persons prescribed TDF-FTC for PrEP in eight Canadian provinces from 2014 to 2018. During this time period, we found an almost 2,000% increase in PrEP users, with an estimated 9,657 individuals using PrEP in the eight Canadian provinces at the end of 2018. This resulted in an estimated PrEP prevalence of 416 per million persons across the eight provinces in 2018. This increase is likely due to several factors: the approval of TDC/FTC for use as PrEP by Health Canada in February 2016 followed by the availability of lower cost generic versions in July 2017; the publication of a Canadian guideline on HIV pre-exposure prophylaxis and non-occupational post-exposure prophylaxis in 2018 (10); the inclusion of PrEP in an increasing number of provincial drug plans between 2014 and 2018; and increased awareness of PrEP as an effective HIV prevention measure among clinical providers and populations that could benefit from PrEP—notably gay, bisexual and other men who have sex with men (gbMSM).

When all eight provinces (for which data were available) were combined, coverage for PrEP prescriptions was consistent over the five-year period with approximately two-thirds of prescriptions being covered by private insurance. When looking at payer type by province, the payer type was consistently private insurance for all provinces except SK where public insurance covered more than 80% of PrEP prescriptions between 2014 and 2018. A recent summary of PrEP coverage across Canada showed that almost all provinces and territories in Canada had coverage for PrEP (11); however, there were variations with respect to coverage requirements, ranging from co-payments to requirements for valid provincial health coverage or for approval from senior public health officials. Each of these requirements may have an impact not only on the type of payment used for the PrEP prescription but may also impact the level of uptake of PrEP across Canadian jurisdictions.

In 2014, among 460 estimated PrEP users, 90% were male. We observed an increasing trend in PrEP use among men, with an almost 23-fold increase in the number of male PrEP users from 2014 to 2018. This increase in the estimated number of males taking PrEP during the five-year period is important, given that the largest proportion of estimated new HIV infections and HIV diagnoses in 2018 were among the gbMSM population (4,12). Although the number of females on PrEP was consistently lower than the number of males, female use of PrEP increased five-fold from 2014 to 2018. National surveillance data show that the rate of HIV diagnoses has increased among females in last five years; from 2.5/100,000 population in 2013 to 4.0/100,000 population in 2018, whereas the diagnosis rate for males remained stable at approximately 9/100,000 population during the same time period (12). This difference highlights the need to develop or refine strategies for identifying women who have PrEP indications.

By age group, the highest proportion of PrEP use was observed in those 36–45 years of age in 2014 and 2015, and then there was a shift to a younger age group (25–35 years) in 2017–2018. This is important since within national HIV surveillance the 30–39 years age group had the highest number and proportion of reported HIV cases, followed by the 20–29 years age group (12). The age group with the lowest proportion of PrEP users was 15–24 years; however, the number of PrEP users among this age group increased by 266% between 2017 and 2018. This increase in PrEP use is encouraging since youth and young adults have been reported to have barriers to PrEP uptake (13).

In more recent years, there was a decreasing trend in PrEP prescribed by specialists (infectious diseases and internal medicine), with an increase in PrEP prescribed by primary care

providers. These findings are important to consider as increased availability of PrEP for individuals at risk for HIV acquisition continues to be a priority in Canada. Primary care providers can play a key role to increase PrEP uptake as part of a sexual health and disease prevention approach given their large representation in the health care work force (14,15).

Pre-exposure prophylaxis use increased across all provinces, although there were jurisdictional differences in the prevalence of PrEP use, age distribution and prescriber types. Several provinces showed PrEP use before 2016, the year when Health Canada approved the drug combination (TDF/FTC) for use as PrEP, and other provinces did not report PrEP use until 2016. Saskatchewan had the highest HIV diagnosis rate in Canada in 2018 at 14.9/100,000 population but had the third highest estimated PrEP prevalence per million—behind only ON and QC. It is important to note that as of April 2018, PrEP became available at no cost to all SK residents; therefore, an increase in PrEP uptake may be observed post-2018 (e.g. 2019–2020 prescription data). The PrEP users tended to be older in some provinces, more frequently prescribed by specialists in some provinces, and commonly covered by private insurance in most provinces: all highlighting the continued need for tailored programs across each jurisdiction in Canada.

Strengths and limitations

This is the first time that estimates of PrEP uptake across Canada have been published, and these data represent a population-based data source for PrEP use; however, there are important limitations to the data. Firstly, the results do not reflect the national picture of PrEP use in Canada, as these data only include eight provinces. British Columbia publishes its own PrEP summary report, which indicated that there were 2,423 PrEP users at the 4th quarter of 2018 (16). The characteristics of PrEP users in British Columbia (BC) were very similar to the eight provinces included in this analysis. For example, 99% of PrEP users in BC were male, the highest proportion of PrEP users was among individuals aged 29–40 years old, and family physicians prescribed 77% of PrEP (16). The addition of information from BC and Alberta would provide a more representative overview of PrEP uptake in Canada. Second, IQVIA data only included prescriptions that were acquired from a community pharmacy. Dispensations from hospital pharmacies, drugs provided at no cost and drugs purchased online were not included.

Additionally, the dispensation data from IQVIA covered approximately 60% of all retail pharmacies in Canada. Patient counts from participating pharmacies were projected to the whole population of each province by IQVIA, and the algorithm used to project dispensations is proprietary. Sensitivity analysis with other data sources to corroborate the accuracy of the projected patient counts was not completed.

Dispensation data do not include information on medical indication; therefore, an algorithm was used to assign a treatment indication to each dispensation. Although the algorithm for classifying TDF/FTC users as PrEP users has been validated, it is possible that some dispensations were misclassified.

Finally, not all dispensed prescription drugs are consumed, as some people may fill a prescription but not consume the medication. These limitations could result in an under or over-estimate of the number of projected patient counts.

Future directions

The preliminary analysis of this administrative data from 2014 to 2018 showed that there has been substantial growth in the uptake of PrEP across eight Canadian provinces. Nonetheless, the PrEP uptake and its potential prevention of HIV transmission is not distributed equitably, as demographic profiles of new HIV diagnoses by sex and age group do not always align with rates of PrEP use, and the growth of PrEP use has not occurred equally for females. A similar study conducted by the United States Centres for Disease Control also found that annual PrEP use increased faster among males than among females, increased fastest among those aged 25–34 years, and that geographic variations in PrEP uptake existed across the country (7,9).

The analysis of prescription data is helpful to understand where PrEP uptake is greatest, or where there are areas for improvement; however, these data alone cannot distinguish the underlying reasons why PrEP use is lower in specific populations. Results from a four-year longitudinal study of gbMSM in Vancouver, BC, demonstrated that awareness of PrEP increased over time; up to 80% in 2016 (17). Canadian results from the European Men-who have-sex-with-men Internet survey (EMIS) indicated that over 85% of participants had heard of PrEP. Among HIV-negative or untested men, 52% reported that they were likely to use PrEP if it was affordable and available, while only 8.4% of participants were using PrEP at the time of the survey (18). Data from the recent Tracks survey of people who inject drugs in Canada (2017–2019) highlighted that only 14% of the participants had heard about PrEP (19). Recent research showed that HIV treatment adherence information can be used to inform PrEP interventions, and that new strategies are needed to engage vulnerable and marginalized populations in PrEP-related programming (20). This research highlights the continued need for complimentary research at the national level, assessing PrEP awareness and willingness to use and factors related to access—focussing on differences between specific populations and across geographic regions. These data, together with data available through population-specific surveys, show an increase in PrEP uptake and awareness (17,19); however, there are gaps in PrEP uptake data for a range of key populations most affected by HIV, including Indigenous people, racialized people (including African, Black and Caribbean communities), transgender and non-binary people, sex workers and people in correctional facilities.

Conclusion

This analysis shows that PrEP use in Canada has increased since 2014, demonstrating increased awareness and uptake of its use for preventing HIV transmission; however, there was uneven uptake of PrEP by different age groups and sex, and across the Canadian provinces. Other Canadian evidence suggests a large unmet need in some population groups (e.g. gbMSM, people who inject drugs), and there is still a need for similar data for other populations.

Presently, the IQVIA prescription database provides the most feasible means to monitor PrEP uptake in Canada; however, sensitivity analysis using provincial prescription databases would help to validate the proprietary IQVIA algorithm for projected patient counts.

Since new HIV infections continue to occur in Canada, the use of PrEP in adult men and women at high risk should continue to be considered in combination with safer sex practices to reduce the risk of sexually acquired HIV infection. In Canada, it will be important to further refine the use of PrEP, as there is progress to be made to ensure that populations at higher risk of HIV infection are offered PrEP as part of comprehensive sexual health care.

Authors' statement

NP — Conceptualization, interpretation of data, writing original draft, review, editing, validation, writing final draft, visualization
QY — Data curation, interpretation of data, contributed to first draft
CA — Conceptualization, review–revision of the paper, final approval

Competing interests

None.

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Salmonella enterica serovars associated with bacteremia in Canada, 2006–2019

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Abstract

Background: Members of the bacterial genus *Salmonella* cause salmonellosis, a disease with a spectrum of clinical presentations from a self-limiting gastroenteritis to more severe bacteremia, organ failure and sepsis. The genus consists of over 2,600 serological variants (serovars). Important differences in the pathogenesis of *Salmonella* serovars have been noted.

Objective: The purpose of this study was to determine which *Salmonella* serovars were more likely to be associated with bacteremia in Canada.

Methods: Information on the total number of *Salmonella* infections and blood isolations reported to the National Enteric Surveillance Program (NESP) from 2006 to 2019 was extracted for each serovar. The risk (proportion) and likelihood (odds) of bacteremia were calculated for all serovars.

Results: Of the 96,082 *Salmonella* cases reported to the NESP during the 14-year study period, 4.4% (95% CI: 4.3%–4.6%) were bacteremic. Twenty nontyphoidal *Salmonella* (NTS) serovars were associated with lower rates of bacteremia compared to all NTS serovars, and 19 NTS serovars were identified as having higher rates. Heidelberg, Oranienburg, Schwarzengrund, Virchow, Panama and Poona among the top 25 most commonly reported serovars in Canada during the study period.

Conclusion: The identification of serovars associated with *Salmonella* bacteremia in Canada is a first step towards understanding differences in pathogenesis and disease presentation.

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Keywords: typhoidal, nontyphoidal salmonellosis, National Enteric Surveillance Program, NESP

Introduction

Salmonella bacteria are an important cause of human illness with a variety of clinical presentations (1). The genus consists of two species, six subspecies and over 2,600 serological variants (serovars). Although all species and subspecies have been reported to cause illness, most human infections are caused by *S. enterica* spp. *enterica* (subspecies I) (2). Subspecies I include typhoidal and nontyphoidal serovars. Typhoidal serovars cause typhoid (enteric) fever, a serious invasive infection that can lead to multiorgan failure, bacteremia and sepsis (3). Nontyphoidal salmonellosis (NTS) mainly results in an acute self-limiting gastroenteritis, although more severe infection can occur (3). In Canada, the majority of reported salmonellosis cases—including about 925 hospitalizations and 17 deaths per year—are due to NTS (4).

One of the defining features of *Salmonella* is the presence of virulence genes encoded on sections of the genome called *Salmonella* pathogenicity islands (SPIs). All 2,659 *Salmonella* serovars possess SPIs and therefore encode the ability to cause infections (5). Nevertheless, only a small proportion of serovars are responsible for the majority of reported human infections, with over 80% of reported salmonellosis cases attributed to 20 serovars despite that over 200 serovars are reported annually in Canada (6). Although some frequently reported serovars are associated with greater exposure risks because they are more prevalent in the environment, the presence of several highly prevalent but rarely reported serovars suggests differences in virulence between serovars (7). This hypothesis is supported by studies on the pathogenesis of the typhoidal serovars and NTS serovars such as Choleraesuis, Dublin, Typhimurium and Enteritidis (1,7). The pathogenesis of most NTS serovars, however, is understudied and therefore poorly understood.

Examining the rates of *Salmonella* bacteremia in humans is one way to compare the relative virulence of serovars. Globally, about 2%–8% of reported NTS infections lead to bacteremia, and in some cases, bacteremia is not preceded by gastroenteritis (8–11). Patients with bacteremia are more likely to experience severe outcomes, including hospitalization and death, unless treated promptly with antibiotics (12,13). Therefore, the early identification of high-risk patients can improve the prognosis of *Salmonella* bacteremia (9,14). Human risk factors for bacterial dissemination from the gut include compromised immunity, underlying medical conditions and extremes of age. Bacterial virulence factors involved in this process include adhesion proteins, immune evasion proteins and other secreted effectors (3,10,15,16).

The objective of this study was to compare bacteremia rates of different *Salmonella* subspecies and serovars to gain a better understanding of the differences in virulence. Identification of *Salmonella* serovars that are more or less likely to be associated with bacteremia is a key step towards the development of better predictors of *Salmonella* bacteremia and, eventually, better standards of care.

Methods

Data sources

The research team obtained data from the National Enteric Surveillance Program (NESP), which is administered by the Public Health Agency of Canada (6). The data are a summary of laboratory data submitted weekly by provincial/territorial public health microbiology labs to the NESP. We extracted data from 2006 to 2019 for this analysis, including the number of *Salmonella* infections by subspecies, serovar and specimen source for extraintestinal isolations. Each reported isolation represents one clinical case. Blood isolates were recovered from blood and taken as a proxy for the number of bacteremia cases caused by *Salmonella* (*Salmonella* bacteremia). Total isolates were those recovered from all specimen sources.

Data analysis

Information on the reporting frequency and distribution of *Salmonella* subspecies and serovars was tabulated using Microsoft Excel 2016 and visualized using GraphPad Prism 8.0.2.

We calculated rates of *Salmonella* bacteremia over time by dividing the number of blood isolates reported every year by the number of total *Salmonella* reports for that year. The chi-square/Cochran–Armitage test for trend was used to determine if there was a linear trend in bacteremia rates over time. This temporal analysis was conducted at the genus level as well as at the level of individual NTS serovars.

Bacteremia proportions (BP) of individual *Salmonella* serovars or groups were calculated by dividing the number of blood isolates of a given serovar/group by the number of total isolates of the same serovar/group for all years combined. The 95% confidence intervals (CI) for BP were calculated using the following formula:

$$\mathrm{BP} \pm \frac{1.96\sqrt{\mathrm{BP}(1 - \mathrm{BP})}}{\mathrm{n}}$$

For some analyses, we grouped serovars according to their subspecies designation (I–VI) and disease presentation (typhoidal or NTS). Significantly higher or lower rates of bacteremia in individual serovars or groups of *Salmonella* were assessed using Fisher exact test. To identify subspecies and serovars with higher rates of blood isolations, we compared the following groups: subspecies I versus all other subspecies (II, IIIa, IIIb, IV and II–VI); typhoidal serovars versus NTS serovars; and individual NTS serovar versus all NTS serovars.

Odds ratios were calculated by comparing the odds of a given serovar to infect the blood (*a*/*b*) to the odds of any NTS strain infecting the blood (*c*/*d*); where *a* and *b* are the respective number of blood and non-blood isolates for each serovar and *c* and *d* are the corresponding numbers for all NTS strains. We used the following formula to calculate the 95% CI for the odds ratio:

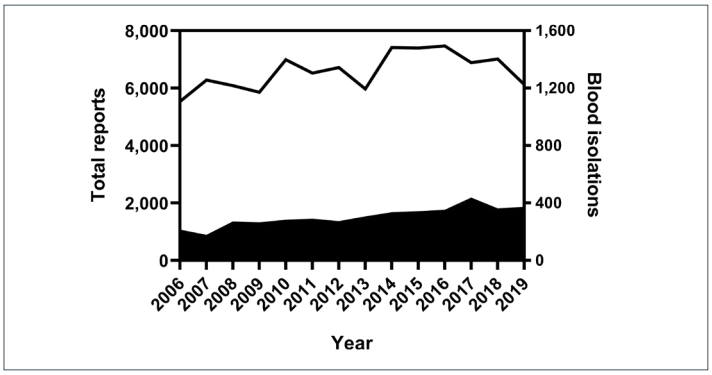
$$e^{\left(\left[ln(OR) \pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{d}\right]}\right)}$$

We conducted all calculations and statistical tests using Microsoft Excel 2016 and GraphPad Prism 8.0.2. A *p*-value of less than 0.05 was considered significant for all statistical tests.

Results

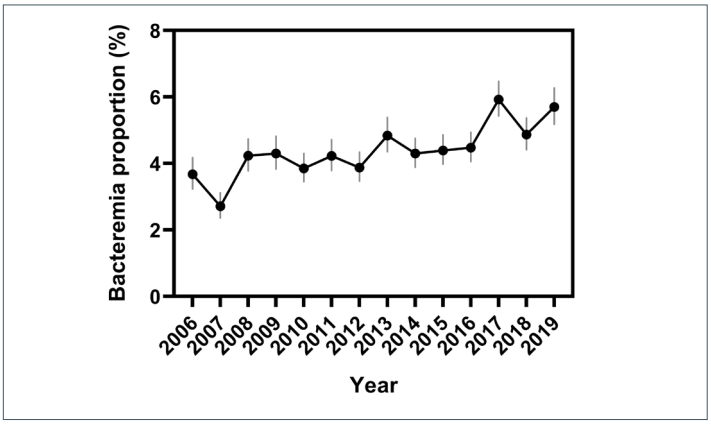
From 2006 to 2019, 96,082 *Salmonella* isolations were reported to the NESP. During this period, 4,252 bloodstream isolations were reported, that is, an overall bacteremia rate of 4.4% (95% CI: 4.3%–4.6%). Investigation of annual rates of bacteremia showed an increasing trend over the 14-year period, with an average annual rate of increase of 0.2% (95% CI: −0.4% to 0.7%) and a range of 2.7% in 2007 (95% CI: 2.4%–3.2%) to 5.9% (95% CI: 5.4%–6.5%) in 2017 (P<0.0001, **Figure 1** and **Figure 2**).

Figure 1: Number of total reports and blood isolations of *Salmonella* bacteremia as reported to the NESP, 2006–2019[a]



Abbreviation: NESP, National Enteric Surveillance Program
[a] Total (line) and blood (solid shape) isolations reported to the NESP

Figure 2: Change in *Salmonella* bacteremia proportions over time, based on reports to the NESP, 2006–2019[a]



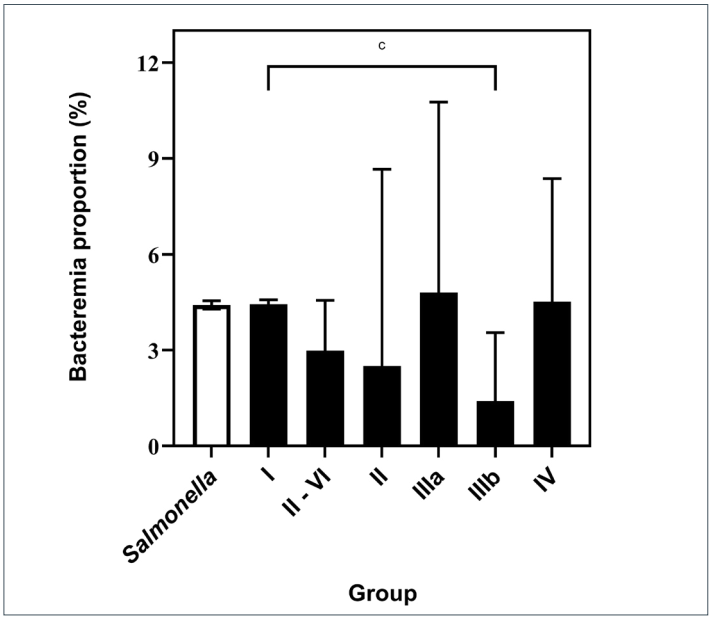
Abbreviation: NESP, National Enteric Surveillance Program
[a] Vertical lines indicate 95% confidence intervals
Note: *P*<0.0001

Of the 96,082 reported *Salmonella* isolates, 95,385 (99.3%) were typed to the serovar level, 258 (0.3%) to the subspecies level and 439 (0.5%) to the genus level. The genus group was excluded from further analysis. Of the 4,252 blood isolates, seven were excluded from further analysis because they were only typed to the genus level.

Table 1 lists the subspecies distribution of the reported typed isolates. There were only two reports of *S. bongori* during the reporting period; both were isolated from stool. The remaining isolates were *S. enterica*, with 99.3% of the total isolates and 99.5% of blood isolates typed as subspecies I.

The bacteremia rate of subspecies I was 4.4% (95% CI: 4.3%–4.6%). With the exception of subspecies IIIb, this rate did not differ significantly from those of the other subspecies even when they were analyzed as an aggregate group to reduce the imprecision associated with low numbers of isolates (*P*=0.0728, **Figure 3**). The bacteremia rate of subspecies IIIb, 1.4% (95% CI: 0.5%–3.5%), was significantly lower than that of other subspecies I (*P*=0.0087).

Figure 3: Comparison of bacteremia proportions of *Salmonella enterica* subspecies, based on reports to the NESP, 2006–2019[a,b,c]



Abbreviation: NESP, National Enteric Surveillance Program
[a] White bar depicts the overall bacteremia proportion of the genus *Salmonella*
[b] Vertical lines indicate 95% confidence intervals
[c] *P*=0.0087

Of the isolates in subspecies I, there were 3,678 total isolations of typhoidal strains (2,350 Typhi, 1,198 Paratyphi A, 124 Paratyphi B and 6 Paratyphi C) and 1,295 blood isolations (794 Typhi, 485 Paratyphi A, 16 Paratyphi B and 0 Paratyphi C). The bacteremia rate of typhoidal strains was 35.2% (95% CI: 33.7%–36.8%), significantly higher than the rate calculated for nontyphoidal strains (3.2%, 95% CI: 3.1%–3.3%, *P*<0.0001, **Figure 4**).

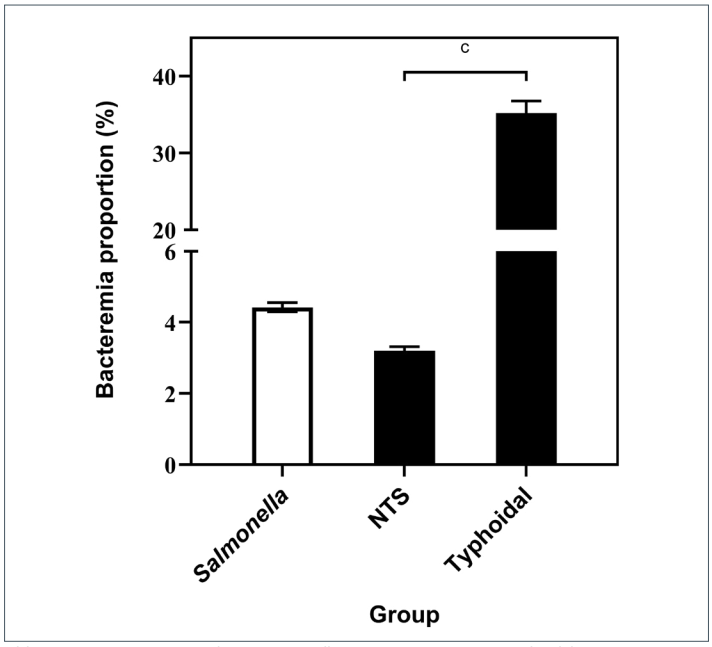
Of the 570 NTS serovars reported to the NESP from 2006 to 2019, 136 were associated with bacteremia. Enteritidis was the most frequently associated with bacteremia, with over 1,000 reports. With Heidelberg, these two serovars accounted for 60% of the blood reports (**Figure 5**). Typhimurium, Dublin and

Table 1: Frequency of *Salmonella* species and subspecies reported to the NESP, 2006–2019

Species	Subspecies	Total reports		Blood reports	
		Number of serovars	Number of isolates	Number of serovars	Number of isolates
Salmonella enterica	*enterica (I)*	574	94,972	139	4,218
	salamae (II)	40	80	2	2
	arizoniae (IIIa)	19	104	4	5
	diarizonae (IIIb)	95	285	4	4
	houtenae (IV)	24	199	4	9
	indica (VI)	1	1	0	0
Salmonella bongori	NA	1	1	0	0

Abbreviations: NA, not applicable; NESP, National Enteric Surveillance Program

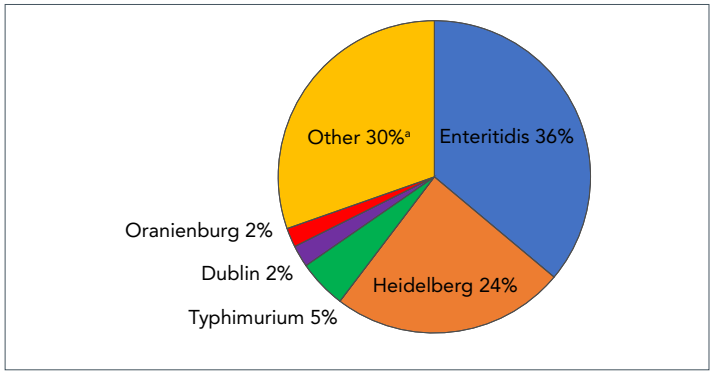
Figure 4: Comparison of proportions of bacteremia of typhoidal and nontyphoidal strains of *Salmonella enterica* subspecies, based on reports to the NESP, 2006–2019[a,b,c]



Abbreviations: NESP, National Enteric Surveillance Program; NTS, nontyphoidal
[a] White bar depicts the overall bacteremia proportion of the genus *Salmonella*
[b] Vertical lines indicate 95% confidence intervals
[c] $P<0.0001$

Oranienburg were, respectively, the third, fourth and fifth most frequently serovars reported in blood (Figure 5).

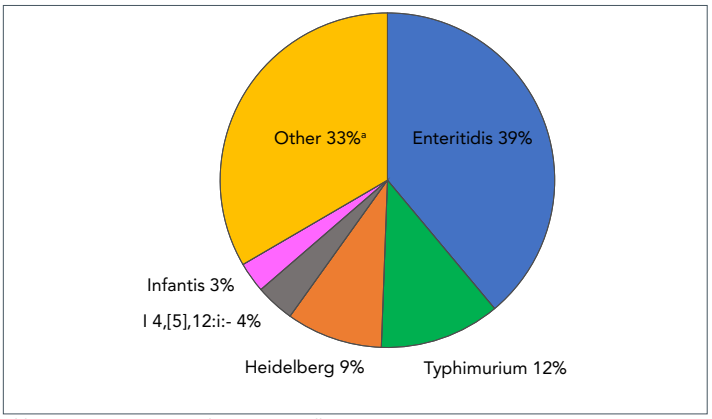
Figure 5: Frequency distribution of the top five *Salmonella enterica* nontyphoidal serovars isolated from blood as reported to the NESP, 2006–2019[a]



Abbreviation: NESP, National Enteric Surveillance Program
[a] Number of serovars represented by "Other"=131

Sixty-three serovars were associated with only one blood report during the 14-year reporting period. As a comparison, the top two NTS serovars from all specimen sources were Enteritidis and Typhimurium, accounting for 50% of the total reports. Serovars Heidelberg, I 4,[5],12:i:- and Infantis rounded out the top 5 (**Figure 6**).

Figure 6: Frequency distribution of the top five *Salmonella enterica* nontyphoidal isolated from all specimen sources as reported to the NESP, 2006–2019[a]



Abbreviation: NESP, National Enteric Surveillance Program
[a] Number of serovars represented by "Other"=565

Bacteremia proportions for individual NTS serovars associated with at least 10 infections are listed in **Table 2** in descending order of frequency.

Nineteen serovars had bacteremia rates significantly higher than that of the NTS group. In terms of frequency, these serovars varied from the third most reported (Heidelberg) to the 85th (I 6.7:c:-). The serovars with the highest rates of bacteremia were Choleraesuis (33 reports, bacteremia rate 36.4%, 95% CI: 22.2%–53.3%); Dublin (187 reports, bacteremia rate 35.3%, 95% CI: 28.8%–42.4%); and I 6,7:c:- (30 reports, bacteremia rate 30.0%, 95% CI: 16.7%–47.9%).

Table 3 lists the NTS serovars with at least 10 reports and no reposted blood isolations. Of these, 20 had significantly lower rates of bacteremia compared to the group of all NTS serovars. Included in this group were Enteritidis and Typhimurium. In addition, 48 serovars reported at least 10 times between 2006 and 2019 were not associated with any blood isolations.

The reporting trends of the three most frequently reported serovars, Enteritidis, Typhimurium and Heidelberg, are shown in **Figure 7**. From 2006 to 2019, the number of blood reports for serovar Enteritidis increased from 15 to 97 and the number of total reports increased from 1,338 to 2,254, a bacteremia rate that increased from 1.1% (95% CI: 0.7%–1.8%) to 4.1% (95% CI: 3.4%–5.0%, $P<0.0001$). The bacteremia rate of Typhimurium also appeared to increase during the reporting period, from 0.4% (95% CI: 0.2%–1.0%) to 2.3% (95% CI: 1.3%–3.9%, $P=0.0031$). The number of blood reports remained relatively stable, with four in 2006 and 13 in 2019, but the number of total reports decreased from 998 in 2006 to 557 in 2019.

Table 2: Bacteremia proportions of nontyphoidal *Salmonella* serovars with at least 10 reports to the NESP, 2006–2019

Serovar[a]	Number of blood isolates	Total number of isolates	Bacteremia rate (%)[b]	95% CI (%)	*p*-value[c]	Odds ratio[d]	95% CI
NTS	2,917	91,088	3.2	3.1–3.3	NA	NA	NA
Enteritidis[e]	1,053[e]	35,459[e]	3.0[e]	2.8–3.2[e]	0.0326[e]	0.9[e]	0.9–1.0[e]
Typhimurium[e]	147[e]	10,617[e]	1.4[e]	1.2–1.6[e]	<0.0001[e]	0.4[e]	0.4–0.5[e]
Heidelberg[f]	707[f]	8,482[f]	8.3[f]	7.8–8.9[f]	<0.0001[f]	2.7[f]	2.5–3.0[f]
I 4,[5],12:i:-[e]	52[e]	3,430[e]	1.5[e]	1.2–2.0[e]	<0.0001[e]	0.5[e]	0.4–0.6[e]
Infantis[e]	28[e]	2,672[e]	1.0[e]	0.7–1.5[e]	<0.0001[e]	0.3[e]	0.2–0.5[e]
Thompson[e]	46[e]	2,582[e]	1.8[e]	1.3–2.4[e]	<0.0001[e]	0.6[e]	0.4–0.7[e]
Newport[e]	38[e]	2,474[e]	1.5[e]	1.1–2.1[e]	<0.0001[e]	0.5[e]	0.3–0.7[e]
Saintpaul	47	1,466[e]	3.2	2.4–4.2	0.9405	1.0	0.7–1.3
Javiana	45	1,384[e]	3.3	2.4–4.3	0.8778	1.0	0.8–1.4
Agona[e]	15[e]	1,255[e]	1.2[e]	0.7–2.0[e]	<0.0001[e]	0.4[e]	0.2–0.6[e]
Braenderup[e]	6[e]	1,208[e]	0.5[e]	0.2–1.1[e]	<0.0001[e]	0.2[e]	0.1–0.3[e]
Hadar[e]	13[e]	1,077[e]	1.2[e]	0.7–2.0[e]	<0.0001[e]	0.4[e]	0.2–0.6[e]
Oranienburg[f]	58[f]	1,063[f]	5.5[f]	4.2–7.0[f]	0.0002[f]	1.7[f]	1.3–2.3[f]
Stanley[e]	19[e]	981[e]	1.9[e]	1.2–3.0[e]	0.0221[e]	0.6[e]	0.4–0.9[e]
Muenchen[e]	11[e]	884[e]	1.2[e]	0.7–2.2[e]	0.0003[e]	0.4[e]	0.2–0.7[e]
I 4,[5],12:b:-	24	880	2.7	1.8–4.0	0.4998	0.9	0.6–1.3
Paratyphi B var. Java[f]	41[f]	874[f]	4.7[f]	3.5–6.3[f]	0.0201[f]	1.5[f]	1.1–2.0[f]
Montevideo	12	544	2.2	1.3–3.8	0.2207	0.7	0.4–1.2
Mbandaka[e]	6[e]	474[e]	1.3[e]	0.6–2.7[e]	0.0122[e]	0.4[e]	0.2–0.9[e]
Virchow[f]	28[f]	425[f]	6.6[f]	4.6–9.4[f]	0.0004[f]	2.1[f]	1.5–3.1[f]
Schwarzengrund[f]	30[f]	422[f]	7.1[f]	5.0–10.0[f]	<0.0001[f]	2.3[f]	1.6–3.4[f]
Panama[f]	47[f]	414[f]	11.3[f]	8.6–14.8[f]	<0.0001[f]	3.9[f]	2.8–5.3[f]
Poona[f]	35[f]	396[f]	8.8[f]	6.4–12.0[f]	<0.0001[f]	2.9[f]	2.1–4.2[f]
Kentucky[e]	1[e]	395[e]	0.3[e]	0.01–1.4[e]	<0.0001[e]	0.1[e]	0.01–0.6[e]
Anatum[e]	3[e]	378[e]	0.8[e]	0.2–2.3[e]	0.0046[e]	0.2[e]	0.1–0.8[e]
Brandenburg[f]	27[f]	346[f]	7.8[f]	5.4–11.1[f]	<0.0001[f]	2.6[f]	1.7–3.8[f]
Derby	5	342	1.5	0.6–3.4	0.0868	0.5	0.2–1.1
Uganda	13	328	4.0	2.3–6.7	0.4292	1.2	0.7–2.2
Litchfield[e]	2[e]	317[e]	0.6[e]	0.1–2.2[e]	0.0055[e]	0.2[e]	0.1–0.8[e]
Bareilly[e]	3[e]	308[e]	1.0[e]	0.3–2.8[e]	0.0216[e]	0.3[e]	0.1–0.9[e]
Reading[f]	28[f]	304[f]	9.2[f]	6.4–13.0[f]	<0.0001[f]	3.1[f]	2.1–4.5[f]
Hartford	6	297	2.0	0.9–4.3	0.3200	0.6	0.3–1.4
Sandiego[f]	32[f]	290[f]	11.0[f]	7.9–15.2[f]	<0.0001[f]	3.7[f]	2.6–5.4[f]
Kiambu	4	275	1.5	0.6–3.7	0.1197	0.5	0.2–1.2
Bovismorbificans	8	255	3.1	1.6–6.1	>0.9999	1.0	0.5–2.0
Berta[e]	2[e]	248[e]	0.8[e]	0.1–2.9[e]	0.0278[e]	0.3[e]	0.1–1.0[e]
Chester[f]	14[f]	198[f]	7.1[f]	4.3–11.5[f]	0.0066[f]	2.3[f]	1.3–4.0[f]
Dublin[f]	66[f]	187[f]	35.3[f]	28.8–42.4[f]	<0.0001[f]	16.5[f]	12.2–22.3[f]
Corvallis	3	185	1.6	0.4–4.7	0.2948	0.5	0.2–1.6
Manhattan	3	182	1.6	0.4–4.7	0.2944	0.5	0.2–1.6
Mississippi	1	170	0.6	0.03–3.3	0.0478	0.2	0.02–1.3
Tennessee	2	160	1.3	0.2–4..4	0.2534	0.4	0.1–1.5
Give	4	150	2.7	1. 0–6.7	>0.9999	0.8	0.3–2.2
Muenster	8	149	5.4	2.7–10.2	0.1536	1.7	0.8–3.5
Hvittingfoss	1	137	0.7	0.04–4.0	0.1379	0.2	0.03–1.6
Rissen	2	134	1.5	0.3–5.3	0.4533	0.5	0.1–2.1
Eastbourne	6	129	4.7	2.1–9.8	0.3125	1.5	0.7–3.3
Havana	2	116	1.7	0.3–6.1	0.5927	0.5	0.1–2.1

Table 2: Bacteremia proportions of nontyphoidal *Salmonella* serovars with at least 10 reports to the NESP, 2006–2019 (*continued*)

Serovar[a]	Number of blood isolates	Total number of isolates	Bacteremia rate (%)[b]	95% CI (%)	*p*-value[c]	Odds ratio[d]	95% CI
I Rough-O:-:-	1	116	0.9	0.04–4.7	0.1905	0.3	0.04–1.9
Oslo	2	106	1.9	0.3–6.6	0.7781	0.6	0.1–2.4
Haifa	4	94	4.3	1.7–10.4	0.5478	1.3	0.5–3.7
London	3	91	3.3	0.9–9.2	0.7681	1.0	0.3–3.3
Indiana	2	91	2.2	0.4–7.7	>0.9999	0.7	0.2–2.8
I 9,12-:-	3	88	3.4	0.9–9.6	0.7610	1.1	0.3–3.4
Ohio	2	85	2.4	0.4–8.2	>0.9999	0.7	0.2–3.0
Durban[f]	8[f]	84[f]	9.5[f]	4.9–17.7[f]	0.0056[f]	3.2[f]	1.5–6.6[f]
Telelkebir[f]	6[f]	75[f]	8.0[f]	3.7–16.4[f]	0.0334[f]	2.6[f]	1.1–6.1[f]
Bredeney	4	71	5.6	2.2–13.6	0.2921	1.8	0.7–4.9
Pomona	2	65	3.1	0.6–10.5	>0.9999	1.0	0.2–3.9
Minnesota	1	57	1.8	0.09–9.3	>0.9999	0.5	0.1–3.9
Carrau	3	54	5.6	1.5–15.1	0.2495	1.8	0.6–5.7
Cubana	1	53	1.9	0.1–9.9	>0.9999	0.6	0.1–4.2
Bonariensis	4	52	7.7	3.0–18.2	0.0487	2.5	0.9–7.0
Aberdeen	2	51	3.9	0.7–13.2	0.6792	1.2	0.3–5.1
Rubislaw	2	51	3.9	0.7–13.2	0.6792	1.2	0.3–5.1
Gaminara	1	51	2.0	0.1–10.3	>0.9999	0.6	0.1–4.4
Cerro	1	49	4.1	0.7–13.7	0.6710	1.2	0.3–5.3
Gatuni	1	46	2.2	0.1–11.3	>0.9999	0.7	0.1–4.9
Worthington	1	45	2.2	0.1–11.6	>0.9999	1.0	0.1–5.0
Urbana[f]	4[f]	42[f]	9.5[f]	3.8–22.1[f]	0.0450[f]	3.2[f]	1.1–8.9[f]
I 6,7:r:-	1	41	2.4	0.1–12.6	>0.9999	0.8	0.1–5.5
Arechavaleta	2	39	5.1	0.9–16.9	0.3566	1.6	0.4–6.8
Agbeni	1	39	2.6	0.1–13.2	>0.9999	0.8	0.1–5.8
Nessziona	2	38	5.3	0.9–17.3	0.3449	1.7	0.4–7.0
Lomalinda[f]	5[f]	35[f]	14.3[f]	6.3–29.4[f]	0.0049[f]	5.0[f]	2.0–13.0[f]
Johannesburg	3	34	8.8	3.0–23.0	0.0944	2.9	0.9–9.6
Choleraesuis[f]	12[f]	33[f]	36.4[f]	22.2–53.3[f]	<0.0001[f]	17.2[f]	8.5–351[f]
Stanleyville[f]	7[f]	33[f]	21.2[f]	10.7–37.8[f]	<0.0001[f]	8.1[f]	3.5–18.7[f]
Ebrie	1	33	3.0	0.2–15.3	>0.9999	1.0	0.1–6.9
Kottbus	1	32	3.1	0.2–15.7	>0.9999	1.0	0.1–7.1
Livingstone	1	32	3.1	0.2–15.7	>0.9999	1.0	0.1–7.1
I 6,7:c:-[f]	9[f]	30[f]	30.0[f]	16.7–47.9[f]	<0.0001[f]	12.9[f]	5.9–28.3[f]
Nima	1	28	3.6	0.2–17.7	0.5981	1.1	0.2–8.2
Chailey	2	26	7.7	1.4–24.1	0.2021	2.5	0.6–10.6
I 6,7:k:-	1	26	3.8	0.2–18.9	0.5710	1.2	0.2–8.9
Daytona	1	25	4.0	0.2–19.5	0.5569	1.3	0.2–9.3
Meleagridis	1	25	4.0	0.2–19.5	0.5569	1.3	0.2–9.3
Colindale	1	24	4.2	0.2–20.2	0.5422	1.3	0.2–9.7
I Rough-O:g,m:-	2	23	8.7	1.6–27.8	0.1671	2.9	0.7–12.3
Monschaui	1	23	4.3	0.2–21.0	0.5270	1.4	0.2–10.2
Baildon	1	22	4.5	0.2–21.8	0.5114	1.4	0.2–10.7
Coeln	1	22	4.5	0.2–21.8	0.5114	1.4	0.2–10.7
Emek	1	22	4.5	0.2–21.8	0.5114	1.4	0.2–10.7
Kintambo	1	20	5.0	0.3–23.6	0.4785	1.6	0.2–11.9
Praha	1	17	5.9	0.3–27.0	0.4250	1.9	0.3–14.2
Michigan	1	16	6.3	0.3–28.3	0.4060	2.0	0.3–15.2
Wandsworth	1	16	6.3	0.3–28.3	0.4060	2.0	0.3–15.2

Table 2: Bacteremia proportions of nontyphoidal *Salmonella* serovars with at least 10 reports to the NESP, 2006–2019 (*continued*)

Serovar[a]	Number of blood isolates	Total number of isolates	Bacteremia rate (%)[b]	95% CI (%)	*p*-value[c]	Odds ratio[d]	95% CI
I Rough-O:r:1,2	1	15	6.7	0.3–29.8	0.3864	2.2	0.3–16.4
Glostrup	1	14	7.1	0.4–31.5	0.3661	2.3	0.3–17.7
I 4,[5],12:e,h:-	1	14	7.1	0.4–31.5	0.3661	2.3	0.3–17.7
Takoradi	1	13	7.6	0.4–33.3	0.3451	2.5	0.3–19.3
Napoli	1	12	8.3	0.4–35.4	0.3234	2.7	0.4–21.3
Nottingham	1	10	10.0	0.5–40.4	>0.9999	3.4	0.4–26.5

Abbreviations: CI, confidence interval, NESP, National Enteric Surveillance Program
[a] Serovars with at least 10 reports are listed in descending order of reported frequency
[b] Bacteremia proportions were calculated as the number of blood isolates as a proportion of total isolates
[c] *p*-values were calculated by comparing bacteremia proportions of each serovar with that of the group of all nontyphoidal serovars
[d] Odds ratios were calculated relative to all nontyphoidal serovars
[e] Serovars associated with significant lower rates of bacteremia in comparison to all nontyphoidal serovars (green)
[f] Serovars associated with significant higher rates of bacteremia in comparison to all nontyphoidal serovars (red)

Table 3: *Salmonella* serovars reported to the NESP in 2006–2019 that were not associated with bacteremia

Serovar	Total isolates	*p*-value[a]
Weltevreden	382	<0.0001
Senftenberg	313	<0.0001
Mississippi	170	0.0478
Blockley	117	0.0568
Miami	105	0.0847
I 9,12:-:1,5	100	0.0804
Adelaide	86	0.1188
Albany	86	0.1188
Alachua	54	0.4216
Concord	53	0.4187
Cotham	46	0.4059
Norwich	46	0.4059
Ealing	45	0.4053
Singapore	44	0.4050
Richmond	38	0.6349
I 4,[5],12:-:1,2	36	0.6309
I 6,7:-:-	31	0.6260
Altona	27	>0.9999
I 4,[5],12:d:-	27	>0.9999
Potsdam	25	>0.9999
I Rough-O:HNM	25	>0.9999
Ago	24	>0.9999
Bardo	24	>0.9999
Irumu	23	>0.9999
Liverpool	23	>0.9999
Othmarschen	23	>0.9999
Istanbul	21	>0.9999
Fluntern	20	>0.9999
Putten	20	>0.9999
I 6,8:e,h:-	20	>0.9999

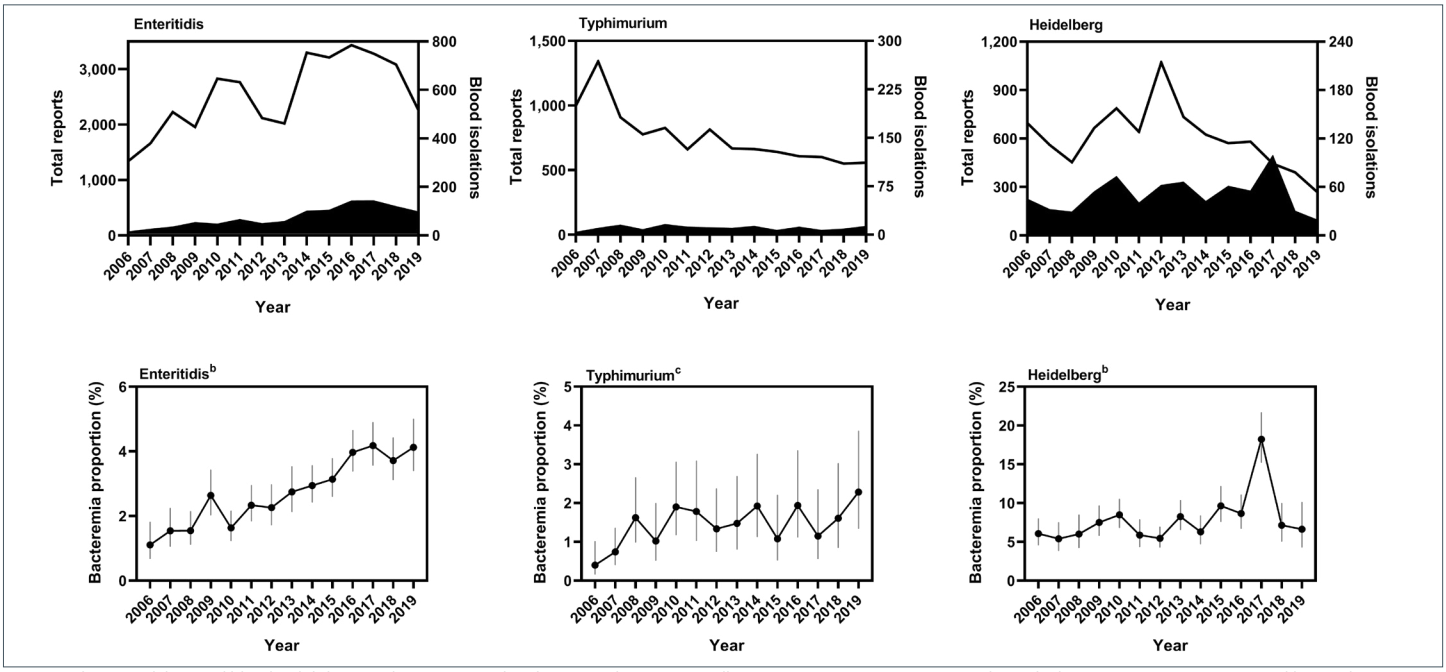
Table 3: *Salmonella* serovars reported to the NESP in 2006–2019 that were not associated with bacteremia (*continued*)

Serovar	Total isolates	*p*-value[a]
Kedougou	19	>0.9999
Larochelle	19	>0.9999
I 6,7:e,h:-	19	>0.9999
Isangi	16	>0.9999
Goettingen	15	>0.9999
Lexington	15	>0.9999
Amsterdam	14	>0.9999
Apapa	14	>0.9999
Kingabwa	13	>0.9999
I 13,23:b:-	13	>0.9999
Abony	12	>0.9999
I Rough-O:i:1,2	12	>0.9999
Kisarawe	11	>0.9999
Saphra	10	>0.9999
I 6,8:-:-	10	>0.9999

Abbreviation: NESP, National Enteric Surveillance Program
[a] *p*-values were calculated by comparing bacteremia proportions of each serovar with that of the group of all nontyphoidal serovars

The reporting frequencies of serovar Heidelberg fluctuated nonlinearly during the reporting period, from a low of 19 blood reports in 2019 to a high of 99 in 2017. The number of total reports varied from a low of 267 in 2019 to a high of 1,071 in 2012. The corresponding bacteremia rate also fluctuated from a low of 5.4% (95% CI: 3.9%–7.5%) in 2007 to a high of 18.2% (95% CI: 15.2%–21.7%) in 2017.

Figure 7: Bacteremia rates of individual nontyphoidal *Salmonella* serovars, 2006–2019[a,b,c]



[a] Top row shows total (line) and blood (solid shape) isolations reported to the National Enteric Surveillance Program (NESP). Bottom row shows the bacteremia proportions. Vertical lines indicate 95% confidence intervals
[b] $P<0.0001$
[c] $P=0.0031$

Discussion

Based on data submitted to the NESP, the overall rate of *Salmonella* bacteremia in Canada was 4.4% (95% CI: 4.3%–4.6%) from 2006 to 2019. Annual rates varied from 2.7% to 5.9% and increased on average by 0.2% per year during the reporting period. Analysis of the bacteremia rate for individual serovars showed that it shifted over time with the number of total and blood reports. The overall rate for the genus then, is expected to reflect changes in the reporting patterns of all *Salmonella* serovars in Canada. The underlying reasons for these changes warrant further study, but could reflect changes in exposure pathways, changes in serovar prevalence, demographic or other changes in the patient population, or a combination of these factors (14,15).

The rate of bacteremia for typhoid isolates was 35.2% (95% CI: 33.7%–36.8%), over the 14-year reporting period. Bacteremia is often a consequence of typhoid fever and the rate reported here is in line with published values (17). The bacteremia rate of NTS isolates was 3.2% (95% CI: 3.1%–3.3%). This rate was slightly lower than estimates from the United States (US; 5%) (18,19) and higher than the 2.1% reported for England (14).

These differences could be due to differences in the reporting periods of the three studies (US: 1996–2006, England: 2004–2015) and differences in serovar prevalence (14,19). The top five serovars reported in the American study were Typhimurium, Enteritidis, Newport, Heidelberg and Javiana (19). In England, the top five serovars were Enteritidis, Typhimurium, Virchow, Newport and Infantis (14). There was considerable overlap in the serovars most commonly associated with bacteremia in Canada, the US and England (14,19). Of the 19 serovars identified as having high bacteremia rates in this study, eight were also identified as having high bacteremia rates in England and the US: Heidelberg, Oranienburg, Virchow, Schwarzengrund, Panama, Poona, Brandenburg and Dublin. Canada shared four additional serovars with the US (Reading, Sandiego, Urbana and Choleraesuis) and two with England (Chester and Paratyphi B var. Java) (14,19).

Geographic variations in serovars were also noted between the three studies. Serovars Durban, Telelkebir, Lomalinda, Stanleyville and I 6,7:c:- were all identified in this study as having higher rates of bacteremia. Collectively, these five serovars are rare and accounted for 257 lab-confirmed cases from 2006 to 2019 (or 0.3% of all NTS reports). These serovars were not listed in the English and American reports, suggesting that exposures are travel related or unique to Canada.

Continued study on the pathogenesis of NTS serovars associated and not associated with bacteremia will provide knowledge on the relative risks of *Salmonella* serovars. Understanding these differences will inform methods to improve patient care through the early identification and treatment of salmonellosis cases that are at a high risk of developing bacteremia.

Strengths and limitations

The rates of bacteremia presented above are estimates of the true rate based on data submitted to the NESP. Data submission

to the NESP is voluntary. The values in this report only represent the isolates submitted by provincial and territorial laboratories, and understate the number of salmonellosis cases in Canada (20).

Data on the isolate source are captured by the NESP based on details collected by the submitting laboratories. As this information is not always available, data on extraintestinal *Salmonella* infections may also be underreported. Although every effort is made to prevent duplications, the limited source data precludes identification of duplicate isolations from different sources from the same patient. In addition, the data include travel-related cases, which does not reflect the true representation of strains endemic to Canada.

The strength of studies such as this rely on the quality and quantity of surveillance data available. Fewer reported isolates lead to greater degrees of imprecision. The numbers presented here are likely to be skewed higher towards bacteremia since patients with more severe symptoms are more likely to seek medical attention than those with a self-limiting form of the disease. With the absence of clinical data, it is assumed that the cases from which *Salmonella* blood isolates were recovered were more severe than those that had positive stool cultures.

Conclusion

Based on data submitted to the NESP, an estimated 4.4% of the cases of salmonellosis that occurred between 2006 and 2019 resulted in bacteremia. Specific *Salmonella* groups and serovars that were associated with higher and lower rates of bacteremia compared to the larger group of *Salmonella* strains were identified. The results of this study will inform future research aimed at predicting and improving the outcomes of *Salmonella* bacteremia in Canada.

Authors' statement

ST — Conceptualization, methodology, formal analysis, writing–original draft, writing–review and editing
BD — Writing–review and editing
KN — Data curation, writing–review and editing

Competing interests

None.

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Beyond flu: Trends in respiratory infection outbreaks in Ontario healthcare settings from 2007 to 2017, and implications for non-influenza outbreak management

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Abstract

Background: Outbreaks cause significant morbidity and mortality in healthcare settings. Current testing methods can identify specific viral respiratory pathogens, yet the approach to outbreak management remains general.

Objectives: Our aim was to examine pathogen-specific trends in respiratory outbreaks, including how attack rates, case fatality rates and outbreak duration differ by pathogen between hospitals and long-term care (LTC) and retirement homes (RH) in Ontario.

Methods: Confirmed respiratory outbreaks in Ontario hospitals and LTC/RH reported between September 1, 2007, and August 31, 2017, were extracted from the integrated Public Health Information System (iPHIS). Median attack rates and outbreak duration and overall case fatality rates of pathogen-specific outbreaks were compared in both settings.

Results: Over the 10-year surveillance period, 9,870 confirmed respiratory outbreaks were reported in Ontario hospitals and LTC/RH. Influenza was responsible for most outbreaks (32% in LTC/RH, 51% in hospitals), but these outbreaks were shorter and had lower attack rates than most non-influenza outbreaks in either setting. Human metapneumovirus, while uncommon (<4% of outbreaks) had high case fatality rates in both settings.

Conclusion: Attack rates and case fatality rates varied by pathogen, as did outbreak duration. Development of specific outbreak management guidance that takes into account pathogen and healthcare setting may be useful to limit the burden of respiratory outbreaks.

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Keywords: disease outbreaks, health facilities, long-term care, metapneumovirus, influenza, human, morbidity

Background

Outbreaks of respiratory infections due to viral pathogens such as influenza, seasonal coronaviruses and rhinovirus occur frequently in healthcare institutions where there are multiple close contacts and an increased risk of complications due to age, underlying illness or other factors (1,2). In addition, respiratory outbreaks place a large burden on the healthcare system each season, with a confirmed outbreak in a healthcare setting having implications for patient or resident admissions and transfers, as well as for staff placements within facilities.

In Ontario, respiratory infection outbreaks in institutions [including long-term care homes (LTC) and retirement homes (RH)] and public hospitals are required to be reported to local public health units for monitoring and outbreak management

guidance (3–5). Most respiratory infection outbreak (referred to as a "respiratory outbreak") guidance in Ontario focuses on general infection prevention and control measures using influenza as the model (6,7).

Given the availability of specific interventions to prevent influenza transmission during outbreaks (e.g. antiviral prophylaxis), laboratory testing for respiratory outbreaks in Ontario has primarily focused on influenza identification. Prior to the 2009 influenza A [(H1N1) pdm09] pandemic, the primary test methods for respiratory pathogens were viral culture and rapid influenza detection tests (RIDTs). Nasopharyngeal swabs collected from LTC/RH residents are typically submitted to the provincial public health laboratory for testing, while hospitals may submit outbreak specimens to the public health laboratory or to their own laboratory. Changes in testing capabilities at the provincial public health laboratory, such as the introduction of real-time reverse transcription–polymerase chain reaction (RT-PCR) in 2009 and a multiplex respiratory viral panel (MRVP) in 2010, have allowed for more sensitive and rapid testing and identification of multiple respiratory pathogens. Similar changes have been implemented in hospital and community laboratories in Ontario, with 23% of these laboratories reporting performing multiplex molecular testing in 2017 (8). Enhanced ability to differentiate between causative pathogens allows for an opportunity to tailor infection prevention and control measures to a specific pathogen and may reduce the need for unnecessary or overly restrictive control measures in certain situations.

The aim of this study was to investigate and describe attack rates, outbreak durations and case fatality rates associated with respiratory outbreak pathogens and how these differ between hospital and LTC/RH settings.

Methods

In Ontario, respiratory outbreaks reported by institutions to local public health units are entered into the integrated Public Health Information System (iPHIS). In this study, we only analyzed outbreaks meeting the provincial definition for a confirmed respiratory outbreak, that is, two cases of acute respiratory infection within 48 hours and with a common epidemiological link, at least one of which is laboratory confirmed; or three cases of acute respiratory infection within 48 hours, with a common epidemiological link and without laboratory confirmation (9). Outbreaks occurring in LTC or RH were combined into a single category (LTC/RH). Reported information used in our analyses included institution identifiers; dates of illness onset in the first and last identified cases; outbreak report dates; laboratory findings; total patient/resident cases; total patients/residents at risk; and deaths among outbreak cases (3,4).

Confirmed outbreaks reported in institutions between September 1, 2007, and August 31, 2017, were extracted from iPHIS. Respiratory outbreak seasons were defined as September 1 to August 31 of the following year based on the date the outbreak was reported or the date the outbreak was entered in iPHIS if the report date was missing (n=67). Outbreak duration was defined as the period in days from the date of symptom onset for the first identified case to that of the last identified case. Outbreaks where the onset date in the first or last reported case was missing or was improbable were excluded from analyses involving duration (n=704).

Attack rates were calculated as the number of patient/resident cases divided by the total number of patients/residents at risk within the affected area (e.g. entire facility, floor or unit). Case fatality rates were calculated as the number of outbreak-related deaths divided by the total number of resident/patient cases, and multiplied by 100. Outbreaks with improbable values, such as attack rates or case fatality rates greater than 100%, were excluded from attack rate and case fatality rate analyses (n=341).

Outbreaks due to enterovirus, rhinovirus or enterovirus/rhinovirus were collapsed into a single category, "entero/rhinovirus," and influenza viruses (A, B, or A and B) were collapsed into a single category, "influenza." Outbreaks where more than one pathogen was detected were classified as "multiple." Outbreaks due to adenovirus were excluded from some analyses due to their low number (n=5). Outbreaks where no specific pathogen was identified were classified as "unknown."

Analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, North Carolina, United States). For statistical significance, differences in median outbreak duration and median resident/patient attack rates between hospital and LTC/RH settings for individual pathogens were assessed using the Wilcoxon–Mann–Whitney test for a difference in medians. Overall, pathogen-specific case fatality rates in either setting were compared using the Pearson Chi-square test or the Fisher exact test. For all analyses, the statistical significance level was 5% (α=0.05).

Research ethics committee approval was not required for this project as the activities described here are considered routine surveillance (10).

Results

As of December 31, 2019, there were 151 hospitals and 1,392 LTC/RH operational in Ontario (11). Over the 10 years of surveillance, 9,870 respiratory outbreaks occurred in Ontario hospitals and LTC/RH (**Table 1**). Most of the outbreaks occurred in LTC/RH (92.0%); 1,210 LTC/RH reported one or more respiratory outbreaks during the study period (86.9%). The number of outbreaks reported by individual LTC/RHs ranged from 1 to 139 with a median of five outbreaks per home. In contrast, 93 hospitals reported one or more respiratory

outbreaks during the study period (61.6%). The number of outbreaks reported by a single hospital ranged from 1 to 133 over the 10-year study period, with a median of two outbreaks per hospital.

Table 1: Confirmed respiratory outbreaks in institutional healthcare settings, by pathogen, Ontario, 2007/2008 to 2016/2017 (n=9,870)

Pathogen	Number and proportion of outbreaks in institutional healthcare settings					
	Hospitals		LTC/RHs		Total	
	n	%	n	%	n	%
Adenovirus	1	0.1	4	0.0	5	0.1
Coronavirus	17	2.2	499	5.5	516	5.2
Entero/rhinovirus	87	11.1	1,654	18.2	1,741	17.6
Influenza	401	51.0	2,900	31.9	3,301	33.4
hMPV	25	3.2	357	3.9	382	3.9
Parainfluenza virus	54	6.9	482	5.3	536	5.4
RSV	70	8.9	560	6.2	630	6.4
Multiple pathogens	77	9.8	1,085	11.9	1,162	11.8
Unknown pathogens	54	6.9	1,543	17.0	1,597	16.2
Total	786	100.0	9,084	100.0	9,870	100.0

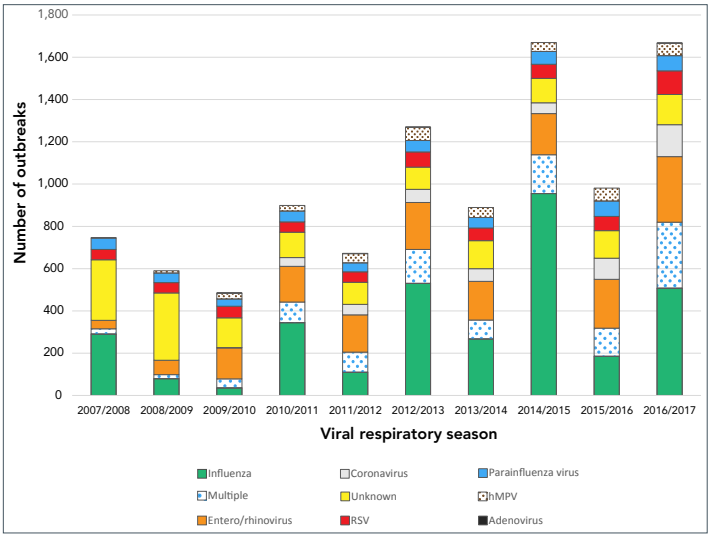
Abbreviations: hMPV, human metapneumovirus; LTC, long-term care; RH, retirement home; RSV, respiratory syncytial virus

Influenza virus was the most commonly reported pathogen in either setting (31.9% LTC/RH; 51.0% hospital). Outbreaks due to coronavirus, entero/rhinovirus and multiple pathogens increased over the study period, while the incidence of outbreaks due to an unknown pathogen decreased from 2008/2009 to 2009/2010 and stabilized in recent years (**Figure 1**). In both hospital and LTC/RH settings, after 2009–2010, the number of influenza outbreaks demonstrated a cyclical pattern, with a higher number of influenza outbreaks every second year, compared to previous and subsequent years (Figure 1).

Attack rates

Median attack rates for each pathogen were generally higher in hospitals than in LTC/RH and were highest in hospitals for outbreaks due to coronaviruses (22.5%) and parainfluenza virus (22.0%), and highest in LTC/RH for outbreaks due to human metapneumovirus (hMPV) (18.0%) (**Table 2**). The difference in median attack rate between LTC/RH and hospitals was significantly different for outbreaks due to entero/rhinovirus, hMPV, parainfluenza virus, multiple pathogens and where the causative pathogen was unknown (Table 2).

Figure 1: Confirmed respiratory outbreaks in institutional healthcare settings by pathogen and season, Ontario, 2007/2008 to 2016/2017 (n=9,870)



Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus

Table 2: Median attack rates and outbreak duration for respiratory outbreaks in institutional healthcare settings, by pathogen, Ontario, 2007/2008 to 2016/2017[a]

Pathogen	Median attack rate (%)					Median outbreak duration (days)				
	Hospital	IQR[b]	LTC/RH	IQR[b]	*p*-value	Hospital	IQR[b]	LTC/RH	IQR[b]	*p*-value
Coronaviruses	22.5	10.5–33.5	16.0	10.0–23.0	0.284	7.0	4.0–12.0	9.0	5.0–14.0	0.283
Entero/rhinovirus	21.0	14.0–34.0	16.0	10.0–24.0	<0.001[c]	8.0	4.0–12.0	8.0	5.0–13.0	0.394
Influenza	16.0	10.0–24.0	15.0	9.0–24.0	0.287	5.0	3.0–8.0	8.0	5.0–12.0	<0.001[c]
hMPV	21.0	15.0–38.0	18.0	11.0–27.0	0.011[c]	10.0	5.0–14.0	11.0	6.0–17.0	0.163
Multiple	20.5	14.0–33.0	16.0	10.0–25.5	0.001[c]	13.0	6.0–20.0	12.0	7.0–19.0	0.879
Parainfluenza virus	22.0	15.0–37.0	17.0	11.0–25.0	0.001[c]	9.5	4.5–16.0	10.0	5.0–16.0	0.516
RSV	18.0	11.0–28.0	17.0	11.0–27.0	0.461	10.0	5.0–16.0	11.5	6.0–18.0	0.081
Unknown pathogens	21.0	13.0–32.0	15.0	9.0–23.0	0.001[c]	7.0	3.0–13.0	8.0	4.0–13.0	0.405

Abbreviations: hMPV, human metapneumovirus; IQR, interquartile range; LTC, long-term care; RH, retirement home; RSV, respiratory syncytial virus
[a] Outbreaks due to adenovirus excluded due to low counts (<5 outbreaks in either setting)
[b] Interquartile range from the 25th to 75th percentile for each median value
[c] Significant at $P<0.05$

Outbreak duration

Outbreak duration ranged from 0 to 105 days in hospitals and from 0 to 122 days in LTC/RH. The difference in median outbreak duration between LTC/RH and hospital settings was only significantly different for outbreaks due to influenza (8.0 days in LTC/RH versus 5.0 days in hospitals; $P<0.001$) (Table 2).

Case fatality rates

Most outbreaks resulted in no deaths, and overall pathogen-specific case fatality rates in either setting were relatively low (**Table 3**). Influenza had the highest case fatality rate in LTC/RH, while hMPV had the highest case fatality rate in hospitals (Table 3). The lowest case fatality rates were observed in entero/rhinovirus and coronavirus outbreaks in hospital and LTC/RH settings, respectively (Table 3). There was a significant ($P=0.003$) difference in overall influenza case fatality rates between hospital (2.35%) and LTC/RH (3.54%) settings, and for those due to unknown pathogens (Table 3).

Table 3: Comparison of case fatality rates for respiratory outbreaks in institutional healthcare settings, by pathogen, Ontario, 2007/2008 to 2016/2017 (n=9,844)[a]

Pathogen[a]	Hospital		LTC/RH		*p*-value
	Case fatality rate (%)	Number of cases reported (n)	Case fatality rate (%)	Number of cases reported (n)	
Coronaviruses	0.88	113	0.96	5,815	1.000
Entero/ rhinovirus	0.82	612	1.62	20,069	0.117
Influenza	2.35	2,296	3.54	41,125	0.003[b]
hMPV	3.43	175	3.25	4,649	0.895
Parainfluenza virus	2.78	431	2.12	6,047	0.357
RSV	2.65	415	2.39	7,628	0.732
Multiple pathogens	2.32	732	3.19	17,912	0.189
Unknown pathogens	3.39	501	1.76	16,040	0.007[b]
Total	2.33	5,275	2.64	119,285	N/A

Abbreviations: hMPV, human metapneumovirus; LTC, long-term care; N/A, not applicable; RH, retirement home; RSV, respiratory syncytial virus
[a] Outbreaks due to adenovirus excluded due to low counts (<5 outbreaks in either setting)
[b] Significant at $P<0.05$

Discussion

Outbreaks of respiratory infection can cause significant morbidity and disruption to residents and patients in healthcare institutions each year. This study found that 61.6% of hospitals and 86.9% of LTC/RH had one or more outbreaks over the surveillance period, with LTC/RH generally having a higher number of outbreaks than hospitals. Compared to LTC/RH residents, hospitalized individuals with respiratory symptoms are more easily isolated from others in a single room, placed in a cohort with others with similar illness or discharged from the facility to limit their potential for transmission within the facility. Conversely, increased independent mobility of residents in LTC/RH and participation in group dining and other activities likely contribute to transmission of illness in these settings.

Differences in the number of outbreaks between facility types may also be due to differences in reporting and facility size. Changes in specimen testing over time have contributed to improving the detection of outbreaks that are not associated with influenza. The ability to identify and differentiate between non-influenza respiratory pathogens may be helpful for outbreak management and control, particularly given the varying degree to which individual pathogens are found to be responsible for outbreaks, and the associated variability in outbreak duration, attack rate and case fatality rate, as observed in this study.

Because of the nature of facility design, hospital outbreaks may be more easily restricted to smaller areas such as a ward, unit or floor, whereas an outbreak in a LTC/RH may be more likely to occur across the facility, increasing the number of residents/staff at risk of illness and reducing overall attack rates. This may have contributed to the higher attack rates in hospitals compared to LTC/RH settings for outbreaks due to each viral respiratory pathogen examined in this study.

In addition, differences in the proportion of respiratory outbreaks due to unknown pathogens may be attributed to different testing algorithms used in hospitals and LTC/RH facilities as LTC/RH primarily rely on the public health laboratory for testing while many hospitals conduct their own testing and may have different testing criteria.

While most respiratory outbreaks in both LTC/RH and hospital settings in this study were due to influenza, influenza outbreaks also had the shortest median duration of all the hospital outbreaks and one of the shortest for LTC/RH. The median duration of outbreaks due to influenza was also significantly lower in hospital settings than in LTC/RH settings. The early introduction of antivirals for both treatment and prophylaxis in influenza outbreaks is known to quickly bring outbreaks under control, shortening outbreak duration and lowering the attack rate (12–14). Adherence to existing influenza outbreak management guidance, which indicates the provision of antivirals to all patients/residents, likely contributed to the low attack rates and short outbreak duration observed in this study.

We observed that peaks of influenza outbreaks followed a biennial trend corresponding to influenza A (H3N2) dominant seasons. This is consistent with previous research that has shown that there are typically increased numbers of influenza outbreaks in hospital settings in influenza A (H3N2) dominant years (15).

Current Ontario respiratory guidance advises that most outbreaks may be declared over eight days after the onset of symptoms in the last identified patient/resident case (consistent with one incubation period plus one communicable period for influenza) (6). As influenza has the shortest incubation period of the pathogens examined in this study, management

of all outbreaks as if these are influenza outbreaks could potentially mean that outbreak control measures are lifted too soon. Identification of a specific pathogen allows for pathogen-specific incubation and communicable periods to be taken into consideration when determining when to declare an outbreak over, ensuring that control measures remain in place for an appropriate length of time.

In this study, outbreaks due to multiple pathogens were associated with significantly higher attack rates in hospital settings than in LTC/RH. Outbreaks due to multiple pathogens were also associated with the longest median outbreak duration in both settings. This may be due to concurrently circulating pathogens or to overlapping outbreaks caused by different pathogens, increasing both the potential for illness among patients/residents and complexity of outbreak management. Where outbreaks are due to several concurrently circulating pathogens, it would be prudent to institute control measures as per the pathogen with the longest incubation and/or communicable period.

Overall, case fatality rates were significantly higher in LTC/RH settings than in hospitals for outbreaks due to influenza and unknown pathogens. Residents in LTC/RH may be at increased risk of death associated with influenza, despite the use of antiviral medications, due to older age as well as the presence of other comorbidities, increasing their risk of severe outcomes from influenza, including pneumonia and death (16,17), and due to advanced directives that may preclude receiving hospital-level care. A study by Iuliano *et al.* (2018) found that influenza-associated excess mortality rates increased with age in Canada, with those aged 75 years and older having the highest influenza-associated excess mortality rates compared to younger age cohorts (17).

Outbreaks due to hMPV were associated with the highest case fatality rate in hospital settings and the second highest case fatality rate in LTC/RH. Several outbreaks due to hMPV have also been described in the literature, where these resulted in high attack rates and case fatality rates in LTC settings in the United States, highlighting the importance of testing to identify hMPV as a causative pathogen, particularly as the seasonality and symptoms associated with hMPV are similar to other respiratory pathogens (18,19). Although outbreaks due to hMPV and parainfluenza virus accounted for a small proportion of outbreaks due to known pathogens in either setting (<4%), their comparatively high median attack rates and the high overall case fatality rate for hMPV may warrant specific outbreak management guidelines, such as stricter isolation, placement in cohorts and restricting movement, which could potentially contribute to reduced attack rates and subsequent mortality in both hospital and LTC/RH settings from these pathogens. Conversely, while entero/rhinovirus were a common cause of outbreaks in both hospital and LTC/RH settings, these outbreaks were associated with generally lower attack rates, case fatality rates and outbreak duration than outbreaks associated with other pathogens. Specific outbreak management guidance for these pathogens could therefore be potentially more permissive.

Strengths and limitations

This study has several limitations. The data only represent outbreaks reported to public health units and recorded in iPHIS. Classification of the population at risk and resulting attack rates, as well as case fatality rates, are based on information reported by individual facilities to public health units and may be subject to variations in surveillance and reporting between facilities and setting type, which may have impacted comparisons between settings. In addition, the implementation of outbreak control measures may vary between settings due to contextual differences that may impact the variability in outcomes observed in this study. Laboratory testing practices in hospital settings performing their own specimen testing may vary regionally across the province, and over time as testing practices change. As current outbreak testing algorithms are hierarchical and initially focused on identifying or ruling out influenza, some outbreaks due to multiple pathogens may have been misclassified as influenza outbreaks only.

Conclusion

Given the increasing burden of respiratory outbreaks on the provincial healthcare system in Ontario and elsewhere, this study highlights potential opportunities where rapid outbreak detection, pathogen confirmation and implementation of pathogen-specific outbreak control measures may have positive implications for limiting transmission of illness and outbreak duration. Current outbreak guidance in Ontario and the United States focuses on influenza (13,20).

In addition, specific guidance for hospitals, recognizing the different challenges in acute care facilities and in LTC/RH facilities, may support outbreak management practices in these settings. Several Canadian provinces have developed respiratory outbreak guidance for acute care settings and LTC/RH, including recommendations for the management of patients with specific pathogens (21,22), a potential model to consider in developing locally applicable resources to guide the management of respiratory outbreaks.

While data analyzed for this study predated the collection of data on outbreaks due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it is anticipated that the widespread implementation of infection prevention and control measures aimed at preventing transmission of SARS-CoV-2 in institutions during the 2020 pandemic will have had an added benefit in reducing transmission of other respiratory pathogens spread via droplet/contact. This benefit is expected to be most evident in LTC and RH, where facilities likely had less on-site expertise and human resources dedicated to infection prevention and control activities.

This study provides a valuable comparator and baseline for future studies that aim to assess the broader impact of SARS-CoV-2 prevention and control measures in institutions.

Authors' statement

KP — Analyzed and interpreted the outbreak data and was a major contributor in writing the manuscript
CA — Analyzed and interpreted the outbreak data and was a major contributor in writing the manuscript
SC — Made substantial contributions to the conception of the work and to the revision of the manuscript
JG — Made substantial contributions to the conception of the work, interpretation of laboratory testing methods and to the revision of the manuscript
KK — Made substantial contributions to the conception of the work and to the revision of the manuscript
MM — Made substantial contributions to the conception of the work and to the revision of the manuscript
HS — Made substantial contributions to the conception of the work and to the revision of the manuscript
BW — Made substantial contributions to the interpretation of the outbreak data and to the revision of the manuscript
MW — Made substantial contributions to the conception of the work and to the revision of the manuscript
GG — Made substantial contributions to the conception of the work and to the revision of the manuscript
MM — Made substantial contributions to the conception of the work, interpretation of the outbreak data and to the revision of the manuscript

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Competing interests

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Bioaerosols from mouth-breathing: Under-recognized transmissible mode in COVID-19?

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Abstract

The whole world has been affected by the coronavirus disease 2019 (COVID-19) pandemic, and many researchers are racing to understand the disease course and to undertake risk analyses to formulate effective treatment strategies. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly transmissible through coughing and sneezing, and through breathing and talking which may account for viral transmission from asymptomatic carriers. Bioaerosols produced during mouth-breathing, an expiratory process in habitual mouth breathers, should be considered in addition to nasal bioparticles as a potential transmissible mode in COVID-19. Oral health professionals are justifiably apprehensive about the exposure risk due to close face-to-face contact and the mode of transmission. The aim of this commentary is to summarize the research conducted in this area and suggested strategies to limit the spread of COVID-19, especially in dental offices.

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Keywords: bioaerosols, coronavirus, COVID-19, mouth-breathing, oral diagnosis, transmission risk

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Note from the Editor: In Canada, the prevalence of COVID-19 infection among the dental profession is very low due to the large amount of personal protective equipment available, the patient's pre-screening routine, and the amount of mandatory training on infection prevention techniques. Furthermore, it is important to clarify the concepts presented in this article. Expiratory particles apply to both droplets and bioaerosols. The difference between droplets and bioaerosols is their size, which impacts their potential "travelling" distance from infected person to the person at risk standing by or passing by. See: COVID-19: Guidance on indoor ventilation during the pandemic.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative virus for coronavirus disease 2019 (COVID-19), is reported to be highly transmissible through respiratory droplets and aerosols emitted during coughing, sneezing, speaking and singing. This paper focus on aerosol-generating procedures in medical and dental fields (1). Recent reports have emphasized the possible role of SARS-CoV-2 transmission through expiratory particles emitted during normal breathing and speaking activities (2,3). Biological aerosols (less than 1 µm in size) are also produced in large quantities during mouth-breathing and the impact of mouth-breathing should also be considered in SARS-CoV-2 transmission (4). This is highly relevant in a dental office where the patients must open their mouths for a considerable time, posing a threat of disease transmission risk through expiratory bioparticles. There are currently no research reports or reviews on this transmission route. Hence, our commentary presents an overview of mouth-breathing and its potential significance in SARS-CoV-2 transmission, especially in a dental practice. This issue affects all dental professionals, including dentists, oral hygienists and dental assistants. In addition, we highlight few research questions pertaining to the mouth-breathing expiratory particles that need urgent answers through appropriate research to effectively control transmission of SARS-CoV-2 in a clinical setting.

Exhaled bioparticles and potential routes of infection in a dental office

Generally, the potential routes of infection for communicable diseases in a dental office include direct contact with body fluids (saliva/blood) of an infected patient, contact with the instruments/environmental surfaces contaminated by patients and through infectious aerosol particles (5). In the particular case of COVID-19 disease, the exhaled bioparticles can be emitted from patients through various respiratory actions, including mouth-breathing, nose breathing, coughing and talking. Pappineni and Rosenthal (6) investigated the exhaled droplets through these various modes using an optical particle counter and an analytical transmission electron microscope. The investigators reported that the quantity of droplets emitted was highest in coughing, followed by mouth-breathing, nasal breathing and talking, respectively. The smaller number of bioparticles emitted through nasal breathing when compared with mouth-breathing may be attributed to the filtration processes that occur in the nasal cavity (6). These expiratory bioaerosol droplets are polydispersed and the droplet size has a huge impact on the disease transmission process (2,4,6). Smaller droplets evaporate quickly and become "droplet nuclei" that can remain airborne for extended periods (7). These smaller aerosol particles (0.5–10 µm in diameter) can penetrate and lodge in the tiny lung passages and provoke high infection risk (8).

Mouth-breathing: An overlooked risk factor in COVID-19?

Alarmingly, COVID-19 is also highly transmissible in the pre-symptomatic/non-symptomatic carriers (9,10). Mouth-breathing, which is characterized by inhalation and exhalation through the mouth resulting mainly from upper airway obstruction or when it becomes a chronic behavioural pattern, it is categorized as an abnormal respiratory function. Mouth breathers are those persons with half-open, dry and cracked lips, an anteriorized tongue, weak mandibular elevator muscles, a deep and narrow palate, dental alterations and predominantly vertical face growth (11).

The most commonly reported causes of mouth-breathing included chronic allergic rhinitis (81.4%), adenoid hypertrophy (79.2%), enlarged tonsils (12.6%) and deviated nasal septum (1.0%) (12,13). Major clinical manifestations of mouth-breathers were sleeping with open mouth (86%), snoring (79%), itchy nose (77%), saliva drooling (62%), nocturnal sleep problems (62%), nasal obstruction (49%) and general irritability (43%) (13). Further, many dental problems, including dental caries, periodontal diseases, halitosis, craniofacial deformity and malocclusion, are commonly observed in mouth breathers (12–14).

Recently, it has been reported that nasal nitric oxide may help to reduce SARS-CoV-2 viral load and the risk of COVID-19 pneumonia by promoting more efficient antiviral defense mechanisms in the respiratory tract (15). However, mouth-breathing significantly reduces the effectiveness of nitric oxide, reducing the antiviral response (in contrast to nasal breathing). This observation highlights the importance of mouth-breathing expiratory bioparticles in COVID-19 transmission, and the importance of differentiating between the mouth and the nose as transmission routes of bioaerosols (15).

Dentists and other oral health professionals in a dental office are at high risk of exposure to these asymptomatic individuals—both those who are chronic mouth-breathers and those who must keep their mouth open for a considerable time during routine dental examination. Since it is well known that these emitted particles can facilitate the spread of various infectious diseases, including influenza (16), it is a concern that they might also facilitate the spread of COVID-19. Since the communicable profile of SARS-CoV-2 may more closely resemble that of influenza than of severe acute respiratory syndrome (SARS), the threat imposed due to aerosols produced from mouth-breathing (in addition to nasal breathing) should be considered (9). Both SARS-CoV-2 and influenza are characterized by increased infectiousness shortly around or even before symptom onset in contrast to that of SARS, wherein, infectiousness peaked around 7–10 days after symptom onset. Hence, the transmission of SARS-CoV-2 through expiratory bioparticles of pre-symptomatic individuals play a significant role (9). However, a careful literature review revealed that no study has considered bioaerosols produced during mouth-breathing as a potential transmissible mode for SARS-CoV-2, despite its high plausibility. Hence, this commentary aims to encourage research on 1) the potential of transmission of SARS-CoV-2 via bioaerosols and 2) methods to limit transmission, especially in a dental office.

Urgent questions that need immediate attention

Many important questions about the transmission of SARS-CoV-2 via mouth-breathing need to be answered by aerosol scientists (2). Do infected but asymptomatic mouth-breathing individuals emit more bioaerosols than healthy mouth breathers? Are mouth-breathing bioaerosols better able to transmit SARS-CoV-2 than normal expiratory bioaerosols? Is rapid saliva sampling for SARS-CoV-2 a useful tool for assessing the infectivity of bioaerosols emitted in healthy/pre-symptomatic/asymptomatic mouth breathers? What are the optimal experimental methods for assessing the virulence of biological aerosols? Summary of these issues are highlighted in **Box 1**.

Box 1: Highlights

- SARS-CoV-2 spreads through expiratory particles emitted during normal breathing, talking, singing, shouting, coughing and sneezing
- Bioaerosols are produced in larger quantities during mouth-breathing vs normal breathing
- Mouth-breathing aerosols present as an overlooked and underestimated risk factor in COVID-19 transmission
- Further, more evidence is needed on COVID-19 spread through expiratory bioparticles to inform preventive measures and help combat the pandemic

Conclusion

To conclude, bioaerosols from mouth-breathing, in addition to the nasal expiratory particles, should also be considered as a potential source of transmission in COVID-19. However, concrete clinical research evidence highlighting the role of mouth-breathing bioparticles in COVID-19 transmission is mandatory to support our hypothesis, though it may sound logically true. Further, with an enormous increase in COVID-19 cases day by day, much more awareness is required amongst the oral health professionals about the disease transmission process and associated risk factors with normal expiratory activities, as mentioned by Anderson *et al.* (3).

Authors' statement

SKB — Conceptualization, writing–preparation of original draft
DV — Conceptualization, writing–review and editing

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OVERVIEW

Demonstrating the capacity of the National Advisory Committee on Immunization for timely responses to post-market vaccine monitoring signals: Canada's experience with the live-attenuated influenza vaccine

Linlu Zhao[1]*, Kelsey Young[1], Althea House[1], Rob Stirling[1], Matthew Tunis[1]

Abstract

Over the last several years, the recommended use of the live-attenuated influenza vaccine (LAIV) for children has evolved in the United States (US) in response to evidence of a potential decrease in LAIV effectiveness based on post-market monitoring. These issues were not observed in Canada or elsewhere; consequently, recommendations from Canada's National Advisory Committee on Immunization (NACI) and the US Advisory Committee on Immunization Practices (ACIP) on whether to use LAIV differed for two influenza seasons (2016–2017 and 2017–2018).

This retrospective describes how NACI arrived at its recommendations in response to post-market signals of reduced LAIV performance from the US in 2013–2014 and again in 2015–2016. NACI's experience with LAIV marks the first time in Canada where a preferential recommendation on the use of an influenza vaccine in a routine immunization program was reversed. This experience highlights the importance of ongoing post-market monitoring of vaccines, international collaboration and careful consideration of local context to inform vaccine recommendations. NACI's capacity for timely responses to post-market vaccine performance signals will facilitate responsiveness to similar post-market monitoring signals from the coronavirus disease 2019 (COVID-19) vaccines.

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Keywords: influenza, LAIV, nasal spray, post-market surveillance, vaccine effectiveness

Introduction

The World Health Organization recommends that every country have a National Immunization Technical Advisory Group (NITAG) of experts to provide independent, evidence-informed vaccine recommendations (1,2). Canada's National Advisory Committee on Immunization (NACI), an external advisory body to the Public Health Agency of Canada (PHAC), is one of the longest standing NITAGs in the world. NACI has been providing ongoing and timely expert and evidence-based advice on the use of vaccines to protect Canadians for over 50 years.

NACI's recommendations are developed using an evidence-based process, which broadly involves the sequential stages of evidence gathering, synthesis and translation to recommendations (3). Triggers for NACI guidance development include—but are not limited to—authorization of new vaccines in the Canadian market; changes to indications for vaccine use; detection of vaccine safety or performance signals through post-market monitoring; the publication of pivotal new research; specific concerns raised by provincial and territorial immunization programs; and significant changes in international guidance.

Findings of suboptimal effectiveness of live-attenuated influenza vaccine (LAIV) in the United States (US) in 2014 and again in 2016 were triggers for NACI to review and deliberate on their guidance on the use of the LAIV in Canada.

This article documents NACI's responses to these signals of potentially decreased LAIV effectiveness in the US and highlights the importance of ongoing post-market monitoring of vaccines.

Triggers and responses

LAIV has been demonstrated to be safe and efficacious through clinical trials, but real-world evidence collected after LAIV was made available for use showed that it may be less effective in some contexts than the more established inactivated influenza vaccines (IIVs).

LAIV was first marketed in Canada as a trivalent formulation for individuals aged 2–59 years in June 2010, seven years after the vaccine was first marketed in the US. It was offered in various provinces and territories as part of publicly funded immunization programs beginning in 2012–2013. The trivalent formulation of LAIV was replaced with the quadrivalent formulation in Canada starting in the 2014–2015 influenza season.

In 2011, NACI made a preferential recommendation for the use of trivalent LAIV over trivalent IIV for children and adolescents aged 2–17 years for the 2011–2012 season (quadrivalent influenza vaccines were not available in Canada at the time) (4).

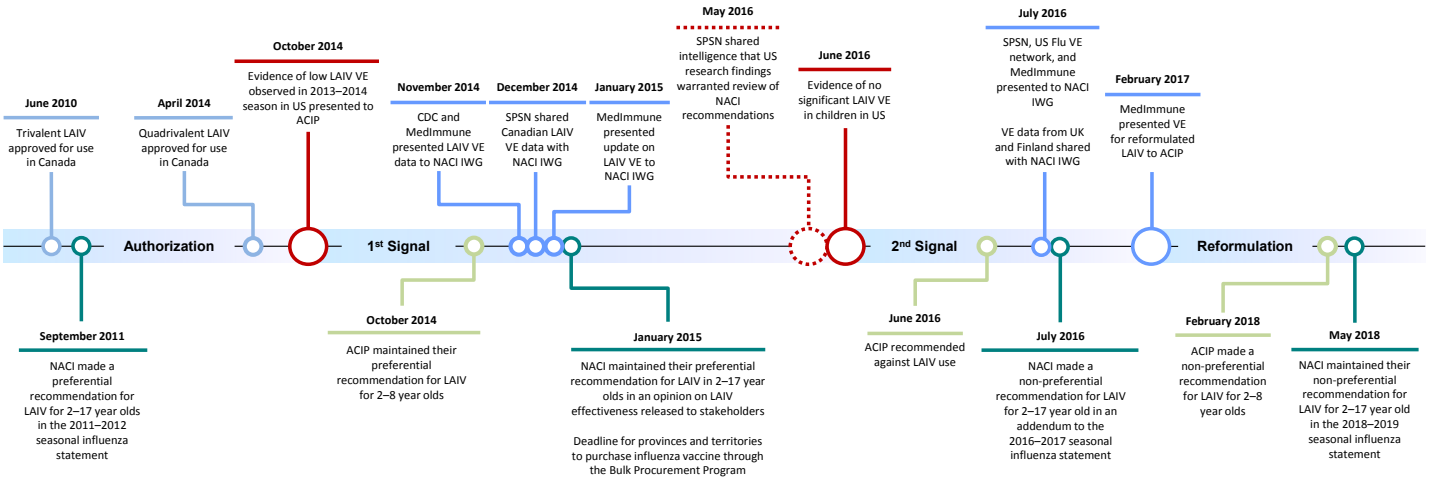
This decision was based upon favourable efficacy data from clinical trials and post-market safety data, with acknowledgement of stronger evidence for superior efficacy in younger children (younger than six years old) than for older children. Based on the efficacy data, in June 2014 the Advisory Committee on Immunization Practices (ACIP)—the US counterpart to NACI—recommended the preferential use of quadrivalent LAIV over trivalent or quadrivalent IIV for the 2014–2015 season for children 2–8 years old. The upper age limit of ACIP's recommendation was chosen based on programmatic consistency (i.e. in the US, eight years of age is also the upper age limit for the receipt of two doses of influenza vaccine in a previously unvaccinated child) (5). These preferential LAIV use recommendations by NACI and ACIP were in place when findings of reduced LAIV effectiveness against influenza A(H1N1) in the 2013–2014 season in the US came to light (4,5).

Figure 1 provides a visual summary of the milestones in the development of recommendations on the use of LAIV in Canada and the US. **Table 1** provides a verbal summary of these events.

First trigger for potential NACI review of LAIV guidance

In October 2014, a few months after ACIP made its preferential recommendation, post-market monitoring studies found evidence of low to no LAIV effectiveness against influenza A(H1N1) in US children and adolescents 2–17 years old in the 2013–2014 season; this evidence was presented to ACIP (6).

Figure 1: Milestones of recommendations on LAIV use in Canada and the US



Abbreviations: ACIP, Advisory Committee on Immunization Practices; CDC, United States Centers for Disease Control and Prevention; IWG, Influenza Working Group; LAIV, live-attenuated influenza vaccine; NACI, National Advisory Committee on Immunization; SPSN, Sentinel Practitioner Surveillance Network; UK, United Kingdom; US, United States; VE, vaccine effectiveness

Table 1: Timeline of NACI responses to the LAIV performance signals from the US

Date	Response
First signal	**On October 29, 2014, evidence of low LAIV effectiveness for the 2013–2014 influenza season in the US was presented to ACIP.**
November 18, 2014	LAIV effectiveness data from the US for the 2013–2014 season were presented to a joint meeting of NACI, NACI IWG and CIC (representing provincial and territorial immunization programs).
Late November to December 2014	Canada's SPSN shared LAIV effectiveness data for the 2013–2014 season with NACI. Based on the available evidence, NACI concluded that no change will be made to the recommendation on LAIV use for the 2015–2016 season.
January 26, 2015	NACI's position on LAIV use in response to the first signal was distributed to provincial and territorial stakeholders.
Second signal	**On June 22, 2016, ACIP recommended against LAIV use for the 2016–2017 season based on evidence of low LAIV effectiveness for two influenza A(H1N1)pdm09 predominate seasons (2013–2014 and 2015–2016) in the US.**
July 4, 2016	PHAC hosted a teleconference with CIC to discuss the LAIV effectiveness signal from the US and NACI's plans to review the available evidence. NACI's secretariat at PHAC started synthesizing available post-2009 LAIV effectiveness data.
July 19, 2016	Post-2009 LAIV effectiveness data, including data from Canada, the US and other jurisdictions for the 2015–2016 influenza season, were presented to NACI's IWG for deliberation. Based on the available evidence, the IWG proposed a recommendation change for NACI's consideration.
July 26, 2016	NACI concluded that the available evidence did not support a recommendation for the preferential use of LAIV over IIV, but LAIV remained an influenza vaccine option for children.
July 29, 2016	NACI's position on LAIV use in response to the second signal was distributed to provincial and territorial stakeholders.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CIC, Canadian Immunization Committee; IIV, inactivated influenza vaccine; IWG, Influenza Working Group; LAIV, live-attenuated influenza vaccine; NACI, National Advisory Committee on Immunization; PHAC, Public Health Agency of Canada; SPSN, Sentinel Practitioner Surveillance Network; US, United States

The low LAIV performance observed in the US led NACI to initiate a rapid review of the evidence to determine whether there was a need to revise its recommendation on how LAIV should continue to be used in Canada. The evidence review needed to be rapid to inform provincial and territorial procurement decisions that would be made early in 2015 for the 2015–2016 influenza season. By November 2014, invited speakers from the US Centers for Disease Control and Prevention (CDC) and MedImmune, the manufacturer of LAIV, had presented their US LAIV effectiveness data to NACI and its Influenza Working Group (IWG). At the time, MedImmune proposed that the reduced effectiveness against influenza A(H1N1) seen in the US may have been due to the vulnerability to heat degradation of the A/California/7/2009(H1N1)pdm09-like strain present in the vaccine, which may have occurred during vaccine distribution. In December 2014, Canada's Sentinel Practitioner Surveillance Network (SPSN) shared with NACI unpublished Canadian LAIV effectiveness data from the 2013–2014 season that showed that the effectiveness of LAIV was similar to IIV, which differed from the US data.

After reviewing this effectiveness data from the 2013–2014 season, NACI published an opinion statement in late January 2015, in time to inform provincial and territorial procurement decisions for the upcoming 2015–2016 season. The opinion statement indicated that no change would be made to NACI's preferential recommendation on LAIV use (7). NACI's decision also took into consideration factors other than vaccine effectiveness, including the different LAIV formulations used in the US (quadrivalent) and Canada (trivalent) in 2013–2014; differences in the temperature-controlled vaccine distribution between the two countries; and the fact that the low LAIV effectiveness seen in the US studies for the 2013–2014 season was not seen in Canadian post-market LAIV effectiveness data from SPSN for the same season (8). In contrast, in February 2015, ACIP reversed its preferential LAIV use recommendation to indicate either LAIV or IIV were appropriate vaccine options in children aged 2–8 years for the 2015–2016 season (9).

As a result of the manufacturer's thermal stability investigations, the A(H1N1)pdm09 component of LAIV was changed for the 2014–2015 season from the A/California/7/2009 strain to the antigenically similar and more heat stable A/Bolivia/559/2013 strain. Whether the strain change for LAIV improved its performance for the 2014–2015 influenza season as compared to the inactivated vaccine was inconclusive as the season was dominated by antigenically drifted A(H3N2) viruses. Both LAIV and IIV performed poorly for the 2014–2015 season; a majority of studies found no evidence that either type of vaccine protected against any influenza and influenza A(H3N2) (10).

Second trigger for potential NACI review of guidance

Post-market monitoring studies completed in the US at the end of the 2015–2016 season again found low vaccine effectiveness for LAIV, but not IIV, against influenza A(H1N1) in children and adolescents aged 2–17 years (11). On June 22, 2016, ACIP recommended against the use of LAIV for the 2016–2017 season. ACIP's decision was driven by the reduced effectiveness observed for LAIV against A(H1N1) in the US over the 2013–2014 and 2015–2016 seasons when predominately influenza A(H1N1) pdm09-like viruses circulated (12,13). This decision garnered widespread attention and generated a high degree of interest from Canadian stakeholders.

The new US LAIV data and ACIP's recommendation against the use of LAIV in the US raised concerns regarding the use of LAIV in Canada from provincial and territorial immunization programs, which had already procured LAIV. All of these factors were triggers for NACI to once again review its guidance on LAIV use in Canada.

NACI's challenge in response to this trigger was the time constraint to provide a very rapid evidence-informed decision on the use of the already procured LAIV mere months from the start of provincial and territorial immunization campaigns (typically October) for the upcoming season. On July 4, 2016, PHAC held a meeting with stakeholders from provincial and territorial immunization programs to brief them about the new LAIV effectiveness data from the US and to inform them of NACI's planned activities to review additional Canadian and international effectiveness data for LAIV to inform NACI's review of its LAIV recommendations.

On July 19, 2016, the NACI IWG reviewed unpublished post-market monitoring data on LAIV effectiveness for the 2015–2016 influenza season from six sources: Canada's SPSN; the US Influenza Vaccine Effectiveness Network (US Flu VE Network); the US Department of Defense; the United Kingdom's influenza vaccine effectiveness network; the National Institute for Health and Welfare of Finland; and MedImmune. The IWG also reviewed published and unpublished post-2009 pandemic data to assess the trend of LAIV effectiveness over the influenza seasons since the A(H1N1)pdm09 pandemic strain displaced the pre-pandemic influenza A(H1N1) strains. These included findings from two Canadian cluster randomized controlled trials that did not find reduced LAIV effectiveness for the 2013–2014 season in Canada (14,15), which aligned with findings from SPSN for that season.

Following reviews of the available evidence, which showed LAIV providing protection against influenza comparable to that afforded by IIV, and discussions with various jurisdictions, the IWG recommended that NACI change its recommendations on the use of LAIV. On July 26, 2016, based on the advice from the IWG and after considering all the available evidence, NACI concluded that the available evidence no longer supported a recommendation for the preferential use of LAIV over IIV, but that LAIV remained an option for the annual influenza vaccination of children aged 2–17 years (6). Although the US data showing LAIV effectiveness to be comparable or lower than IIV effectiveness contributed to NACI's revised, non-preferential recommendation on LAIV use, the reduced effectiveness seen in the US for the 2015–2016 season was again not observed in Canada or other countries that investigated the issue (10). The difference in LAIV performance data from Canada and other international jurisdictions compared to data from the US played an important role in informing NACI's decision to continue to recommend LAIV use in Canada for the 2016–2017 season (16). NACI's official position was communicated to stakeholders in late July 2016 (6,10,16). The effectiveness data supporting NACI's decision has been detailed elsewhere (10).

Epilogue

The poor performance of the A(H1N1) component of LAIV in the 2015–2016 influenza season was attributed to reduced replicative fitness of the vaccine A(H1N1)pdm09-like strain. Similar to the 2013–2014 season, differences in the temperature-controlled vaccine distribution between Canada and the US could be a factor in the differential performance of LAIV in the two countries for the 2015–2016 season. Due to the finding of reduced replicative fitness, the A(H1N1)pdm09-like strain in the 2015–2016 vaccine formulation (A/Bolivia/559/2013) was replaced with a new strain (A/Slovenia/2903/2015) for the 2017–2018 season (13).

ACIP maintained their recommendation against LAIV use for the 2017–2018 season. However, in February 2018, ACIP voted to reinstate LAIV as a vaccine option for the 2018–2019 season, with no preference given to LAIV or IIV for the paediatric age group, based on data provided from the manufacturer suggesting that the new A(H1N1)pdm09-like strain (A/Slovenia/2903/2015) has improved replicative fitness over previous A(H1N1)pdm09-like vaccine strains in LAIV (12). This non-preferential recommendation is maintained by ACIP in their latest statement for the 2020–2021 season (17). NACI's recommendation for the non-preferential use of LAIV in children and adolescents aged 2–17 years remains unchanged going into the 2021–2022 influenza season (18).

Discussion

NACI and ACIP arrived at different conclusions on the use of LAIV in response to the post-market LAIV performance signals from the US for the 2013–2014 and 2015–2016 seasons, but differing recommendations by NITAGs are not unusual. NITAGs consider a multitude of factors when making their recommendations, including vaccine characteristics (efficacy, effectiveness, immunogenicity and safety), local burden of disease, and vaccine effectiveness data. Based on this complex multifactorial analysis and differential weighting of these factors in their analyses, it is not surprising that NITAGs often arrive at different conclusions about which immunization strategy will best address the needs of their specific country.

NACI's rapid evidence appraisal and decision-making in response to the low LAIV effectiveness data from the US was facilitated by several critical factors. Being able to depend on seasonal influenza vaccine effectiveness assessments from established Canadian influenza surveillance networks was one facilitator. Canada's SPSN provided a near real-time assessment of their data to NACI and PHAC to inform NACI's deliberations on LAIV use in children.

Another facilitator was having Canadian influenza vaccine effectiveness data from studies that were specifically designed and appropriately powered to compare LAIV and IIV, such as

the cluster randomized clinical trials that corroborated the SPSN surveillance findings from the 2013–2014 season. (SPSN was not designed to compare the effectiveness of specific vaccine products.)

A third facilitator was collaboration with international and industry partners. Sharing of intelligence on emerging signals and unpublished data was pivotal to informing NACI's guidance development with the best available evidence in these time-sensitive situations. There were also several critical factors that contributed to successfully meeting the evidence-to-guidance challenge from an operational perspective. These included having established processes to facilitate stakeholder engagement and mobilizing surge capacity within PHAC to provide technical and logistical support to NACI.

Conclusion

NACI's response to the post-market LAIV performance signals from the US represents an example of its capacity to respond rapidly and comprehensively to the dynamic landscape of international vaccine research and infectious disease epidemiology. These responses highlight the importance of establishing and leveraging existing channels for intelligence sharing and knowledge exchange with evidence producers, partners and users and the importance of considering evidence from multiple sources and the local context for informing decision-making. NACI's experience with and capacity for timely responses to post-market vaccine performance signals will facilitate responsiveness to similar post-market monitoring signals from the coronavirus disease 2019 (COVID-19) vaccines.

Authors' statement

LZ — Conceptualization, writing–original draft, writing–review and editing
KY — Conceptualization, writing–review and editing
AH — Conceptualization, writing–review and editing
RS — Conceptualization, writing–review and editing
MT — Conceptualization, writing–review and editing

Competing interests

None.

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Environmental scan of provincial and territorial planning for COVID-19 vaccination programs in Canada

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Abstract

Background: Public health departments in Canada are currently facing the challenging task of planning and implementing coronavirus disease 2019 (COVID-19) vaccination programs.

Objective: To collect and synthesize information regarding COVID-19 vaccination program planning in each province and territory of Canada, including logistic considerations, priority groups, and vaccine safety and effectiveness monitoring.

Methods: Provincial/territorial public health leaders were interviewed via teleconference during the early planning stage of COVID-19 vaccination programs (August–October 2020) to collect information on the following topics: unique factors for COVID-19 vaccination, intention to adopt National Advisory Committee on Immunization (NACI) recommendations, priority groups for early vaccination, and vaccine safety and effectiveness monitoring. Data were grouped according to common responses and descriptive analysis was performed.

Results: Eighteen interviews occurred with 25 participants from 11 of 13 provinces/territories (P/Ts). Factors unique to COVID-19 vaccination included prioritizing groups for early vaccination (n=7), public perception of vaccines (n=6), and differing eligibility criteria (n=5). Almost all P/Ts (n=10) reported reliance on NACI recommendations. Long-term care residents (n=10) and healthcare workers (n=10) were most frequently prioritized for early vaccination, followed by people with chronic medical conditions (n=9) and seniors (n=8). Most P/Ts (n=9) are planning routine adverse event monitoring to assess vaccine safety. Evaluation of effectiveness was anticipated to occur within public health departments (n=3), by researchers (n=3), or based on national guidance (n=4).

Conclusion: Plans for COVID-19 vaccination programs in the P/Ts exhibit some similarities and are largely consistent with NACI guidelines, with some discrepancies. Further research is needed to evaluate COVID-19 vaccination programs once implemented.

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Keywords: COVID-19, vaccination, vaccine, pandemic, vaccination program

Introduction

The race for the development of coronavirus disease 2019 (COVID-19) vaccines is well underway, with the first vaccines now approved for use in Canada (1). Canadian public health officials are facing the next major challenge of the pandemic: planning and implementing the COVID-19 vaccination programs. Planning has been particularly challenging in comparison with other vaccines given the speed at which vaccine development has occurred, the need to manage multiple new but differing vaccines, and the fact that a large proportion of the population will need to be vaccinated to significantly interrupt the spread of the virus among the general population (2,3). As initial vaccine supply is limited (3,4), one important consideration is

the prioritization of target groups for COVID-19 vaccination. The National Advisory Committee on Immunization (NACI) has released guidance outlining key populations for receiving initial vaccine supply (3,5). However, it is ultimately up to provincial/territorial governments whether to follow these guidelines, and to determine the logistics of COVID-19 vaccination programs, including vaccine dose allocation, delivery, storage, administration, monitoring and reporting (6). Conversely, the role of the federal government is vaccine approval and procurement, and to provide guidance on vaccine use (6).

It is important to understand and document the processes and strategies that have been employed by each of the provinces/territories (P/Ts) in their COVID-19 vaccination planning. Identifying the range of strategies, highlighting new and innovative approaches, and learning from successful and unsuccessful approaches will enhance our capacity to respond to similar challenges we will undoubtedly face in the future. As such, the objective of this study was to use key informant interviews to collect and synthesize information regarding planned COVID-19 vaccination programs in each of the P/Ts, including logistic considerations, priority groups, and vaccine safety and effectiveness monitoring.

Methods

This pan-Canadian environmental scan involved structured key informant interviews of public health leaders from P/Ts across Canada. The research team included researchers from six P/Ts, as well as knowledge users from the NACI Secretariat and three P/T health departments. Knowledge users assisted in recruitment, identified topics of value to include in the interview guide, and were provided the study findings for their reference in decision-making. The goal of the scan was to capture and synthesize the perspectives of public health leaders actively involved in P/T immunization program planning. We recruited P/T members of the Canadian Immunization Committee (CIC), and when they were unavailable to participate, we asked them to designate a replacement. Additional participants were identified through our research team members, P/T health departments and the NACI Secretariat who are knowledgeable of P/T vaccine program leadership. Key informants were contacted via an initial email sent by the NACI Secretariat, inviting them to participate in the study. Interested individuals were emailed an information sheet and consent form. To optimize response rate, up to two email reminders were sent. Some participants were identified through snowball sampling, with study participants suggesting additional key informants. Interviews took place from August to October 2020, prior to release of NACI's preliminary guidance (3) and the approval of any COVID-19 vaccines in Canada. Interviews (35–60 minutes long) were conducted by members of the research team (HS, AA, MK) via teleconference.

Interview questions included key topics related to COVID-19 vaccination, as identified in scientific literature and news articles, and augmented with input from the immunization experts on the research team and knowledge users, including the NACI Secretariat (see **Supplemental material**). The structured interview guide consisted of mainly open-ended questions about the following topics: unique factors to be considered in COVID-19 vaccination program planning, the extent of reliance on NACI recommendations, the use of a geographical prioritization framework for vaccine allocation, target groups for prioritization for early vaccination, and plans for monitoring vaccine safety and effectiveness. The interview guide was reviewed and edited by immunization experts and pilot tested with an individual who worked in provincial immunization program planning, but was not involved in the study, to check face and content validity, flow, and comprehension. The inclusion of multiple perspectives within and between P/Ts enhanced the credibility of findings. The guide was shared with participants prior to the interview. Ethical approval for this study was obtained from the Health Research Ethics Board at the University of Alberta.

Interviews were audio-recorded and transcribed verbatim by one member of the research team and any personally identifying information was removed. The same team member then coded and categorized participant responses. Given the very structured nature of the interviews, analysis involved little subjective interpretation. However, to ensure rigor, coding and categorization were validated by three other team members to ensure they accurately reflected and were fully representative of participants' responses. Descriptive analysis of response counts was performed using Microsoft Excel. Participant responses were synthesized and presented by P/T.

Results

Invitation emails from NACI were sent to 35 potential participants: 13 agreed to participate; one declined; and 21 did not respond. Twelve participants were recruited from other participants, five through referrals and seven joined the interviews of their colleagues. Therefore, some interviews contained more than one participant. In total, there were 18 interviews with 25 participants from 11 of the 13 P/Ts. **Table 1** shows the demographics of the study sample.

Unique factors for COVID-19 vaccination programs

A wide array of factors that are unique to planning for COVID-19 vaccination programs were identified (**see Table 2**). Participants from slightly over half of P/Ts (n=7) indicated the need to prioritize target groups for early vaccination. Many P/Ts (n=5) also highlighted the possibility of having different eligibility

Table 1: Demographic information of the study sample (N=25)[a]

Characteristic	Number of participants, n
Province/territory	
British Columbia	1
Alberta	4
Saskatchewan	3
Manitoba	4
Ontario	3
Québec	3
Newfoundland and Labrador	1
Nova Scotia	3
New Brunswick	0
Prince Edward Island	1
Nunavut	1
Northwest Territories	1
Yukon	0
Perspective	
Provincial/territorial	12
Regional/municipal	9
Both	4
Job title	
Director of Immunization or Communicable Disease Control	2
Immunization Program or Policy Manager	7
Medical Officer of Health	5
Public Health or Medical Consultant	3
Policy Analyst	2
Public Health or Communicable Disease Specialist	2
Other	4

[a] Some province/territory responses fell into more than one category

Table 2: Provinces/territories' unique factors planned for consideration for COVID-19 vaccination programs (N=11)

Unique factor	Number of P/Ts[a], n
Priority groups	
Prioritization of target groups	7
Differing eligibility criteria	5
Equity in delivery	1
Public engagement	
Public perception of the vaccine, including vaccine hesitancy	6
Clear communication with public	3
Logistics and supply	
Logistics, storage, cold-chain management	4
Limited vaccine supply, availability of vaccine	3
Availability of PPE and other vaccination supplies (other than the vaccine itself)	3
Vaccine distribution	2
Resource issues (in general)	2
Vaccine procurement	1
Delivery	
COVID-19 related restrictions, public health measures, PPE	4
Vaccine provider (e.g. physicians, pharmacists, public health)	4
Appointment-based delivery versus mass clinics	3
Need to vaccinate everyone, large volume of people	3
Less human resources due to COVID-19 redeployment	3
Training for providers	2
Uncertainty, not having enough information to plan	2
Vaccine characteristics	
Possibility of needing more than one dose	4
Vaccine safety	3
Dealing with a new vaccine	3
Considerations for the route of administration	3
Possibility of having more than one vaccine	2
Speed with which vaccine development is occurring	2

Abbreviations: COVID-19, coronavirus disease 2019; PPE, personal protective equipment; P/T, province/territory
[a] Some P/T responses fell into more than one category

criteria for each vaccine (i.e. if one vaccine is more effective in older adults), which may impact the order of priority groups.

Some participants from P/Ts also discussed factors related to public engagement, including having clear communication with the public regarding safety implications, eligibility criteria and priority groups (n=3 P/Ts). Likewise, six P/Ts highlighted the need to manage public perception of COVID-19 vaccines. Specifically, one P/T felt that vaccine hesitancy for COVID-19 vaccines would be greater than for previous vaccines.

The P/Ts also discussed unique factors related to logistics and supply of COVID-19 vaccines. Four P/Ts highlighted the unique storage requirements of some of the vaccines, with some P/Ts stating that it was unlikely that all providers currently had the capacity to store vaccines at the appropriate temperature. Others noted that supply of the vaccine (n=3) and other vaccination supplies (n=3) will likely be limited.

Planning for the delivery of the COVID-19 vaccines was anticipated to be challenging, with some P/Ts (n=4) reporting that they were unsure about which providers would deliver the vaccines (e.g. public health, physicians, pharmacists), or whether

they would have appointment-based clinics or mass clinics (n=3). Similarly, four P/Ts mentioned the need for adapting vaccination clinics to follow COVID-19 recommendations, including physical distancing, personal protective equipment, layout, one-way flow of traffic and ventilation. One P/T mentioned including industrial engineers on their planning team to consider these factors. A full list of P/T responses is provided in Table 2.

Reliance on NACI recommendations

Almost all P/Ts (n=10) indicated that they would likely rely on the NACI recommendations for target groups in planning their COVID-19 vaccination strategies. One P/T indicated that they would more likely rely on their provincial/territorial immunization committee recommendations.

Priority group ranking

Participants were asked to rank their top five priority groups, with rank 1 representing the group that should receive COVID-19 vaccination first. For reporting purposes, we used the ranking of the respondent from each P/T that had the most cross-provincial perspective based on their job position and whether they stated they had a provincial perspective as opposed to regional/municipal. One P/T did not answer, for a total of 10 P/Ts. All of the P/Ts ranked long-term care residents (n=10) and healthcare workers (n=10) in the top five priority groups for receiving COVID-19 vaccination. Specifically, six P/Ts indicated long-term care residents as top priority, three indicated healthcare workers and one indicated seniors. Three P/Ts ranked healthcare workers second, followed by long-term care residents (n=2), people with chronic medical conditions (n=2), seniors (n=2), and essential workers (n=1). Groups ranked third included seniors (n=3), long-term care residents (n=2), healthcare workers (n=1), people with chronic medical conditions (n=1), people of Indigenous ancestry (n=1), those with socio-economic disadvantage (n=1) and people living in remote communities (n=1). **Figure 1** provides a full summary of P/T rankings.

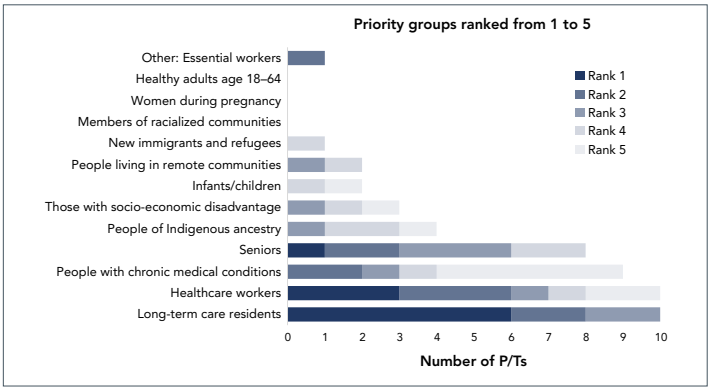
Use of a geographical prioritization framework

None of the P/Ts had firm plans for a geographical prioritization framework based on disease incidence (i.e. target groups in high COVID-19 incidence areas are prioritized over target groups in low incidence areas). The majority of P/Ts (n=7) were open to this approach if advised by NACI (n=1), or if the vaccine characteristics (n=1) or number of doses available (n=3) warrants it. Three P/Ts were against using a geographical prioritization framework due to concerns with the equity of this approach (n=1) or due to their jurisdiction's small geography or dense population (n=2). One P/T did not know if they were planning on using a geographical prioritization framework.

Monitoring vaccine safety and effectiveness

With regards to post-market vaccine safety monitoring, most P/Ts (n=9) planned to conduct their routine adverse event monitoring, while some (n=3) anticipated enhanced surveillance of adverse events (see **Table 3**). Some P/Ts (n=4) anticipated that this will be done by federal/provincial/territorial committees and groups. For post-market vaccine effectiveness monitoring, some P/Ts (n=3) anticipated that their P/T public health departments would do this, with a similar number (n=3) stating that this will be routine information collected. Others (n=3) expected that this will be done by researchers or research organizations.

Figure 1: Provinces/territories' priority group choices to include in their top five groups to be considered for early vaccination in the presence of limited vaccine supply (N=10)[a,b]



Abbreviation: P/Ts, provinces/territories
[a] One province/territory chose not to answer this question
[b] For those who selected seniors (n=8), seven indicated that they would target seniors aged 65+ years, while one indicated that they would target those 60+ years

Table 3: Provinces/territories' planned approach to COVID-19 vaccine safety and effectiveness monitoring (N=11)

Planned approach	Number of P/Ts[a], n
Safety	
Regular adverse event reporting	9
Enhanced surveillance of adverse events	3
Reliance on federal/provincial/territorial committees and groups (e.g. CIC, CIRC)	4
Reliance on what NACI recommends	1
Undecided	1
Do not know	2
Effectiveness	
Reliance on provincial public health (e.g. surveillance teams)	3
Reliance on researchers/research organizations	3
Reliance on NACI or other national guidance	4
Collect routine monitoring information (e.g. number of clients who tested positive after vaccination, vaccine coverage)	3
Undecided	2
Do not know	1
No answer	2

Abbreviations: CIC, Canadian Immunization Committee; CIRC, Canadian Immunization Registry and Coverage Network; NACI, National Advisory Committee on Immunization; P/T, province/territory
[a] Some responses by P/T fall into more than one of the above categories

Discussion

Although P/T rankings of potential priority groups were collected prior to the publication of NACI's guidance documents, the overall P/T rankings aligned somewhat with NACI recommendations. Specifically, the groups ranked highest in this study were healthcare workers and long-term care residents, followed by people with chronic medical conditions and seniors. The most recent NACI recommendations prioritize healthcare workers, long-term care residents and staff, seniors aged 70 years and older (with those 80+ years having highest priority) and adults in Indigenous communities (5). The notable difference between the P/T rankings in our study and NACI recommendations is that less than half of P/Ts ranked Indigenous communities in the top five prioritized groups, and that people with chronic medical conditions (ranked third by most P/Ts) were not included in NACI's most recent guidance on early vaccination (5).

A common consideration among P/Ts was the potential negative public perception of COVID-19 vaccines. Many P/Ts recognized the important role public health will have in the development of communication strategies to counter these concerns. A Statistics Canada survey in June 2020 reported that 76.5% of Canadians would be very likely or somewhat likely to get a COVID-19 vaccine when available (7), but data from a national Leger survey in November 2020 estimate this number to be 65% (8).

The P/Ts also highlighted the challenging logistics of vaccine delivery and the need to ensure that vaccination clinics follow public health recommendations on distancing, using personal protective equipment, disinfection and ventilation, etc. Multiple P/Ts viewed the 2020–2021 seasonal influenza program as a trial for how COVID-19 vaccine delivery may occur. Following the H1N1 pandemic, it was noted that well-functioning influenza vaccination programs are essential for ensuring that adequate infrastructure is available for pandemic vaccination response (9). Guidance on strategies for influenza vaccine delivery during the pandemic were provided by NACI early in the pandemic (10).

Having a unified approach to COVID-19 vaccination in Canada may be beneficial for providing consistent public messaging and clarifying why certain priority groups have been selected for early vaccination. Public communication strategies are important to prevent vaccine hesitancy and mistrust (9). Furthermore, a unified approach to vaccination may improve equity and produce cost-savings (11). Critics of Canada's long-standing provincial and territorial variability in immunization programs and schedules have argued that lack of consistency in eligibility and modes of delivery results in inconsistencies in public messaging which can undermine public confidence when the rationale for differences is unclear (11,12). Conversely, diversity across P/Ts enables flexibility to adapt to the unique circumstances of each jurisdiction, given the variation in geography, population, and COVID-19 cases across P/Ts (13). Although P/Ts will inevitably develop their own plans for COVID-19 vaccination, results from this study suggest that there will likely be many similarities.

Strengths and limitations

The strength of this study is the wide variety of perspectives that were obtained on COVID-19 vaccination program planning from most P/Ts. As well, the use of key informant interviews allowed us to gather in-depth perspectives on COVID-19 vaccination program planning in each P/T. However, as only a few select individuals were interviewed from each P/T, the perspectives gathered are not representative of the entire P/Ts. Furthermore, there may be variation in individual perspectives across a single P/T, although the perspectives shared were very consistent within a given P/T. Generalizability may be limited due to the small sample size and non-random sampling. Interviews were conducted during a period when COVID-19 vaccination planning was in its early stages. It will be interesting to follow whether early plans have changed since the release of NACI guidance documents (3,5).

Implications

The implementation of COVID-19 vaccination programs in Canada is in the early stages. There is an opportunity to expand on this study's findings through a variety of research avenues, including the assessment of each P/T's finalized COVID-19 vaccination plan, and how variation in vaccination programs ultimately affects vaccine uptake and effectiveness in each P/T.

This study adds to existing literature by synthesizing P/T public health perspectives on COVID-19 vaccination programs at a planning stage. Results can inform policymakers and program planners and can assist NACI in future development of national guidelines. We anticipate that the information in this study will enable P/Ts to learn from one another by comparing their approach to COVID-19 vaccination with others across Canada.

Conclusion

The key informant interview findings show that Canadian P/Ts are facing similar challenges in planning for COVID-19 vaccination. The majority will be relying on NACI recommendations regarding how to allocate limited vaccine supply. Further research is needed to evaluate provincial/territorial COVID-19 vaccination programs once they are implemented.

Authors' statement

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Authors' statement (*continued*)

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

Competing interest

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Supplemental material

Study interview guide

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The National Collaborating Centre for Methods and Tools (NCCMT): Supporting evidence-informed decision-making in public health in Canada

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Abstract

The National Collaborating Centre for Methods and Tools (NCCMT) is part of a network of six National Collaborating Centres for Public Health (NCC) created in 2005 by the federal government following the severe acute respiratory syndrome (SARS) epidemic to strengthen public health infrastructure in Canada. The work of the NCCMT, to support evidence-informed decision-making (EIDM) in public health in Canada, is accomplished by curating trustworthy evidence, building competence to use evidence and accelerating change in EIDM. Ongoing engagement with its target audiences ensures NCCMT's relevance and ability to respond to evolving public health needs. This has been particularly critical during the coronavirus disease 2019 (COVID-19) pandemic, which saw NCCMT pivot its activities to support the public health response by conducting rapid reviews on priority questions identified by decision-makers from federal to local levels as well as create and maintain a national repository of in-progress or completed syntheses. These efforts, along with partnering with the COVID-19 Evidence Network to support Decision-Making (COVID-END), sought to reduce duplication, increase coordination of synthesis efforts and support decision-makers to use the best available evidence in decision-making. Data from website statistics illustrate the successful uptake of these initiatives across Canada and internationally.

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Overview—National Collaborating Centres for Public Health

Funded by the Public Health Agency of Canada (PHAC) each of the six National Collaborating Centres for Public Health (NCCs) focuses on a specific public health area: Determinants of Health, Healthy Public Policy, Knowledge Translation Methods and Tools, Infectious Diseases, Environmental Health, and Indigenous Health. Each is hosted by an academic institution or government-based organization, which are geographically dispersed across the country (1–3). In 2019, PHAC renewed funding for the NCCs for an eight-year period (2020–2028), reaffirming their value in Canada's public health infrastructure.

The NCCs synthesize and disseminate high-quality evidence and knowledges, foster collaboration among diverse groups and support the use of the best available evidence in public health decision-making to improve health outcomes for Canadians.

Expert advisory boards, comprising public health practitioners, senior decision-makers, policy makers and Indigenous leaders, provide advice to their respective NCC on goals and objectives and annual workplans, prior to their submission to PHAC for approval. The NCC priorities are established through national gatherings, participation in networks and committees and needs assessments. Detailed descriptions of the NCCs have been reported previously (3,4).

National Collaborating Centre for Methods and Tools—Mandate

This article, the third of six, describes the work of the National Collaborating Centre for Methods and Tools (NCCMT; the Centre) generally, and its response to coronavirus disease 2019 (COVID-19) specifically. The NCCMT (5) acts as an evidence intermediary, curating trustworthy evidence, and building

capacity in public health for evidence-informed decision-making (EIDM) including finding, appraising, interpreting, adapting and implementing evidence into decision-making.

The Centre's strategic direction and workplans are guided through extensive consultation with its advisory board members and target audiences, including front-line public health practitioners and decision-makers, policy makers at all levels of government, those working in other public health organizations, post-secondary institutions that provide education and training to future public health professionals, public health researchers, the Public Health Network and PHAC. Engagement with these audiences ensures NCCMT's agility and responsiveness to evolving public health needs, as illustrated below in relation to COVID-19. Core objectives for 2020–2028 include developing methods and tools to facilitate synthesis of a wide array of evidence beyond research evidence, facilitating organizational change and supporting ongoing EIDM capacity development.

The NCCMT's work and related resources and services can be categorized into three domains: access to the evidence on what works; capacity development in EIDM; and system change (**Table 1**).

Access to evidence

To ensure access to evidence on what works in public health, the NCCMT maintains and continuously updates two curated repositories: Health Evidence™ (6) contains research evidence related to public health practice and The Registry of Evidence-Informed Decision-making Tools contains methods and tools for EIDM (7). The repositories are primarily visited by public health nurses, managers, project specialists and government representatives and policy makers, students and researchers.

Capacity development

A diverse suite of capacity development resources and services are available both online, through a skills assessment, learning modules, and videos, and face-to face, including self-paced

Table 1: National Collaborating Centre for Methods and Tools' work and related resources and services

NCCMT resource	Description	Launch date	Audience use
Supporting access to evidence			
Health Evidence™ (6)	A searchable repository of over 6,900 critically appraised systematic reviews evaluating the effectiveness and cost-effectiveness of public health interventions	2005	Annual average: 90,000 visits from 181 countries
Registry of Evidence-Informed Decision-Making Tools (7)	A curated, searchable repository of over 150 methods and tools in EIDM	2007	Annual average: 250,000 visits from 195 countries
Capacity development for EIDM			
Online learning modules (8)	Twelve interactive modules focused on one or more steps in the EIDM process	2011	Completed over 35,000 times
Understanding Research Evidence videos (9,10)	Eleven short videos explaining research terms	2014	Viewed over 300,000 times
Evidence-Informed Decision-making Skills Assessment (11)	A 20-item tool of multiple-choice questions that assess EIDM knowledge and skill	2018	Completed over 3,000 times by 1,400 unique users
Knowledge Broker Mentoring program (12)	A 16-month training program to support organizational capacity development for EIDM	2014	Completed by 55 participants from 10 public health organizations
Workshops (13)	Half, full, and multi-day sessions to build EIDM capacity	2010	Delivered to 28 Canadian public health organizations
Webinars (14)	90-minute sessions to explore and practice EIDM competencies	2012	Annual average: 10 webinars; 1,500 attendees Over 90% agree participation increased understanding of EIDM
Systems change resources			
Applicability and Transferability of Evidence Tool (15)	Assesses the feasibility and generalizability of evidence to public health practice in specific jurisdictions	2011	Accessed more than 5,500 times since 2017
Rapid Review Guidebook (16)	Step-by-step guide to the rapid review process	2017	Accessed over 10,000 times
Quality Assessment of Community Evidence (QACE) Tools (17)	Two tools that can be used to assess community evidence to ensure it is relevant, trustworthy and equity-informed	2020	Accessed over 2,300 times

Abbreviation: EIDM, evidence-informed decision-making

and virtual workshops and mentoring programs. Briefly, the skills assessment (11) assesses individual and/or organizational knowledge and skill for EIDM. The learning modules (8) focus on one or more steps in the EIDM process, while the Understanding Research Evidence video series (9,10) explains regularly used research terms (relative risk, odds ratios). The NCCMT also provides education and mentorship through webinars (14), tailored workshops (13) and the knowledge broker mentoring program (12). The knowledge broker mentoring program is an intensive training program to build organizational capacity in EIDM.

Systems change resources

At the systems level, resources are available that can be embedded within decision-making mechanisms such as how to conduct a rapid review, assess community level evidence and assess the applicability and transferability of evidence to a jurisdiction. The Rapid Review Guidebook (16) outlines the steps of rapid reviews. The Quality Assessment of Community Evidence (QACE) Tool (17) assesses the quality of community evidence (local surveillance and contextual evidence, and societal and political preferences). Finally, the Applicability and Transferability of Evidence Tool (15), evaluates the feasibility and generalizability of evidence in different settings.

Measures of impact

Internal contact data illustrate the NCCMT has provided education and mentorship to over 435 organizations in every province and territory in Canada, and 40 governments in six countries, 42 public health organizations in seven countries, 54 health care organizations in seven countries, 281 post-secondary institutions in 23 countries and 145 countries with at least one person accessing the learning modules.

Personalized quarterly outreach, to 215 senior decision-makers (e.g. Medical Officers of Health, senior management) in Canada has led to 88 new projects in the last five years. Routine communication with 27 public health programs/schools in academic institutions resulted in the integration of resources into curricula, and 14 Master of Public Health student practicum placements with the NCCMT, contributing to students' preparedness for a future in public health (18).

Results from embedded pre-post knowledge and self-efficacy assessments in the online learning modules show statistically significant increases in knowledge ($p<0.0001$) and self-efficacy ($p<0.01$) (*C. Howarth, personal communication, March 21, 2018*), and pre-post evaluation of the Understanding Research Evidence videos also show statistically significant increases in knowledge ($p<0.001$) (10). Statistically significant increases in knowledge have also been observed in pre-post evaluations of EIDM workshops ($p<0.001$) (*M. Dobbins, personal communication, June 20, 2017*) and the knowledge broker mentoring program ($p<0.001$) (*J. Yost, personal communication, April 28, 2016*), and the Rapid Review Guidebook has been adopted by several public health organizations.

National Collaborating Centre for Methods and Tools' response to COVID-19

In March 2020, the NCCMT pivoted its work to support public health's response to the COVID-19 pandemic by creating a rapid evidence service, developing a COVID-19 public health review repository, and partnering with others to increase coordination of evidence syntheses.

Rapid evidence service

In April 2020, in response to requests from the Pan-Canadian Public Health Network's Special Advisory Committee on COVID-19, its supporting Technical Advisory Committee, and public health decision-makers at the local, regional and provincial levels, the NCCMT started conducting rapid reviews on public health topics in close collaboration with the Office of the Chief Science Officer within PHAC. Living reviews were registered with PROSPERO. The reviews informed public health measures related to re-opening of schools, and transmission in long-term care facilities, gyms and restaurants. Other reviews informed early thinking on surface transmission, the incubation period, wastewater as a surveillance strategy and COVID-19 re-infection risk. NCCMT's Rapid Review Guidebook (16,19) guided such processes as discussions with the requestor to refine questions, appraising and GRADing the evidence, and identifying key messages and knowledge gaps. Reviews were completed in five to ten days, posted on NCCMT's website (20) and widely disseminated. Public interest in "hot topics" generated substantial media uptake with news coverage by more than 30 media outlets. As of December 2020, the NCCMT had completed 43 full reviews or updates on 25 unique questions that are indexed in global databases and have been downloaded an average of 250 times per review from people in 82 countries (*S. Neil-Sztramko, personal communication, December 15, 2020*). Additionally, the NCCMT connected with Canadian and international evidence synthesis organizations to discuss duplication of reviews, rapid review methods and to share capacity building resources.

COVID-19 repository

The NCCMT created the COVID-19 public health repository for Canadian reviews in April 2020. Both currently underway and completed rapid reviews were eligible for inclusion. As of December 2020, 215 rapid reviews were included in the repository, and it had received over 43,000 page views from people in 108 countries (*S. Neil-Sztramko, personal communication, December 15, 2020*). Anecdotal evidence shows that duplication of effort was avoided when visitors to the site identified a review in progress or completed on a topic they intended to conduct a review on.

Systematic reviews to support public health system recovery

The NCCMT is completing two systematic reviews to 1) identify effective strategies to support the mental health of frontline workers responding to COVID-19 and 2) identify strategies for post-pandemic public health system recovery. Both reviews are registered with PROSPERO and follow methods outlined in the Cochrane handbook. Once completed, the reviews will be disseminated broadly.

Amplifying networks and collaborations

The NCCMT was an early partner of the COVID-19 Evidence Network to support Decision-making (COVID-END) (21), an international network of more than 50 evidence synthesis and knowledge translation organizations. COVID-END's aim is to support decision-makers in finding and using evidence, while reducing duplication. Of the seven working groups, NCCMT's Scientific Director co-leads the engaging workgroup, which supports those supporting decision-makers via an online discussion group and monthly webinar series by disseminating resources related to evidence synthesis (22). The NCCMT is also participating in COVID-END Canada, a Canadian Institutes of Health Research Operating Grant, which is conducting evidence syntheses to support health care, public health and health systems decision-making.

Challenges and next steps

The NCCMT's quick pivot was not without its challenges. Some staff required training in rapid review methods, the pace of work changed dramatically from projects that generally took months to complete to projects needing to be competed in just days, the demand for reviews outweighed the Centre's capacity to complete them, the evidence, particularly in the early months, changed almost daily, and the rapid review methods had to be modified as the evidence evolved (19). In addition, given the abundance of evidence there were challenges ensuring decision-makers were aware of the best available and up to date evidence, and it was impossible to stay abreast of all rapid reviews in progress, resulting in some duplication of effort.

As the sprint of the pandemic transitioned to a marathon, it was important to reduce the work pace to avoid staff burnout, and horizon scanning was important but challenging to do given decision-makers' limited availability. As the anniversary of the COVID-19 pandemic passes, it is important to start planning for post-COVID, although many uncertainties remain as to what the needs of public health will be. In the days and months ahead, engagement with the Centre's target audiences will assist the NCCMT to be ready to transition again to meet the evidence and capacity development needs of the public health sector.

Conclusion

Since its launch in 2007, the NCCMT has contributed to evidence-informed public health decision-making by ensuring resources and services that directly address the EIDM needs of the public health sector are readily available. Its extensive network and long-standing collaborative relationships with decision-makers at all levels contributed to NCCMT recognizing the need to quickly pivot its activities as the pandemic took hold. This experience highlights the important role autonomous organizations, at arms-length to government, with the flexibility to change their proposed workplans, can have in times of crisis.

Authors' statement

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