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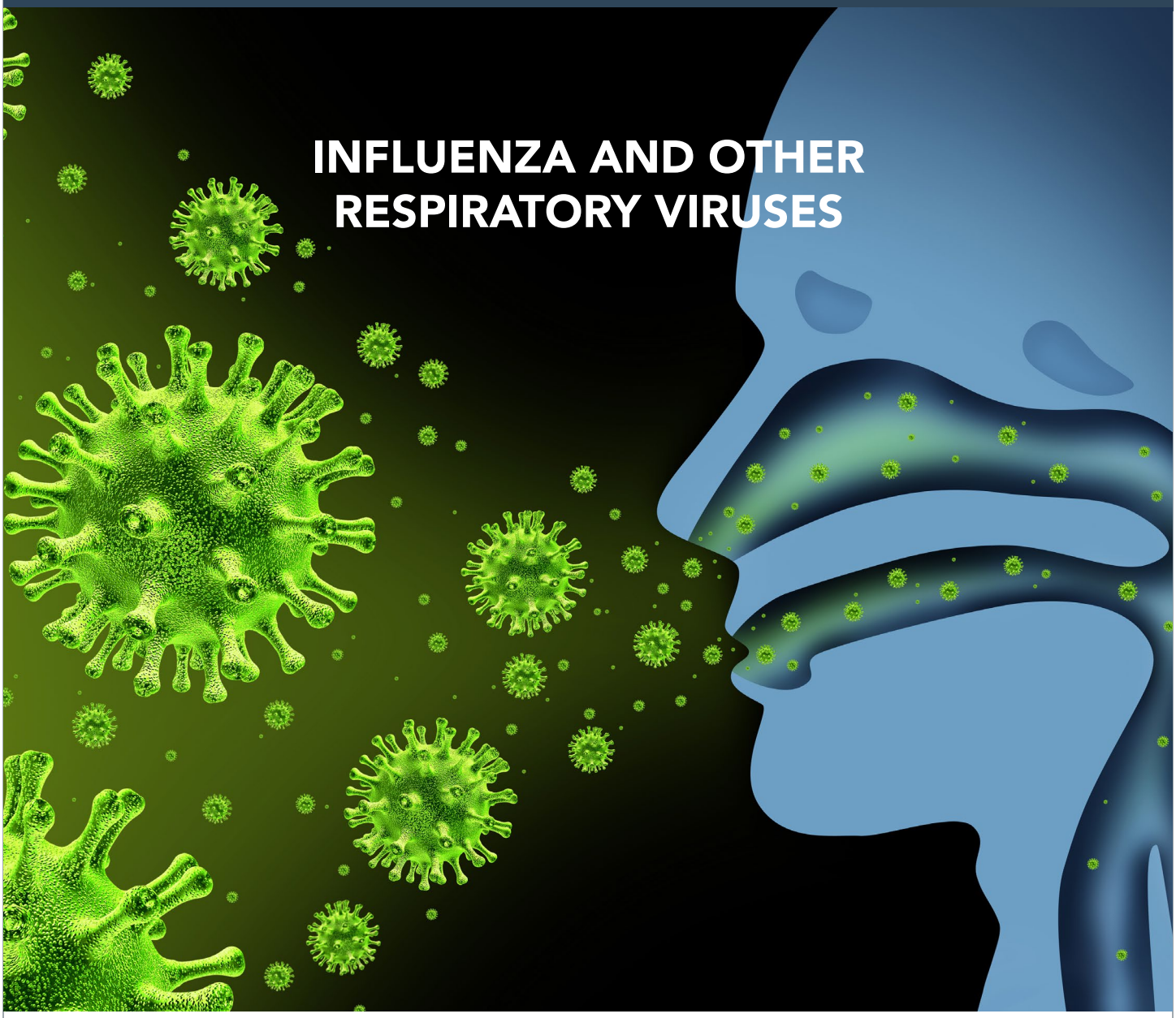
INFLUENZA AND OTHER RESPIRATORY VIRUSES



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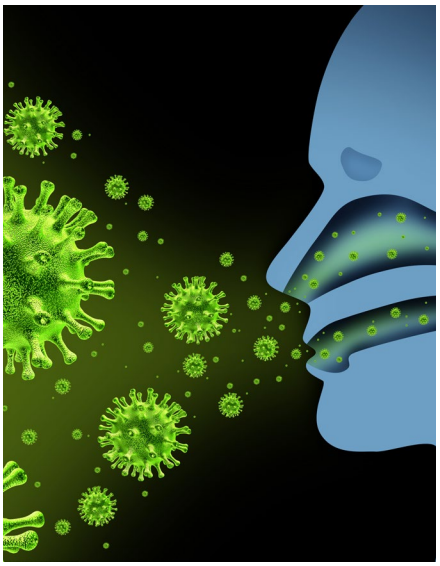

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COMMENTARY

Vaccine against SARS-CoV-2: Challenges and considerations

Ruchi Chaube[1]*

Abstract

It is essential to consider challenges previously faced and addressed while developing a vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Considering the severity of the health crisis that SARS-CoV-2 has caused worldwide, and with so little known about the virus, our focus should be drawn towards approaches that can bring better development outcomes in a relatively short period of time. This commentary discusses the use of nucleic acid (deoxyribonucleic acid and ribonucleic acid) vaccines against viral infections and pandemic-like settings. The potential advantages of the nucleic acid vaccines over conventional vaccines are presented, and the nucleic acid vaccines currently in development against viral infections and the challenges these vaccines face entering clinical trial are discussed.

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Keywords: vaccine, SARS-CoV-2, nucleic acid

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Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), entered the human population and rapidly spread around the world in the early months of 2020, causing a global pandemic. This pandemic, as defined by the World Health Organization, is "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people" (1), led the scientific and medical communities to initiate serious efforts to limit the wave of viral spread by developing preventative vaccines.

A vaccine (or vaccines) against SARS-CoV-2 would help develop community immunity against the virus and thus prevent the spread and recurrence of the disease at the population level. There has been a surge in vaccine candidates since the pandemic started; however, vaccine protection from SARS-CoV-2 hinges on two questions: first, how soon a vaccine can be made available for use; and second, will the vaccine(s) be protective enough to completely prevent the further spread of the virus. While the first point is temporal and, at present, we are much ahead in the game with respect to COVID-19 vaccines, the second point is fundamental to vaccine development defining a strong and lasting immunological response.

In the past few decades, there has been rapid spread of numerous severe viral infections, including human immunodeficiency virus (HIV), influenza A, severe acute respiratory syndrome (SARS), Ebola and Zika. These infections have necessitated the rapid development and comprehensive distribution of vaccines; however, the development of these vaccines has proven to be extremely difficult. In addition, many of these viruses represent zoonoses (zoonotic diseases), increasing the risk of introducing a virus with completely new immunogenic properties into the human population. Furthermore, it is impossible to predict the characteristics of these viruses, the severity of the diseases they might induce and the scope of the outbreaks they can cause. For example, influenza A virus/H1N1 led to a phase 6 pandemic alert in 2009 but caused relatively mild symptoms compared with the 1918 pandemic (the "Spanish flu") that resulted in the death of 50 million people (2).

Vaccines

Conventional vaccines

Conventional vaccines—live attenuated or inactivated—have proved to be beneficial against a number of infectious diseases in the past. However, they may not always be suitable for use in outbreak situations, as they bear the risk of reversion and are capable of causing severe adverse effects, making this approach unfavourable for highly pathogenic organisms. This reversion was seen with the Ebola vaccine (3). Furthermore, conventional vaccines pose challenges with commercial production, as they require whole pathogen cultivation and propagation, which require the use of biosafety level labs.

As these viruses are largely uncharacterized before an outbreak occurs, time becomes a crucial factor for effective vaccine development. Currently, the average development time for conventional vaccines from preclinical stage is more than 10 years (4), underscoring the urgent need to explore methods that allow expeditious development—to prevent an emerging outbreak from becoming a pandemic.

Viral vector-based vaccines

A valuable alternative to a conventional vaccine is a viral vector-based vaccine, as this technique represents a highly versatile platform. The viral vectors can be exploited to encode for heterologous antigens that can be delivered into the host cells. Inside the host they express the encoded antigens, prompting the host to induce an immune response. This platform appeared to be effective against the Ebola virus, and rVSV ZEROV currently represents the most promising candidate for a licensed vaccine (5). However, viral vectors are not widely used as they are considered potential risks to human health and environment because they are genetically modified organisms (GMOs). Moreover, these vectors always bear the risk of integration into the host genome, and too high or persistent replication in the host raises concerns for their use in humans (6).

Nucleic acid vaccines

Nucleic acid vaccines, both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) vaccines, come with potential benefits over conventional vaccines, as they are more stable, are more cost-effective, are easy to manufacture and handle, provide broad-spectrum immunity (meaning a multi-antigen vaccine can be designed that can effectively target constantly evolving strains of viruses) and can induce both humoral and cellular immune responses (7,8). Nucleic acid vaccines also have an edge over the viral-vector-based vaccines because they are derived from recombinant plasmids of bacterial origin, and persistent replication and host genome integration, though a possibility, have remain a low risk (9,10). Furthermore, the United States Food and Drug Administration has recommended that the termination of a study is not required if plasmid DNA remains below 30,000 copies per µg of host DNA in host tissues (11).

The DNA vaccines against Middle East respiratory syndrome coronavirus (MERS-CoV) showed promising results in preclinical trial and thereafter entered the phase I clinical trial. However, the vaccines did not progress further, mainly because this illness is characterized by a changing epidemiology; meaning that by the time the vaccine candidate entered into clinical trial, the incidence of the disease had significantly declined, presenting a potential barrier for an efficacy trial (12). In 2016, during the Zika crisis, a preclinical study conducted in non-human primates using a vaccine containing DNA constructs that expressed precursor membrane and envelope (prM-E) protein of the virus demonstrated correlation of antibody levels and protection. With this success, a phase I clinical study was initiated and preliminary results showed that the vaccine was safe and induced neutralizing antibodies in 62% of the participants (13). Importantly, this initiative was undertaken soon after the DNA sequences of the virus antigens were decoded, indicating the speed with which DNA vaccines can be produced.

In the spring of 2009, with the novel H1N1 influenza becoming a global pandemic, a phase I clinical trial was initiated. By August 2009, using a DNA-based approach encoding the hemagglutinin protein of A/California/04/2009 (H1N1pdm09) was developed. Although the DNA vaccine was able to generate hemagglutination inhibition antibody titres in only 30% of the subjects, the titres were increased to 72% within four weeks after boosting with a licensed conventional influenza vaccine. These data suggested that the virus can be controlled by employing DNA as an initial priming agent, followed by boosting with a conventional vaccine (14). A vaccine against HIV had been difficult to develop due to the changing nature of the virus. Of the six HIV-1 vaccine efficacy trials to date, only one (RV144) performed well and entered the phase III efficacy trial. Development of this vaccine was achieved after several hits-and-misses by adopting a stratagem of priming with DNA constructs expressing clade C gp120 and clade B gp41, gap and protease proteins and boosting with bivalent subtype C gp120 protein complex of the virus (15).

The RNA vaccine (using messenger RNA; mRNA) appears to have certain benefits over its DNA and viral-vector counterparts. As mRNA does not interact with the host-cell DNA, mRNA vaccines are free from the potential risk of integration into the host genome. Furthermore, mRNA vaccines have a simple vector structure containing an open reading frame (ORF) encoding the target antigen flanked by specific regulatory genes and thus are not capable of inducing anti-vector immunity (16). Currently, mRNA vaccines against Zika, Chikungunya and certain strains of influenza virus are undergoing phase I clinical trials (11).

Coronavirus-specific issues

Coronaviruses are single-stranded positive-sense RNA viruses. These viruses are of four genera (alpha, beta, gamma and delta coronaviruses); SARS-CoV-2 is a beta coronavirus. It consists of four structural proteins, namely spike, envelope, membrane and nucleocapsid, that are believed to be involved in invading the host cells. Although studies are still underway to better understand the biology of SARS-CoV-2, there has been an array of vaccine candidates launched into clinical testing and some have already been approved for use worldwide. The vaccines developed by Pfizer, AstraZeneca and Moderna are shown to be effective in the 90% range and interestingly they are nucleic acid vaccines. Despite the widespread use of these vaccines, some critical questions still need to be addressed: 1) are neutralizing antibodies and a SARS-CoV-2-specific T cell response sufficient to prevent the disease and subsequent spread; 2) how long does the protective immunity last following infection or vaccination; 3) what are the factors responsible for dysregulated immune response in patients with severe symptoms; and 4) does the

vaccine cause any severe adverse reactions. So far, none of the approved COVID-19 vaccines have shown any serious safety concerns; however, there are lingering questions around their safety with long-term use and will they be effective against the variant strains of SARS-CoV-2. Typically, when a vaccine is approved for use by the general public, it goes through stringent safety assessments to detect problems by testing it in tens of thousands of study participants, studies that span several years. Apparently, this did not happen with the COVID-19 vaccines; these vaccines went on clinical trials with small sample sizes of participants and in less than a year the vaccines were approved for use in humans. This was done because we were in the midst of a global pandemic and controlling the virus was an urgent necessity; thus, leaving some safety and effectiveness issues to be addressed mainly via post-marketing studies.

Going forward, whether it is with a modification of the currently approved COVID-19 vaccines or with a new COVID-19 vaccine, it is prudent to consider the developmental challenges faced by other viral vaccines in developing COVID-19 vaccines. A multi-faceted approach, such as the prime-boost stratagem that was used for the influenza and HIV vaccines or directions derived from preclinical studies, would be worthwhile to explore. For instance, in a recent preclinical study (17), six DNA constructs expressing different forms of SARS-CoV-2 spike proteins were used to vaccinate rhesus macaques. The macaques exhibited both humoral and cellular immune responses and a significant reduction in viral loads upon challenge with SARS-CoV-2 following vaccination. Although the sample size was small (n=4) for each of the vaccine candidate groups, the study did hint that neutralizing antibodies and antibody-dependent complement deposition could be useful benchmarks to study while developing vaccine against SARS-CoV-2.

Conclusion

Time is of the essence in controlling pandemics, but the efficacy and safety of any vaccine are also fundamental. Notably, when designing a vaccine against viral infection, it is essential to look at which approaches worked and which did not work with other viral vaccines.

Author's statement

RC conceived and wrote the manuscript

Competing interests

None.

Funding

None.

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OVERVIEW

Seasonality of coronaviruses and other respiratory viruses in Canada: Implications for COVID-19

Philippe Lagacé-Wiens[1,2]*, Jared Bullard[1,3,4], Roy Cole[3], Paul Van Caeseele[1,3,4]

Abstract

Background: Like endemic coronaviruses, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is believed to have emerged in humans from a zoonotic source and may ultimately develop a seasonal pattern. A seasonal pattern, particularly if combined with other seasonal outbreaks of respiratory virus infections, may have significant impacts on the healthcare system. We evaluated the seasonal pattern of existing endemic coronaviruses and several other common respiratory viruses to determine the potential impacts of added burden of respiratory disease should SARS-CoV-2 establish seasonality.

Methods: National surveillance data for laboratory confirmations of endemic coronaviruses, influenza A and B viruses, rhinovirus/enterovirus, human metapneumovirus, respiratory syncytial virus and parainfluenza virus for the past 10 years were obtained from the Government of Canada Open Data and FluWatch. Epidemic curves were generated from total case numbers and percent of samples testing positive for each respiratory virus by epidemiological week.

Results: In Canada, endemic coronaviruses and other common respiratory viruses cause annual seasonal outbreaks in the winter months. Should SARS-CoV-2 develop a seasonal pattern similar to endemic coronaviruses and respiratory viruses, co-circulation would be expected to peak between January and March. Peak endemic coronavirus activity occurs during the nadir of rhinovirus/enterovirus and parainfluenza activity.

Conclusion: Healthcare settings, assisted-living and long-term care homes, schools and essential services employers should anticipate and have contingencies for seasonal outbreaks of SARS-CoV-2 and co-circulating respiratory viruses during peak seasons. Given the likelihood of co-circulation, diagnostic multiplex testing targeting co-circulating pathogens may be more efficient than single target assays for symptomatic individuals if a seasonal pattern to coronavirus disease 2019 (COVID-19) is established.

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Keywords: coronavirus, SARS-CoV-2, COVID-19, epidemiology, Canada, seasonality

Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged and spread rapidly and globally via efficient human-to-human transmission (1). The virus is currently believed to have emerged from a zoonotic reservoir and is most closely related to known bat coronaviruses; however, the exact zoonotic path to efficient human-to-human transmission remains unknown (2). Zoonotic emergence of human coronaviruses is hardly surprising and has historically been the common origin of all human coronaviruses (2). While zoonotic origin is common to all coronaviruses, some have established human endemicity while others have not. The highly pathogenic beta-coronaviruses, severe acute respiratory coronavirus 1 (SARS-CoV-1), the cause of the 2003 sudden acute respiratory syndrome (SARS) outbreak and the cause of Middle East respiratory syndrome (MERS) virus, both emerged from bat coronaviruses via intermediate hosts (civet cats and camels, respectively) but never established human endemicity. In addition, there are four endemic coronaviruses

that have been circulating in humans (since prior to SARS-CoV-2); each of which had emerged from zoonotic reservoirs at different times in the past (**Table 1**) (2). Molecular analysis of coronavirus genomes has shown that coronaviruses crossed into human populations periodically throughout history, likely resulting in epidemics at the time of emergence. Prior to the widespread emergence of SARS-CoV-2, the most recent global emergence of a now-endemic human coronavirus was OC43, which is estimated to have occurred around 1890, coinciding with, and bringing into question the cause of the so-called "Russian flu" (2,3). While the factors associated with a virus establishing endemicity are not known, viruses that establish endemicity have common features: efficient person-to-person spread; global expansion; and limited severity (severe symptomatology contributes to rapid containment of cases). Seasonality likely adds an element of sustainability for a viral pathogen as well because sustained epidemics eventually lead to herd immunity while intermittent or seasonal epidemics allow a return of susceptible hosts in interepidemic periods.

Table 1: Currently circulating endemic human coronaviruses prior to zoonotic transfer to humans and emergence timeline based on molecular analysis

Endemic coronavirus	Reservoir	Intermediate host	Estimated emergence in humans	Discovery
NL63	Bats	Unknown	560–820 years ago	2004
229E	Bats	Camelids	~200 years ago	1966
HKU1	Rodents	Unknown	~1950s	2004
OC43	Rodents	Bovines	~1890	1967

Adapted from references (2–4)

All four of these endemic coronaviruses followed a common path from animals to humans and established endemic circulation through efficient human-to-human spread, modest symptomatology and seasonality. Thus, we hypothesize that zoonotic emergence and the spread of SARS-CoV-2 may result in establishing human endemicity. The understanding the seasonality of endemic coronaviruses as a whole may predict the eventual seasonality of SARS-CoV-2. We sought to describe the seasonal pattern of endemic coronaviruses, as well as other common respiratory viral infections, using national laboratory surveillance to better understand the possible implications of SARS-CoV-2 becoming a seasonal epidemic. In addition, we provide guidance for efficiencies in laboratory testing strategies that may be helpful in the eventual management of influenza, respiratory syncytial virus (RSV), SARS-CoV-2 and other respiratory pathogens.

Methods

National respiratory virus surveillance is coordinated by the Public Health Agency of Canada (PHAC) under a program known as FluWatch. Data from multiple sentinel public health and hospital laboratories across Canada are collected and published on a weekly basis. For coronavirus and viruses other than RSV and influenza A and B, epidemiological surveillance by FluWatch is nationally comprehensive and includes data from all major laboratories in Canada that perform testing. Both the number of positive detections and test volumes for each virus are supplied to FluWatch. These laboratories include all the provincial public health laboratories, and, in Ontario, they include the additional hospital laboratories that perform virus diagnostics: Children's Hospital of Eastern Ontario (Ottawa); University Health Network/Mount Sinai Hospital (Toronto); Sick Kids Hospital (Toronto); Sunnybrook Health Sciences Centre and Women's College Hospital (Toronto); St. Joseph's Hospital (London); and St. Joseph's Healthcare (Hamilton). Combined, these sentinel laboratories represent all laboratory-confirmed detections of coronavirus and respiratory viruses in Canada, with the exceptions of SARS-CoV-2, influenza and RSV. For influenza and RSV, the laboratory data are comprehensive for all provinces except Ontario, where detections may occur outside of the sentinel surveillance system. However, FluWatch captures more than 60% of cases through the Ontario provincial laboratory network and the majority of the remaining cases are likely captured through the sentinel hospital laboratories in Ontario. The data are supplied to the PHAC on a weekly basis and validated in a year-end report.

We retrieved the public data on laboratory-confirmed cases and testing volumes for endemic coronaviruses (NL63, 229E, HKU1 and OC43), influenza A and B viruses, rhinovirus/enterovirus (considered together because some molecular assays cannot distinguish between them), RSV, human metapneumovirus and parainfluenza virus. The study period for all viruses spanned the 2010–11 respiratory virus season (starting epidemiological week 35 of 2010, beginning August 30, 2010) through epidemiological week 10 of the 2019–20 season (ending March 7, 2020). Detections and test volumes were obtained from the Canadian open data website (https://www.open.canada.ca/en/open-data) and FluWatch reports (https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html). These data sets came from open-access sources of ongoing public health surveillance and are exempt from research ethics board approval. Data were complete for the entire study period. Data from 2011 through 2019 have been finalized by FluWatch for their year-end report; however, data from 2020 were collected in real-time and minor reporting delays from provinces may have occurred. Data from the most current three weeks was occasionally adjusted as updated information was received in the following weeks. At the time of this publication, all data up to and including epidemiological week 16 (April 19, 2020) were considered final.

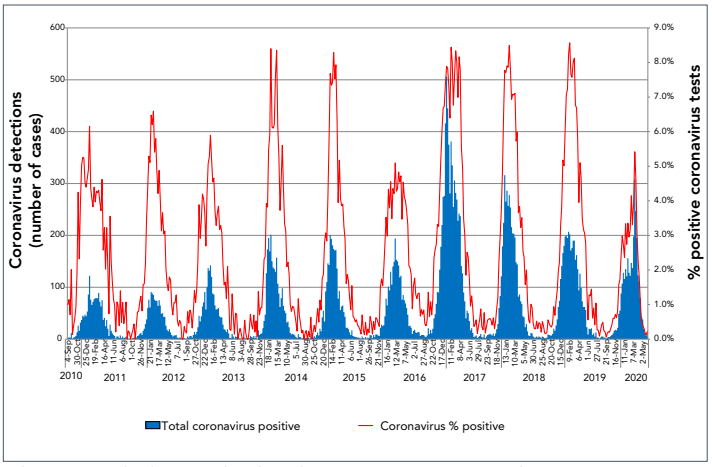
Weekly cases and percent of tests positive were used to provide an average number of cases per week and average percent-positive specimens per week for each virus. Peak activity

of each virus was defined as the maximum percent-positive samples and, if a distinct epidemic wave was observed in the combined 10-year data, the start and end of the virus season was defined as the first week and last week that percent positive exceeded 10% of the peak percent positive, respectively.

Results

Endemic coronaviruses demonstrated strong and predictable seasonality in Canada with modest variation in intensity from year to year. This was consistent with other descriptions of global coronavirus periodicity that reported winter seasonality (5,6). Both the number of cases of endemic coronavirus and proportion of positive coronavirus tests had dramatic periodicity with minimal year-to-year variation in onset and duration of the seasonal epidemic (**Figure 1**). Coronavirus seasonality in Canada, as determined by the ten-year average of positive test proportion and average number of cases detected by epidemiological week, is shown (**Figure 2**). A typical coronavirus season, defined here as the time above 10% percent of the highest percent positivity, began around epidemiological week 43 (typically the end of October), peaked in week five (end of January) and lasted until week 23 (early June), yielding an epidemic wave lasting 30 weeks, with significant activity between January and March and peak activity in week six (early February).

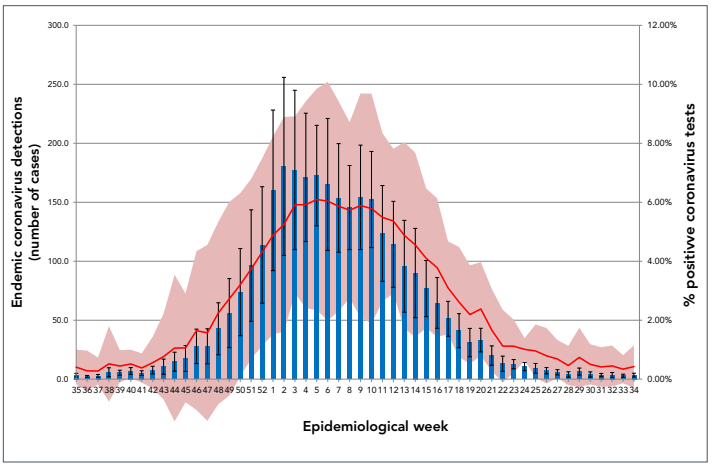
Figure 1: Seasonal pattern of endemic coronavirus detections and percent of coronavirus tests positive for endemic coronaviruses for the past ten years[a]



[a] The pattern is clearly seasonal; with epidemics occuring in winter months
Data from Public Health Agency of Canada Open Data (https://open.canada.ca/en/open-data) and FluWatch (https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html)

The laboratory detection of endemic coronaviruses demonstrated several differences from the seasonal epidemics of other viruses.

Figure 2: Ten-year average weekly detections and average percent of coronavirus tests positive for endemic coronaviruses in Canada[a]



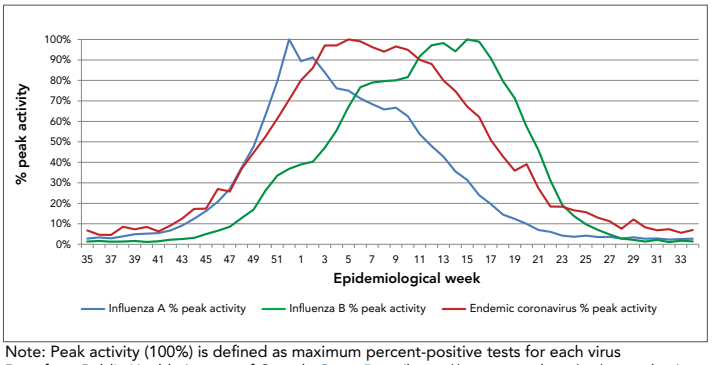
[a] Peak seasonal activity occurred between January and March. Error bars on coronavirus detections are 95% confidence intervals for the 10 year period and the red shaded area represents the 95% confidence interval around the percent of tests positive for endemic coronavirus
Data from Public Health Agency of Canada Open Data (https://open.canada.ca/en/open-data) and FluWatch (https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html)

Influenza A and B

In Canada, the ten-year average influenza A season started around week 44 (early November). While this is roughly the same time as the coronavirus season, the influenza A season peaked considerably earlier than the coronavirus season.

The influenza B season typically occurred later than Influenza A, with the 10-year average starting around week 48 (late November), peaking around week 15 (early April) and ending around week 25 (mid-June). While the peak was somewhat later than coronaviruses, substantial overlap exists between the seasonal endemic coronavirus season and the influenza B season (**Figure 3**).

Figure 3: The 10-year average activity of influenza A, influenza B and endemic coronaviruses by epidemiological week

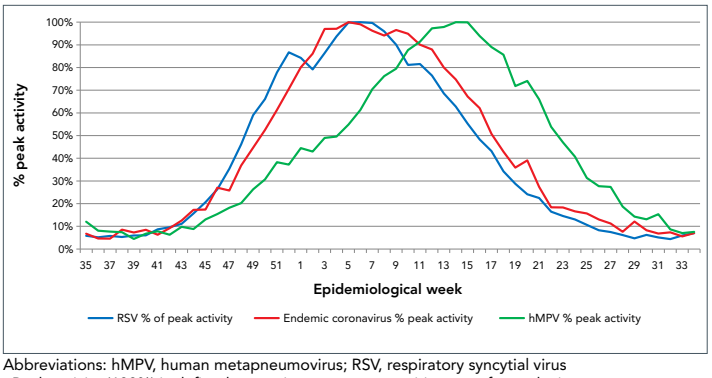


Note: Peak activity (100%) is defined as maximum percent-positive tests for each virus
Data from Public Health Agency of Canada Open Data (https://open.canada.ca/en/open-data) and FluWatch (https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html)

Respiratory syncytial virus and human metapneumovirus

There was almost perfect overlap of the Canadian RSV and endemic coronavirus seasons (**Figure 4**). Both seasonal coronavirus and RSV seasons started around week 42 human metapneumovirus also had seasonalities that overlapped somewhat with coronaviruses and RSV, peaking eight weeks later than RSV and nine weeks later than endemic coronaviruses.

Figure 4: The 10-year average activity[a] of respiratory syncytial virus, human metapneumovirus and endemic coronaviruses by epidemiological week



Abbreviations: hMPV, human metapneumovirus; RSV, respiratory syncytial virus
[a] Peak activity (100%) is defined as maximum percent-positive tests for each virus
Data from Public Health Agency of Canada Open Data (https://open.canada.ca/en/open-data) and FluWatch (https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html)

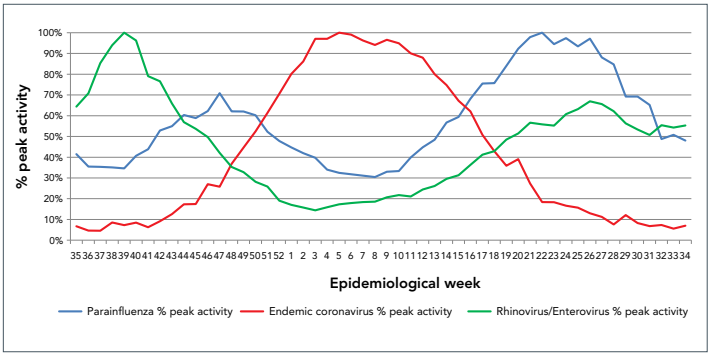
Rhinovirus/enterovirus and parainfluenza viruses

Contrasting sharply with the seasonal pattern of coronaviruses, rhinovirus/enterovirus and parainfluenza viruses had a pronounced bimodal seasonal pattern with the nadir occurring at the peak of the coronavirus season (**Figure 5**). Should SARS-CoV-2 adopt a similar seasonal pattern to other endemic coronaviruses, one would expect minimal activity of rhinovirus and parainfluenza virus during peak coronavirus activity.

Prevalence of viral illness

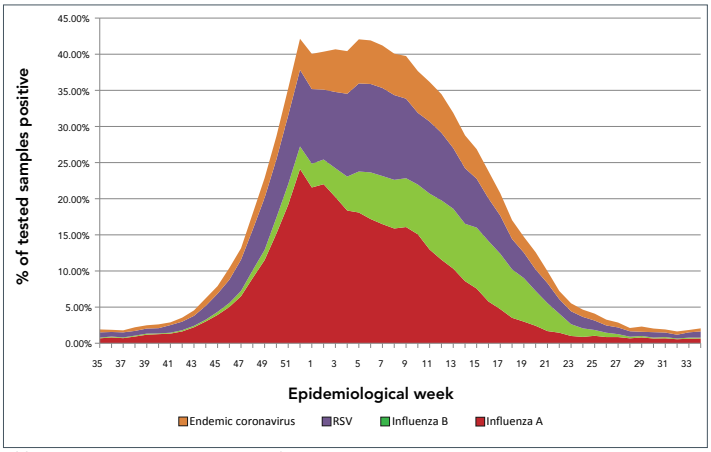
Figure 6 demonstrates the proprotion of tests positive for endemic coronavirus, RSV, influenza A or influenza B in reporting Canadian laboratories by epidemiological week. Co-circulation of multiple viruses between late-December and early March produced an extented period where more than 40% of samples were positive for at least one respiratory virus, suggesting a substantial burden of respiratory viral disease during this period.

Figure 5: The 10-year average activity of parainfluenza virus, rhinovirus/enterovirus and endemic coronaviruses by epidemiological week



Note: Peak activity (100%) is defined as maximum percent-positive tests for each virus
Data from Public Health Agency of Canada Open Data (https://open.canada.ca/en/open-data) and FluWatch (https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html)

Figure 6: The 10-year averageof the proprotion of tests positive for endemic coronavirus, respiratory syncytial virus, influenza A or influenza B in reporting Canadian laboratories by epidemiological week



Abbreviation: RSV, respiratory syncytial virus
Note: Peak activity of these viruses, with >40% of tests positive for at least one of the viruses occurs between early January and early March
Data from Public Health Agency of Canada Open Data (https://open.canada.ca/en/open-data) and FluWatch (https://www.canada.ca/en/public-health/services/diseases/flu-influenza/influenza-surveillance.html)

Discussion

Circulating endemic coronaviruses (NL63, 229E, HKU1 and OC43) have established a seasonal pattern of late-winter peak activity in Canada. While the laboratory assays used for these data did not discriminate between coronavirus species, and the seasonality described here represented a composite season for the four endemic coronaviruses, these data clearly demonstrate

that the overall pattern of the four endemic coronaviruses together show seasonality of circulation. Our data suggest that substantial overlap between clinically important respiratory viruses would be expected to occur if SARS-CoV-2 established a seasonal pattern similar to the existing endemic coronaviruses. For influenza A, the peak percent-positive occurred in week 52 (end of December), approximately five weeks before coronaviruses. A distinguishing feature of influenza A is the explosive nature of the early part of the epidemic, with an onset-to-peak time of approximately eight weeks. This contrasts with the slow increase in coronavirus detections; taking 14 weeks from onset to peak. This is partly explained by the shorter incubation period of influenza A; however, the percent-positive influenza A detections declined relatively slowly, and the influenza A season was not typically over until week 20 (early May). Thus, considerable overlap between the annual influenza A epidemic and coronavirus seasonal epidemics would be expected due to this trailing decline in influenza A cases. Likewise, while the peak of influenza B activity occurred later than seasonal coronavirus activity, substantial overlap is expected and the known burden of disease of influenza B in the elderly is likely to be compounded by co-circulation of SARS-CoV-2. While SARS-CoV-2 may be clinically less relevant in the paediatric population, co-circulation of RSV and SARS-CoV-2 could significantly impact paediatric healthcare workers and adults caring for children with COVID-19. The need to isolate hospitalized children with RSV bronchiolitis as presumed cases of COVID-19 pending diagnostic testing could also strain infection control measures.

If, as we hypothesize, SARS-CoV-2 eventually establishes a seasonal pattern similar to currently endemic coronaviruses, then planning for this added burden to the respiratory season is necessary, particularly because the coronavirus season overlaps with the influenza and RSV seasons. The most concerning implication of SARS-CoV-2 establishing seasonality similar to other coronaviruses is the additional burden expected on a healthcare system already strained by common viral respiratory tract infections. This strain may be seen as shortages of regular hospital beds, isolation and critical care beds, staff (in part due to staff absenteeism due to illness), drugs and more. In addition, staffing, laboratory resources and reagent supply chains may be taxed by increased testing, with resulting increased turnaround time or test service disruptions. These stresses may ultimately result in delayed or missed diagnosis of COVID-19 and other respiratory illnesses leading to clinicians being less comfortable making a clinical diagnosis when COVID-19 is in the differential diagnosis. If SARS-CoV-2 adopts a seasonal pattern similar to other coronaviruses, co-circulation of RSV, influenza A, influenza B and SARS-CoV-2 may be considerable between January and March, leading to a significant burden of respiratory disease during this period. Historically, before the emergence of SARS-CoV-2, more than 40% of samples tested in Canadian laboratories were already positive for RSV, influenza A, influenza B or seasonal coronaviruses between early January and early March (Figure 6), revealing a pre-existing and significant burden of disease. The addition of SARS-CoV-2 to the endemic coronavirus seasonal pattern would likely increase the respiratory virus disease burden during this period.

Within a specific healthcare geographical area, a seasonal SARS-CoV-2 may peak at the same time as RSV, resulting in considerable burden of disease in the paediatric care settings. While the majority of cases of both these illnesses are relatively mild in paediatric patients, one could nevertheless anticipate increased strain on paediatric health care facilities resulting from the small proportion of more severe cases and possibility of increased severity as a co-infection, including increased presentations for bronchiolitis and viral pneumonia (6,7).

The potential co-occurrence of influenza A, influenza B and SARS-CoV-2 is potentially devastating to the older population, who often have comorbidities that are disproportionately affected by all of three of these illnesses. The mitigation of the impact of seasonal SARS-CoV-2 epidemiology should therefore be a priority for long-term care and assisted living facilities.

Lastly, the co-circulation of multiple viruses during this period of time would be expected to cause significant absenteeism in young and middle-aged adults, given possible requirements for isolation and testing of patients to exclude SARS-CoV-2 infection from workplaces and schools.

Another potential implication of SARS-CoV-2 adopting a seasonal pattern is the need for an appropriate diagnostic test utilization and streamlining strategy. Use of single target (simplex) nucleic acid tests are inefficient in terms of regent and labour utilization in laboratories. For this reason, multiplexed tests that target co-circulating pathogens should be developed so that clinicians can accurately differentiate symptomatic patients in order to implement appropriate therapy and institute appropriate infection or disease control measures. Given the possibility of co-occurring seasonal epidemics, priority should be given to development of multiplex assays for influenza A, influenza B, RSV and SARS-CoV-2 to simplify testing and to reduce labour and material costs. The benefit of additional multiplexing (rhinovirus, parainfluenza virus) is more questionable given the added cost and the relatively low activity of these viruses during peak influenza, RSV and coronavirus activities. Furthermore, influenza, RSV and SARS-CoV-2 are all priority pathogens that have a greater healthcare impact and benefit from diagnosis and differentiation in the healthcare settings for therapeutic (e.g. oseltamivir for influenza) and infection control purposes (isolation). Parainfluenza, rhinovirus and enterovirus are low priority pathogens due to limited virulence and limited burden to healthcare. Despite the efficiencies associated with multiplexing nucleic acid amplification assays, there is likely still a role for SARS-CoV-2 simplex assay in the evaluation and tracing of asymptomatic individuals and contacts of COVID-19 cases directed by public health authorities, where detection of influenza and RSV are of no benefit.

Limitations

While comprehensive, these data have several limitations. They do not take into account differences in testing algorithms or populations for these respiratory viruses that will vary from province to province, season to season and year to year. The number of tests performed is not uniform across the population of Canada, with some provinces or territories over-represented by a higher rate of testing and others under-represented. Because of these limitations, positive proportion of tests rather than absolute case counts should primarily be used as an indicator of seasonality. However, given the uniformity of the findings and consistency with other published reports, this limitation is unlikely to affect the interpretation of respiratory virus seasonality data. Another limitation is that we cannot with any certainty predict if and when SARS-CoV-2 will establish a seasonal pattern of infection. We hypothesize this will occur due to comparable biology of the viruses, effective person-to-person transmission, significant host susceptibility and global prevalence. These factors may, however, be dramatically altered by human interventions such as public health measures, vaccinations and, eventually, treatment. It is also impossible to determine if and how SARS-CoV-2 virulence will change over time. Currently, unlike influenza, endemic coronaviruses have minimal impact on disease burden in hospitals and healthcare settings due to limited virulence. Our assumptions on additional burden with co-circulation of influenza and RSV assume that SARS-CoV-2 maintains relatively high virulence compared with the currently endemic coronaviruses.

Conclusion

Like SARS-CoV-2, endemic coronaviruses that infect humans have common zoonotic origins and have established seasonal epidemic patterns in human populations that coincide with influenza A, influenza B and RSV. While it remains unclear if SARS-CoV-2 will establish a similar seasonal pattern, the virus is clearly established in the human population and eventual seasonality should be assumed to be a strong possibility given the well-established pattern of seasonality in commonly circulating endemic coronaviruses. Preparation for seasonal outbreaks of SARS-CoV-2 and other respiratory viruses could include appropriate staff and bed management in healthcare facilities and other essential services as well as anticipation of increased absenteeism in all workplaces, particularly in the first three months of the calendar year. Within laboratories, development of combined tests and associated protocols for commonly co-circulating viruses should be prioritized to optimize the efficiency of diagnostic and surveillance testing.

Authors' statement

PLW — Conceived the study idea, analyzed and interpreted the data and drafted and edited the manuscript
JB — Provided critical, scientific and editorial review and edits of the manuscript
RC — Provided critical, scientific and editorial review of the manuscript
PVC — Provided critical, scientific and editorial review and edits of the manuscript

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

Competing interests

None declared.

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Canadian national COVID-19 genomics surveillance priorities for existing and emerging variants of concern

on behalf of the Genome Canada Canadian COVID-19 Genomics Network (CanCOGeN) and the Canadian Public Health Laboratory Network CanCOGeN Working Group

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Keywords: Genomic surveillance, genomic sequencing, COVID-19, variants of concern, SARS-CoV-2, Canada, public health, surveillance

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Introduction

The Canadian COVID-19 Genomics Network (CanCOGeN) (COVID-19, coronavirus disease 2019) is performing genomic surveillance of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Canada to track its spread, monitor for variants of concern (VOCs) that might impact transmissibility or disease severity, assist in outbreak investigations and assess the impact of public health interventions. Recent reports of emerging VOCs with enhanced transmissibility have been reported in the United Kingdom (UK) and South Africa (SA). The potential for rapid spread of these variants affirms the need for ongoing and enhanced genomic surveillance in Canada and worldwide. In this guidance document, we set out the national priorities for genomic surveillance, including targeted surveillance of existing and emerging VOCs.

Targeted genomic surveillance of variants of concern (VOC-202012/01) and N501Y.V2

The COVID-19 variant, VOC-202012/01, was first detected in October 2020 in the UK. Its presence was correlated with increased transmissibility in the UK and has been reported in other countries, including Canada. Another newly emerged SA VOC, designated N501Y.V2, similarly correlates with increased transmissibility. As of January 7, 2021, the N501Y.V2 variant has not yet been detected in Canada. Both variants are defined by an "N501Y" mutation in the SARS-CoV-2 spike protein's receptor-binding domain. There is currently no evidence that either VOC results in increased severity or impacts vaccine efficacy. The CanCOGeN has identified both VOCs as priorities for targeted genomic surveillance.

- **Prospective targeted genomic surveillance (Priority: highest)**
  This includes all international travellers, including from the United States, and close contacts, from the present until further notice.

- **Retrospective targeted genomic surveillance (Priority: medium)**
  This includes all international travellers, including from the United States, and close contacts, from September 1, 2020, to the present.

- **Multi-target COVID-19 RT-PCR tests with S-gene target dropouts (Priority: high)**
  The UK VOC-202012/01 variant can test negative for the S-gene target but positive for other targets using the three-target assay (N, ORF1ab, S) from Thermo Fisher (TaqPath). Multi-target reverse transcription polymerase chain reaction (RT-PCR) assays that include a S-gene target that are affected by the deletions present in the variant can be used as a signal for follow up confirmatory genome sequencing.

Genomic surveillance of emerging variants of concern

- **Suspected reinfection (Priority: medium)**
  We define suspected reinfection as clinical recurrence of symptoms compatible with COVID-19, accompanied by positive polymerase chain reaction (PCR) (Ct less than 35), more than 90 days after the onset of the primary infection, supported by close contact exposure or outbreak settings, and no evidence of another cause of infection (1). Reinfection indicates possible infection by immune-escape variants.

- **Severe acute COVID-19 in individuals younger than 50 years old without significant comorbidities (Priority: medium)**
  Disproportionately severe disease in individuals who are otherwise healthy may indicate a change in pathogen virulence resulting in a more florid clinical phenotype, and is thus relevant for surveillance and potentially for patient management.

- **Vaccinated individuals with subsequent laboratory-confirmed SARS-CoV-2 infection (Priority: medium)**
  Although there is a limited number of vaccinated individuals at this time, that number is expected to grow. It is anticipated that with the rollout of vaccines there will be a need to monitor for and characterize potential vaccine-escape variants. This likely would require simultaneous monitoring for immune correlates of vaccine response, assessment of seroprotection and systematic genomic testing of post-vaccine infections to monitor for vaccine-escape mutants.

- **Known or suspected super spreading events (Priority: medium)**
  Given the proposed potential for increased transmissibility of VOC-202012/01 and N501Y.V2, and the N501Y mutation that they share, sequencing multiple samples from a known or suspected superspreading event may identify such mutations. Sampling the index cases in outbreaks may provide the highest yield.

  DEFINITION: A superspreading event is a type of outbreak where there is additional epidemiological and/or genomic evidence of one person with overdispersed transmission of COVID-19, (i.e. directly transmitting to at least five non-household individuals). The statistical concept of overdispersion refers to the few individuals disproportionately and directly infecting a large number of secondary cases relative to the "average" infectious individual, whose infectiousness may be represented by R0, which is estimated at 2.0 for COVID-19 (2).

  EXCLUSIONS: This definition excludes large or propagated outbreaks with no evidence of overdispersion.

- **Geographic sampling in subregions with a pronounced increase in the case notification rate (Priority: high)**
  A rapid increase in the case positivity rate in a geographic region may indicate either the possible presence of the UK and/or SA variants potentially contributing to increased cases/positivity (given the proposed potential for increased transmissibility of the UK and SA VOCs, and the N501Y mutation), or represent the context within which VOCs with increased transmission potential can take off. Public health authorities could perform geographic sampling in subregions where the positivity rate or per-capita rates or estimated reproductive rate is of higher magnitude and especially if increasing faster (or the doubling time is shorter and/or decreasing) as compared with the provincial average. Ideally, identifying the subregions for sampling would exclude cases in congregate settings (e.g. long-term care homes). Such subregions may overlap with the density of physical contact networks (e.g. greater household density and/or occupational exposures). These could be at the sub-provincial level (e.g. public health unit, city, etc.) or sub-regional level (e.g. neighbourhood).

Other priorities

- **Continued random sampling for routine national genomic surveillance (Priority: high)**
  The CanCOGeN sampling guidelines for national priorities include random sampling for routine SARS-CoV-2 genomic surveillance. Routine surveillance is used to monitor existing variants of concern, identify emerging variants of concern, track viral transmission and assess the effectiveness of public health interventions. Random sampling for routine genomic surveillance is ongoing and will continue.

- **Continued sampling to investigate SARS-CoV-2 outbreak clusters (Priority: medium)**
  The CanCOGeN sampling guidelines include strategies to investigate and respond to SARS-CoV-2 outbreak clusters. Sampling for outbreak investigations is ongoing and will continue.

Recommended response

Individuals with SARS-CoV-2 infections that are compatible with the above groupings may signal an existing or new variant of concern. As a result, beyond the existing suite of public health measures in place, it is recommended that obtaining samples that enable downstream sequencing is a high priority. Following collection, specimens from such cases should be forwarded to the public health lab in their region to be sequenced in a timely manner to identify cases of the new variant. If the UK or SA variants are detected, enhanced genomic surveillance should be conducted in the community/region/event.

Competing interests

None.

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Impact of nonpharmaceutical interventions on laboratory detections of influenza A and B in Canada

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Abstract

Background: The first coronavirus disease 2019 (COVID-19) case was reported in Canada on January 25, 2020. In response to the imminent outbreak, many provincial and territorial health authorities implemented nonpharmaceutical public health measures to curb the spread of disease. "Social distancing" measures included restrictions on group gatherings; cancellation of sports, cultural and religious events and gatherings; recommended physical distancing between people; school and daycare closures; reductions in non-essential services; and closures of businesses.

Objectives: To evaluate the impact of the combined nonpharmaceutical interventions imposed in March 2020 on influenza A and B epidemiology by comparing national laboratory surveillance data from the intervention period with 9-year historical influenza season control data.

Methods: We obtained epidemiologic data on laboratory influenza A and B detections and test volumes from the Canadian national influenza surveillance system for the epidemiologic period December 29, 2019 (epidemiologic week 1) through May 2, 2020 (epidemiologic week 18). COVID-19-related social distancing measures were implemented in Canada from epidemiologic week 10 of this period. We compared influenza A and B laboratory detections and test volumes and trends in detection during the 2019–20 influenza season with those of the previous nine influenza seasons for evidence of changes in epidemiologic trends.

Results: While influenza detections the week prior to the implementation of social distancing measures did not differ statistically from the previous nine seasons, a steep decline in positivity occurred between epidemiologic weeks 10 and 14 (March 8–April 4, 2020). Both the percent positive on week 14 ($p \leq 0.001$) and rate of decline between weeks 10 and 14 ($p=0.003$) were significantly different from mean historical data.

Conclusion: The data show a dramatic decrease in influenza A and B laboratory detections concurrent with social distancing measures and nonpharmaceutical interventions in Canada. The impact of these measures on influenza transmission may be generalizable to other respiratory viral illnesses during the study period, including COVID-19.

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Keywords: social distancing, physical distancing, influenza, COVID-19, SARS-CoV-2, public health, nonpharmaceutical interventions, NPI

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been recognized as a public health crisis. As the number of cases has increased in Canada and abroad, governments have imposed measures to reduce transmission of severe acute respiratory coronavirus 2 (SARS-CoV-2). Among these have been massive public health campaigns, invocation of public health emergencies

and the enactment of laws under emergency measures legislation to reduce person-to-person transmission.

Such broad nonpharmaceutical interventions have not been applied on a universal scale since the advent of modern laboratory surveillance, and while these actions are supported by epidemiologic theory, approaches combining multiple nonpharmaceutical control measures have not been rigorously attempted beyond a relatively limited scale.

Evidence from similar smaller-scale or regional interventions (e.g. school closures, travel restrictions, business closures) has shown only slight effects on interrupting respiratory virus epidemics (e.g. influenza) (1,2). In addition, recent meta-analyses suggest a modest benefit of physical measures like hand washing on community transmission of influenza (3). Since these physical measures have been strongly encouraged along with restrictions on social interactions and gatherings, there may be an additive effect on community transmission. A number of studies have shown that similar interventions have been effective for control of COVID-19 (4,5). To demonstrate the benefit gained versus the enormous social and financial cost of universal social distancing measures, it is critical that we confirm the effectiveness of these measures on the transmission of respiratory viral infections. Because of the short incubation period of influenza viruses (mean 0.6–1.4 days) (6) compared to SARS-CoV-2 (mean 5.2 days, 95% confidence intervals [CI]: 4.1–7.0 days) (7), the impact of such measures should be evident within two to three weeks of their implementation. The effect of the measures could be detected using existing surveillance systems for influenza.

We analyzed laboratory surveillance data for evidence of changes in influenza transmission with voluntary "social distancing" measures that began in Canada along with public health messaging in early March 2020. These voluntary measures were followed by more aggressive public health measures as of March 12, 2020 (i.e. school closures, closure of non-essential businesses and strict border controls).

Background

Provincial and territorial health authorities implemented social distancing measures gradually, starting in early March (epidemiologic week 10). The measures included physical distancing between individuals, restrictions on group gatherings, cancellation of sporting and arts events, closures of businesses and recreational areas where people congregate, country-wide school and daycare closures, cancellation of religious events, and efforts to dramatically reduce the active "on-site" workforce by encouraging employees to work from home. In general, these interventions were in keeping with recommendations outlined in Canada's pandemic plans, *Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector* (8).

In the first days of March, media announcements and public health messaging recommended physical distancing between individuals, avoiding gatherings and reinforcing cough etiquette. Within two weeks, these recommendations were legally reinforced. Québec was the first province to declare a public health emergency through their *Public Health Act* on March 13, 2020 (9). By March 18, 2020, over 90% of the Canadian population was legally directed under various emergency acts to engage in strict measures to prevent the spread of COVID-19. By March 22, 2020, all Canadian provinces and territories were under various forms of public health emergency legislation (9).

Across Canada, by the third week of March, all personal, community and travel restrictions were in place to varying degrees of enforcement under public health regulations recommended by the Public Health Agency of Canada (PHAC, or the Agency). This was the first time in the history of modern influenza surveillance that all the recommended social distancing measures in pandemic preparedness planning guidance were implemented simultaneously across the entire country. In addition, health authorities dramatically increased messaging to do with physical interventions (hand washing and use of personal protective equipment), resulting in increased utilization of these interventions during this period. The use of face masks was neither recommended nor imposed during this period.

We hypothesized that these collective interventions would have an impact on laboratory detections of influenza, heralding a potential effect on other respiratory viral infections including COVID-19.

Methods

National influenza surveillance is coordinated by PHAC. The Agency's influenza surveillance program receives data on several indicators of influenza activity from a network of labs, hospitals, doctor's offices, members of the public, and provincial and territorial ministries of health on a weekly basis (10). Sentinel public health and hospital laboratories provide PHAC with weekly summaries of influenza test results and test volumes, and the Agency collates the data and provides the public with updates. Data have been continuously collected since 1993, and long-term analysis of seasonal trends is made possible both by the continuity of laboratory data and absence of any influenza pandemics since 2009.

We analyzed the post-2009 trends using national data to determine if any changes in trends in influenza A and B epidemiology during the 2020 season could be attributed to social distancing. Only one sentinel laboratory has been added to those providing surveillance data over the previous 10 seasons: St. Joseph's Healthcare in Hamilton, Ontario, during the 2019–20 influenza season. While this laboratory contributed

7.8% of the 2019–20 surveillance sample numbers in this study, analysis excluding the data from St. Joseph's did not appreciably change the results.

The sentinel laboratories provide limited information on testing modality or demographics. While most laboratories perform nucleic acid amplification testing (NAAT) for influenza viruses, data from both cell culture and NAAT are accepted.

Laboratories provide limited demographic information and no clinical information on positive cases and no information on negative cases. The limited demographic information was not accessed as part of this study.

The study population included all influenza tests conducted at sentinel laboratories in Canada during the study period of 2011–20. During the control period of 2011–19, there were no universal control interventions for respiratory viral infections based on social distancing.

For the purpose of this analysis, we defined a case as any laboratory-confirmed positive test for either influenza A or B reported to the Agency. Weekly influenza-positive percentage was defined as the number of cases reported over the total number of tests performed for the epidemiologic week under surveillance, expressed as a percentage.

The control period included the 2011 through 2019 influenza seasons. To account for seasonal variations in influenza season onset and duration, we aligned the peak epidemic activity weeks for each control season, defined as the week with the highest proportion of influenza-positive laboratory detections. Our analysis included the portion of the 2019–20 influenza season from December 29, 2019 (epidemiologic week 1) through May 2, 2020 (epidemiologic week 18). The intervention period is defined as weeks 10 through 18 of 2020.

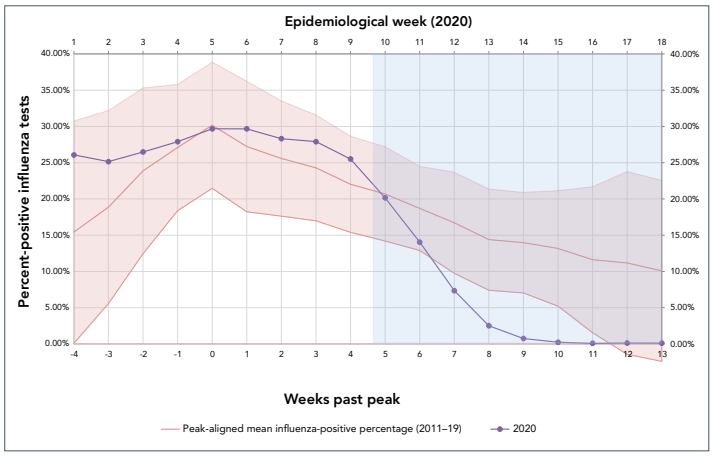
We retrieved data on laboratory detections of influenza A and B and test volumes for the past 10 years from the Canadian Open Data website (10), maintained by the Government of Canada Open Data website, and FluWatch reports (11) for the study period. These datasets come from open-access sources of ongoing public health surveillance and are exempt from research ethics board approval. Data were complete for the entire study period. Data from 2011 through 2019 have been finalized by FluWatch for their year-end report, but data from 2020 were collected in real-time and minor reporting delays from provinces could have occurred. Data from the most current three weeks is occasionally adjusted as updated information is received in the subsequent weeks. At the time of this publication, all data up to epidemiologic week 18 were considered final.

Data from the control period were expressed as weekly influenza-positive percentage by week pre or post-peak activity. We determined mean influenza-positive percentage and standard deviations for each week, and the *z* score and *p* value for each of the weekly influenza-positive percentages during the 2020 surveillance period compared to the peak-aligned control season means. Using least squares linear regression analysis, we compared the slope of influenza-positive percentage by epidemiologic week from the first 4 weeks of the 2020 intervention period (epidemiologic weeks 10–13, post-peak weeks 5–8) to the slope in the equivalent portion of the control seasons using a Student *t* test with pooled variance. We determined descriptive statistics and *z* scores and corresponding *p* values using Microsoft Excel 2010 (Redmond, Washington, United States) and performed linear regression analysis using JMP statistical analysis software (SAS Institute Inc., Cary, North Carolina, United States).

Results

Positive influenza tests were reported by week of the laboratory report. Data were complete for all epidemiologic weeks between 2011 and 2019, with no omissions. **Figure 1** shows the mean influenza-positive percentage and 95% CI by week, pre and post-peak. Observed values for the corresponding weeks in 2020 are overlaid on the control period values. **Table 1** shows the *p* values for the percent positive influenza tests for weeks 10 through 18 of the 2019–20 influenza season compared to historical values. The data demonstrate an unexpected decline in influenza-positive percentage starting in epidemiologic week 10, corresponding to March 1 through March 7, compared to the control period. By early April (week 14, post-peak week 9), there was a marked difference between 2020 percent positive (0.75%) and control period mean percent positive (13.97%, $p \leq 0.001$). Between epidemiologic weeks 10 and 13 of the 2020 season, the mean absolute rate of decline in percent positive was 4.41% per

Figure 1: Mean influenza-positive percent for peak-aligned control period (2011–19) and influenza-positive percent for the 2020 study period by pre and post-peak week and 2020 epidemiologic week



Note: Each influenza seasonal peak (maximum influenza-positive percentage) between 2011 and 2019 was aligned to generate mean and confidence intervals for the control period. The 2020 season peak is aligned to control period peak for comparison. Social distancing intervention period started in early March 2020, week 10 (shaded blue) and 95% confidence interval (shaded red)

Table 1: Influenza tests and positive detections at sentinel laboratories in Canada for epidemiologic weeks 10 through 14 of the 2019–20 season

Week number	Week dates	Influenza A positive	Influenza B positive	Total influenza positive	Total influenza tests (2020)	Mean influenza tests (control period)	% influenza positive[a]	Relative decline from prior week	*p* value (versus peak-aligned control period)[b]
10	March 1–7	2,412	1,151	3,563	17,686	7,709	20.16	N/A	0.436
11	March 8–14	2,326	1,016	3,342	23,787	7,242	14.05	30.3	0.058
12	March 15–21	1,141	594	1,735	23,566	6,658	7.35	47.7	0.004
13	March 22–28	273	266	539	21,299	6,043	2.51	65.9	≤0.001
14	March 29–April 4	68	88	156	20,760	5,857	0.75	70.1	≤0.001
15	April 5–11	21	18	39	16,699	5,460	0.23	69.4	≤0.001
16	April 12–18	4	11	15	16,758	4,793	0.09	60.9	0.012
17	April 19–25	6	14	20	15,967	4,489	0.13	N/A[c]	0.043
18	April 26–May 2	4	9	13	11,514	4,016	0.11	N/A[c]	0.058

Abbreviation: N/A, not applicable
[a] Percentage reduction in influenza-positive percent compared to week 10
[b] *p* value of the influenza-positive percent for each week compared to the same weeks during the control period (2011–19)
[c] No further decline after week 16

week, compared to 1.58% per week for the peak-aligned control period. Linear regression analysis of the slopes during this period showed the downward slope of the 2020 season to differ statistically significantly compared to the linear regression slope of the 2011–19 seasons ($p \leq 0.001$).

Discussion

The national epidemic curve of influenza in Canada, as described by influenza-positive percent, follows a predictable pattern of increasing percentage of positive tests into the winter months, peaking around the end of December or early January, and a subsequent slow decline into the inter-epidemic period. At the beginning of the intervention period, the mean influenza-positive percentage for the 2011–19 seasons was 20.69%. By week 14, this mean influenza-positive percentage had declined to 15.61%.

The 2020 influenza epidemic shows comparable values in week 1 through 10 (see Figure 1), with a steep decline in influenza-positive percentage by week 14. Linear regression also indicates that the rate of decline during the intervention period was statistically unlikely to occur at this point of an influenza epidemic based on nine years of historical data. This decline was evident by week 11, shortly after increasing federal and provincial/territorial and local messaging around social distancing. The weekly relative rate of decline incrementally increased between weeks 11 and 14, suggesting that the escalation in social distancing measures was having a sustained or increasing impact on influenza transmission. Because the incubation periods of influenza A (1.4 days; 95% CI: 1.3–1.5) and B (0.6 days; 95% CI: 0.5–0.6) are relatively short (6), such rapid rates of decline would be predicted if these interventions were effective at reducing the apparent reproductive number of these illnesses.

While it is not possible to identify precisely when modifications in behaviours leading to reduced transmission occurred, this decline in transmission appears to have occurred prior to declarations of public health emergencies and shortly after the increased public health messaging around social distancing and barrier interventions. While legislation of social/physical distancing through the public health or emergency measures acts in mid-March likely reinforced these behaviours, the decline in influenza transmission prior to these would suggest that the voluntary social/physical distancing practices recommended in early March may have affected influenza transmission.

Several other studies, primarily from Asian countries, have reported an effect of nonpharmaceutical public health measures, including a broad range of interventions and behavioural changes, on influenza epidemiology (12–17). In previous reviews of nonpharmaceutical interventions for influenza control, reactive school closures (as those in Canada in response to the COVID-19 pandemic) reportedly decreased influenza transmission by 7% to 15% (2,18). Broad working-from-home approaches have been shown to reduce transmission by 20%–30%, while travel restrictions (>50%) may delay influenza peak transmission (2).

Limitations

The most significant limitation of this observational study is that we cannot definitively confirm that the decline in proportion of influenza-positive samples was caused by the intervention. Nevertheless, several observations support an element of

causality based on Bradford–Hill criteria (19): the observed effect of the social distancing period is very strongly associated with declining influenza positivity; the effect was consistent across all provinces and territories (data not shown); the effect is temporarily associated with the intervention, which started with voluntary distancing in early March; there is a plausible mechanism for causality (interruption of person-to-person transmission); and there are analogous observations of such dramatic declines in infectious diseases with other effective population-level interventions, for example, vaccination, as well as reports of smaller-scale social distancing interventions resulting in less dramatic reductions in influenza transmission in the studied population (2).

Although we recognize that the complexities of public health interventions do not lend themselves to use of the Bradford–Hill criteria as effectively as specific exposures (19), the evidence is strong that the interventions had an effect on the proportion of influenza-positive samples. It is also impossible to ascertain the relative effect of each intervention. While our data reveal the net impact of the period in which nonpharmaceutical interventions were imposed, they cannot identify whether social distancing was exclusively responsible or if co-occurring interventions such as enhanced physical methods (hand washing and masking) or concurrent pharmaceutical interventions (e.g. oseltamivir use, vaccination) played a role in the decline. Nevertheless, the collective impact of these measures was significant.

Alternative explanations for the decline in influenza test positivity are possible if unlikely. One example is change in surveillance input, such as testing individuals with a wider variety of clinical presentations, as well as a testing a more diverse patient population than usually represented in influenza surveillance data, including those for whom testing for influenza was directly or indirectly influenced by clinical suspicion of COVID-19. In addition, population behaviours such as healthcare avoidance as COVID-19 circulation in Canada increased might produce similar effects. However, all of these effects are unlikely to have resulted in the abrupt decline in influenza detections. An increase in testing volume due to over-testing individuals with mild clinical symptoms or those not typically represented in influenza data should have resulted in a similar or slightly increased absolute number of influenza cases with a decline in the percent positive due to over-representation of samples from asymptomatic individuals. However, the data during the intervention period clearly show a steep decline in the absolute number of influenza cases as well as percent-positive samples (Table 1). Likewise, reduced healthcare-seeking behaviours during the intervention period cannot explain the findings as the volume of influenza testing sharply increased from baseline (Table 1) during the intervention period, likely in response to population and public health concerns to do with the COVID-19 pandemic.

Lastly, a reduction in absolute influenza detections might have been expected if testing was restricted to more severely ill patients during the intervention period. However, this should have resulted in an increase in the percent positive, not a decrease, adding further support to the likelihood that the control measures did result in decreased transmission.

We conclude, based on the observed trend in the percentage of influenza-positive samples, that the dramatic decline was a result of the population-level interventions collectively referred to as social distancing. However, our data does not allow us to conclude that co-occurring pharmaceutical interventions (e.g. increased usage oseltamivir and vaccination) and physical, nonpharmaceutical interventions (hand washing, use of personal protective equipment and masks) may have added to this effect.

Conclusion

This study contributes to the global evidence by showing that, through a combination of multiple voluntary and legislated nonpharmaceutical measures, a relative decline of 96.6% in influenza transmission (as measured by percent-positive samples) was achieved over four weeks. Given the dramatic effect of the national-level interventions on influenza positivity, it is clear that universal application of multiple social distancing measures results in considerable reduction in influenza transmission, far greater than those reported for localized and limited interventions. Achieving reductions on a national scale is also feasible, albeit at great economic and personal cost.

While this observation does not necessarily mean that the intervention effects are generalizable to COVID-19, given the similar modes of transmission of the influenza and SARS-CoV-2 viruses, we could expect a similar effect. These findings are also consistent with other reports of reduction in transmission of both influenza and COVID-19 (12). However, because the incubation of SARS-CoV-2 is longer than that of influenza, any impact on the epidemic curve of COVID-19 would likely occur over a considerably longer period than that observed with influenza. In addition, differences in basic reproductive number of seasonal influenza (1.19–1.37) (20) and SARS-CoV-2 (2.24–3.58 to 3.8–8.9) (21,22) likely mean that a greater intensity of interventions in a susceptible population are required to reduce the apparent reproduction number to below one.

Authors' statement

PLW — Co-conceived the study idea, analyzed and interpreted the data and drafted the manuscript
CS — Co-conceived the study idea, participated in data acquisition, analysis and interpretation and edited the manuscript
LL, AN, TS — Participated in data acquisition and edited the manuscript

Competing interests

None.

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Measles surveillance in Canada, 2019

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Abstract

Background: The Public Health Agency of Canada (PHAC) has conducted enhanced measles surveillance since 1998, the year endemic measles transmission was eliminated in Canada. The objective of this annual national measles surveillance report is to provide an epidemiologic summary of measles activity reported in Canada for 2019 in order to provide evidence to support the continued verification of Canada's measles elimination status.

Methods: Measles surveillance data are housed in the Canadian Measles and Rubella Surveillance System (CMRSS) database. Descriptive analyses of demographics and risk factors were performed. Outbreak characteristics were summarized and genotypic analyses conducted. Surveillance, laboratory and vaccine coverage data for 2019 were used to assess Canada's status against the Pan American Health Organization (PAHO) essential criteria for the verification of measles elimination.

Results: In 2019, 113 measles cases were reported in Canada (crude incidence rate of 3.0 cases per 1,000,000 population). Of these cases, 42 (37%) were imported into Canada, and of the imported cases, 12 (29%) resulted in further transmission. Infants younger than one year had the highest age-specific incidence rate at 13.1 cases per 1,000,000 population. Only 29% of cases had one or more documented doses of measles-containing vaccine. One-fifth (19%) of cases were hospitalized; no deaths were reported. Genotype information was available for 100% of outbreaks reported in 2019 and 90% of non-outbreak-related measles cases; of cases with genotype information available, 27% were B3 and 73% were D8.

Conclusion: Despite meeting/partially meeting only three out of four of PAHO's essential criteria for measles elimination status, there is no evidence that endemic measles transmission has been reestablished in Canada.

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Keywords: measles, travel health, surveillance, measles elimination, vaccination

Introduction

Although vaccine preventable, measles is still a major cause of morbidity and mortality, especially in children younger than five years (1). In 2018, the last year for which estimates are available, there were approximately 9.8 million measles cases and 142,000 measles-related deaths worldwide (2). Global efforts to eliminate measles (which is defined as the absence of endemic measles transmission for at least 12 months in a defined geographic area with a well-performing surveillance system) began in 1963 with the introduction of the first measles vaccine (1,3).

In 1998, Canada was one of the first countries to eliminate endemic measles transmission following the pan-Canadian introduction of routine two-dose measles-mumps-rubella (MMR) vaccination for children in 1996–1997 (3,4). However, Canada's elimination status is threatened by infected travellers importing measles into Canada, particularly into pockets of the Canadian population that have suboptimal measles vaccination coverage rates (3–5). As such, it is critical that Canada has a strong measles surveillance capacity, including laboratory capacity, to rapidly identify measles cases so that public health actions can be taken to reduce spread and prevent the reestablishment of endemic measles (6).

The Public Health Agency of Canada (PHAC), including the National Microbiology Laboratory (NML), works with provinces and territories to conduct national measles surveillance. The Agency reports on measles activity weekly both publicly on the canada.ca website and to the Pan American Health Organization (PAHO) (7,8).

The objective of this annual national measles surveillance report is to provide an epidemiologic summary of measles activity reported in Canada for 2019 in order to provide evidence to support the continued verification of measles elimination status.

Methods

Surveillance data

The Canadian Measles and Rubella Surveillance System (CMRSS) is an active, enhanced surveillance system supported by all Canadian provinces and territories. Confirmed cases of measles meeting the national case definition were reported weekly to PHAC by provinces and territories and housed in the CMRSS database (7,8). All confirmed cases of measles with rash onset between January 1, 2019, and December 31, 2019, were included in this report. PHAC assigns epidemiologic weeks of rash onset with week one ending on the first Saturday of the year. A data validation process was conducted with all provinces and territories; this process included querying for missing data, identifying incorrect entries and confirming values with reporting jurisdictions. Cases with missing data were included in the analysis as appropriate. Visitors to Canada who were diagnosed with measles during their stay were included in this analysis.

A case was considered to have received a dose of measles-containing vaccine if the date of the vaccination is documented; otherwise, the case was considered unvaccinated. Cases with an unknown vaccination history were considered unvaccinated. A case was considered to be hospitalized if admitted to hospital due to measles or due to measles-related complications, but not if they were only seen in the emergency department.

The reporting province or territory identified the source of exposure in the course of the public health investigation. The sources of exposure were classified as outside Canada (imported); within Canada and linked to an imported case (import-related); within Canada and linked to a case of unknown origin; or unknown source/sporadic.

Verification of measles elimination through national and international goals and targets

PAHO set out four criteria for the ongoing verification of measles elimination (9), (**Table 1**). The indicators, established by PAHO, of a well-performing surveillance system are based on investigation of measles-like illness (i.e. suspected cases), whereas only confirmed cases are nationally notifiable in Canada. As such, these data can only indirectly address the PAHO criteria.

Table 1: Pan American Health Organization essential criteria for the verification of measles elimination

Criterion	Indicator
Verify the interruption of endemic measles cases for a period of at least 3 years from the last known endemic case, in the presence of high-quality surveillance	Zero cases of endemic transmission
Maintain high-quality surveillance sensitive enough to detect imported and import-related cases	>2 suspect cases per 100,000 population adequately investigated
Verify the absence of endemic measles virus strains through viral surveillance	Measles genotype assessed in 80% of outbreaks
Verify adequate immunization in the population	95% of population cohorts aged 1–40 years have received a measles-containing vaccine

Genotyping

NML routinely performs virus genotyping of all reverse transcription polymerase chain reaction (RT-PCR) confirmed cases for which viral specimens (respiratory swabs and/or urine) are available. The terminal 450 nucleotides of the measles nucleoprotein (N) gene (the N-450) were sequenced in accordance with World Health Organization (WHO) guidelines (10,11). Sequences were aligned with WHO genotype reference sequences and maximum parsimony phylogenetic trees generated in MEGA X software (12). Measles viral sequences were deposited in the WHO Measles Nucleotide Surveillance (MeaNS) database and distinct sequence identifiers (IDs) acquired. Sequences were also compared to designated named strains and to sequences deposited by other members of the global measles laboratory network (11,13). All confirmed cases of measles with rash onset between January 1, 2019, and December 31, 2019, that had been genotyped were included in this report (n=73). The sequences were deposited in GenBank, the National Institutes of Health (NIH) genetic sequence database, with accession numbers MT386938 to MT387010.

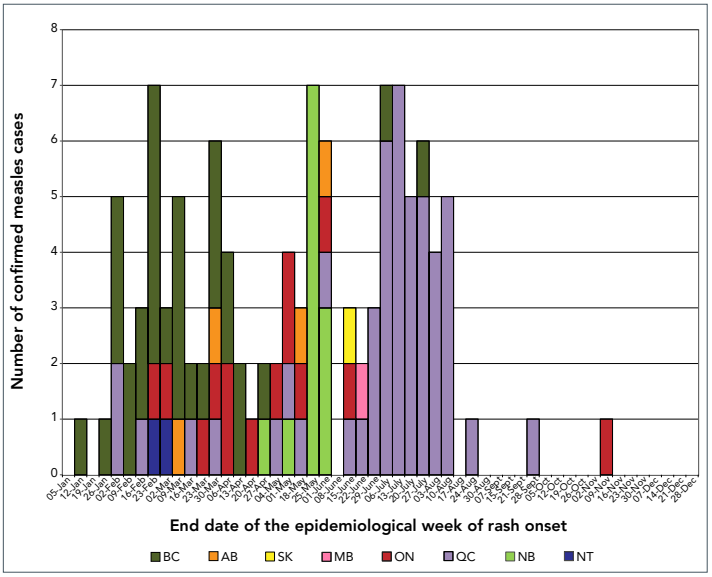
Analysis

Descriptive epidemiologic analyses were performed based on the available variables in the CMRSS database, including age, sex, location, onset date, vaccination, hospitalization, source of exposure and genotype (8). Statistical comparisons between frequencies were completed using Mid-P exact test, as appropriate. Measles outbreaks, defined as two or more confirmed cases linked epidemiologically, virologically or both, were described based on available information (14). Incidence rates were calculated using Statistics Canada population estimates for July 1, 2019.

Results

A total of 113 confirmed measles cases (incidence rate of 3.0 cases per 1,000,000 population) were reported from seven provinces and one territory, in 2019 (**Figure 1**). Approximately one-third of these cases were related to one outbreak in the province of Québec. Of the 113 total confirmed cases, 73 (65%) were genotyped. The genotypes detected were B3 (n=20) and D8 (n=53), both of which circulated globally in 2019, based on data submitted to the WHO MeaNS database (15). Altogether,

Figure 1: Number of reported measles cases (N=113), by epidemiologic week of rash onset and reporting province or territory, Canada, 2019



Abbreviations: AB, Alberta; BC, British Columbia; MB, Manitoba; NB, New Brunswick; NT, Northern Territories; ON, Ontario; QC, Québec; SK, Saskatchewan

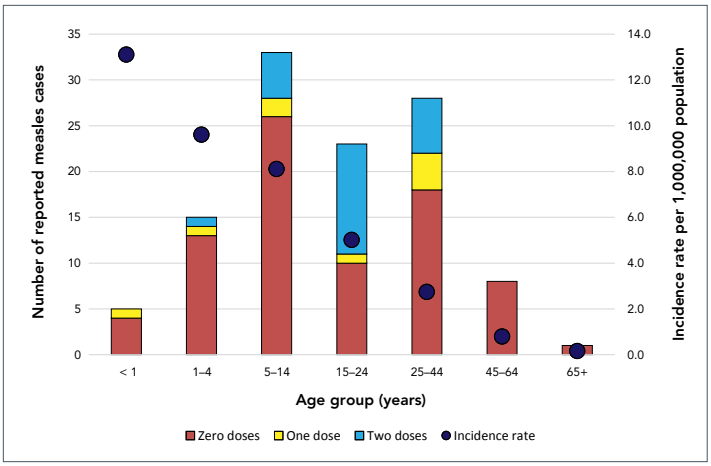
102 cases were laboratory-confirmed and 11 cases were epidemiologically linked to a laboratory-confirmed case.

Information on age, sex and province or territory of residence was complete for all measles cases reported in 2019. The cases were aged from younger than one year to 73 years, with a median age of 15 years. Cases were most often in the 5–14 year age group (29%, n=33) or the 25–44 year age group (25%, n=28). The incidence rate of measles declined across age groups, with the highest incidence rate reported in infants younger than one year (13.1 cases per 1,000,000 population) and the lowest in adults 65 years and older (0.15 cases per 1,000,000 population; **Figure 2**). The majority of cases (65%, n=73) were male.

Vaccination

Of the 113 measles cases reported in Canada in 2019, 71% (n=80) had no documented doses of measles-containing vaccine; of these, 16 cases had an unknown vaccination history. Over 40% of the unvaccinated measles cases (n=34) were related to an outbreak in a non-vaccinating community (see Outbreaks section, below). Of note, 57% (n=13) of cases in the 15–24 year age group had at least one documented dose of measles-containing vaccine; this is significantly higher than the proportion of cases with at least one dose of documented measles-containing vaccine in any other age group ($p<0.01$; Figure 2).

Figure 2: Confirmed measles cases (N=113) and incidence rates (per 1,000,000 population) by age group and vaccination status, Canada, 2019



Hospitalization

All 113 measles cases reported had hospitalization information complete. In total, 19% of cases (n=21) were hospitalized, resulting in a hospitalization rate of 0.6 per 1,000,000 population. The mean age of hospitalized cases was 31 years (median: 34 years, range: 1–73 years). On average, hospitalized cases were significantly older than non-hospitalized cases ($p<0.001$). Of the 21 hospitalized cases, only three (14%) had any documented doses of measles vaccination.

Molecular epidemiology by source of exposure

Of the 113 confirmed cases of measles in 2019, 42 (37%) were imported into Canada after exposure to measles during travel (**Table 2**). Twelve of these imported cases transmitted measles within Canada, which resulted in an additional 60 import-related cases (**Table 3**). In total, imported and import-related cases accounted for 90% (n=102) of the total cases, while 10% (n=11) had an unknown or sporadic source of measles exposure (Table 2, Table 3).

Table 2: Summary of imported measles cases by source of exposure (n=42) and by genotype, 2019

WHO region (number of cases)	Country	Number of cases	Genotype (number of cases)	WHO-named strain, if applicable, MeaNS Distinct Sequence ID (Number of cases)
Western Pacific (n=25)	Philippines	11	B3 (n=11)	MVi/Marikina City.PHL/10.18/, 5306 (n=4); N/A, 6018 (n=2); MVi/Gombak.MYS/40.15/, 4274 (n=1); N/A, 5654 (n=1); N/A, 5793 (n=1); N/A, 5904 (n=1); N/A, 6083 (n=1)
	Viet Nam	11	D8 (n=6)	MVs/Gir Somnath.IND/42.16/, 4683 (n=3); N/A, 5840 (n=2); N/A, 5823 (n=1)
	Cambodia	1	D8 (n=1)	MVs/Gir Somnath.IND/42.16/, 4683 (n=1)
	Multiple countries	2	D8 (n=1)	MVs/Gir Somnath.IND/42.16/, 4683 (n=1)

Table 2: Summary of imported measles cases by source of exposure (n=42) and by genotype, 2019 (*continued*)

WHO region (number of cases)	Country	Number of cases	Genotype (number of cases)	WHO-named strain, if applicable, MeaNS Distinct Sequence ID (Number of cases)
Europe (n=6)	France	1	B3 (n=1)	N/A, 5852 (n=1)
	Poland	1	D8 (n=1)	MVs/Gir Somnath.IND/42.16/, 4683 (n=1)
	Ukraine	1	D8 (n=1)	MVs/Gir Somnath.IND/42.16/, 4683 (n=1)
	United Kingdom	1	D8 (n=1)	MVs/Gir Somnath.IND/42.16/, 4683 (n=1)
	Multiple countries	2	D8 (n=1)	MVs/Gir Somnath.IND/42.16/, 4683 (n=1)
Americas (n=3)	United States of America	3	D8 (n=3)	MVs/Gir Somnath.IND/42.16/, 4683 (n=2); MVs/Dagon Seikkan.MMR/5.18, ID (n=1)
South-East Asian (n=3)	Bangladesh	2	B3 (n=2)	N/A, 5622 (n=1); N/A, 6218 (n=1)
	India	1	D8 (n=1)	N/A, 5970 (n=1)
Other (n=5)	Pakistan	2	B3 (n=1)	N/A, 5309 (n=1)
			D8 (n=1)	MVs/Gir Somnath.IND/42.16/, 4683 (n=1)
	Multiple countries and regions	3	B3 (n=1)	MVi/Marikina City.PHL/10.18/, 5306 (n=1)
			D8 (n=2)	MVs/Gir Somnath.IND/42.16/, 4683 (n=1); N/A, 5601 (n=1)

Abbreviations: ID, identifier; MeaNS, Measles Nucleotide Surveillance, N/A, not applicable; WHO, World Health Organization

Table 3: Summary of measles with an unknown source of exposure (n=11), by earliest date of rash onset, 2019

Case number	Exposure category	End date of the epidemiologic week of rash onset	Genotype (WHO-named strain if applicable, MeaNS Distinct Sequence ID)[a]	Description
1	Unknown (exposed either in Canada or abroad)	February 16	B3 (N/A, 5800)	• The case travelled to France, where active measles outbreaks were ongoing, and spent time in Canada during the exposure period • Genotyping data excludes a link to other known active measles cases present in the case's area of Canada during the exposure period • The identified measles strain was not detected in any other case genotyped in 2019 • The case had no documented doses of measles-containing vaccine
2	Exposed in Canada, not linked to any case	February 23	B3 (N/A, 5654)	• The case did not travel outside of Canada during the exposure period and had no known epidemiologic links to other confirmed measles cases • The identified measles strain was detected in one earlier case with travel history to the Philippines • The case had two documented doses of measles-containing vaccine
3	Unknown (exposed either in Canada or abroad)	March 30	D8 (MVs/ Gir Somnath. IND/42.16, 4683)	• The case travelled to the Dominican Republic during the exposure period. At the time of travel, no known active cases or outbreaks were ongoing in the Dominican Republic • The case was also present in an area of Canada with other active measles cases during the exposure period • The identified measles strain was detected in 45 other cases and has been circulating globally since 2018 • The case had no documented doses of measles-containing vaccine
4	Exposed in Canada, not linked to any case	March 30	D8 (MVs/ Gir Somnath. IND/42.16, 4683)	• The case did not travel outside of Canada during the exposure period and had no known epidemiologic links to other confirmed measles cases • The identified measles strain was detected in 45 other cases and has been circulating globally since 2018 • The case had one documented dose of measles-containing vaccine

Table 3: Summary of measles with an unknown source of exposure (n=11), by earliest date of rash onset, 2019 (*continued*)

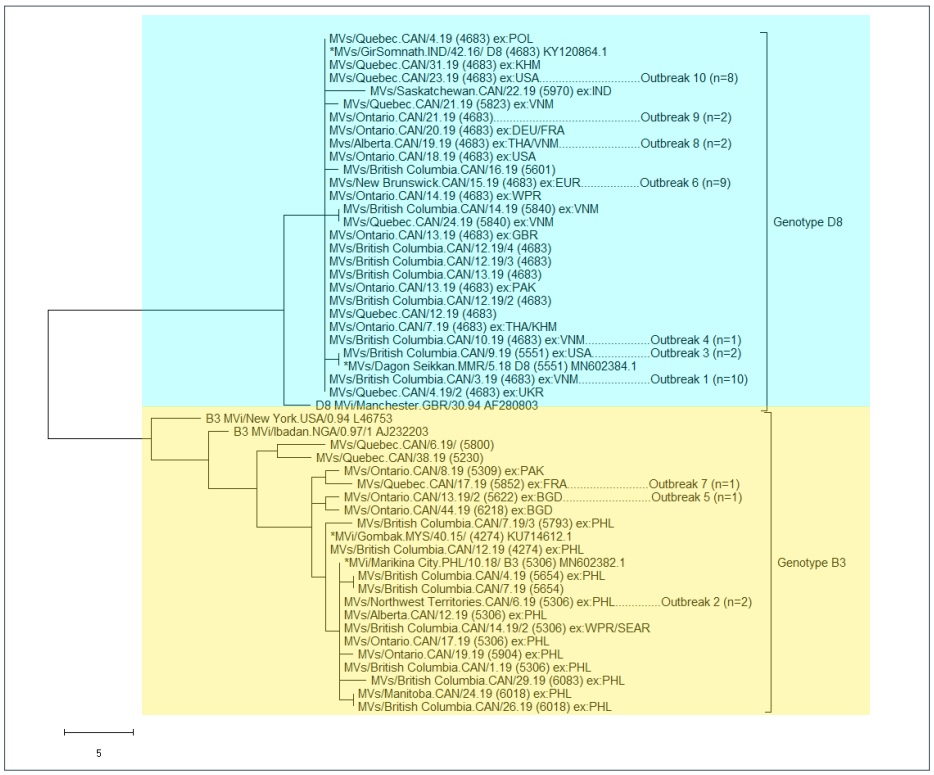
Case number	Exposure category	End date of the epidemiologic week of rash onset	Genotype (WHO-named strain if applicable, MeaNS Distinct Sequence ID)[a]	Description
5	Exposed in Canada, not linked to any case	March 30	D8 (MVs/ Gir Somnath. IND/42.16, 4683)	• The case did not travel outside of Canada during the exposure period and had no known epidemiologic links to other confirmed measles cases • The identified measles strain was detected in 45 other cases and has been circulating globally since 2018 • The case had two documented doses of measles-containing vaccine
6	Exposed in Canada, not linked to any case	April 6	D8 (MVs/ Gir Somnath. IND/42.16, 4683)	• The case did not travel outside of Canada during the exposure period • Although the case had no known epidemiologic links to other confirmed measles cases, they were present in an area of Canada with other active measles cases during the exposure period • The identified measles strain was detected in 45 other cases, including some that were active in the area, and has been circulating globally since 2018 • The case had no documented doses of measles-containing vaccine
7	Exposed in Canada, not linked to any case	April 6	D8 (MVs/ Gir Somnath. IND/42.16, 4683)	• The case did not travel outside of Canada during the exposure period and had no known epidemiologic links to other confirmed measles cases • The identified measles strain was detected in 45 other cases and has been circulating globally since 2018 • The case had two documented doses of measles-containing vaccine
8	Exposed in Canada, not linked to any case	June 1	D8 (MVs/ Gir Somnath. IND/42.16, 4683)	• The case did not travel outside of Canada during the exposure period and had no known epidemiologic links to other confirmed measles cases • The identified measles strain was detected in 45 other cases and has been circulating globally since 2018 • The case had no documented doses of measles-containing vaccine
9	Exposed in Canada, linked to a sporadic case of unknown origin	June 15	D8 (MVs/ Gir Somnath. IND/42.16, 4683)	• One case was a household contact of a previous case whose source of exposure was unknown. Both cases had the same measles strain • The case had no documented doses of measles-containing vaccine
10	Exposed in Canada, not linked to any case	July 20	Not determined	• The case did not travel outside of Canada during the exposure period and had no known epidemiologic links to other confirmed measles cases • The case had two documented doses of measles-containing vaccine
11	Exposed in Canada, not linked to any case	September 28	B3 (N/A, 5230)	• The case did not travel outside of Canada during the exposure period and had no known epidemiologic links to other confirmed measles cases. The case did fly on multiple domestic flights during the exposure period and may have come in contact with the virus in an airport • The identified measles strain was not detected in any other case genotyped in 2019 • The case had no documented doses of measles-containing vaccine

Abbreviations: ID, identifier; MeaNS, Measles Nucleotide Surveillance; N/A, not applicable; WHO, World Health Organization
[a] GenBank accession number for the listed named strain is KY120864

Unknown source

Eleven cases (10%) were neither imported nor import-related: eight had no recent history of travel or known links to other confirmed measles cases (sporadic cases); one was linked to a sporadic case of unknown origin; and the exact source of exposure for the other two cases could not be determined (unknown source) because exposure may have occurred either in another country with known measles activity or in Canada (Table 3). These cases originated from British Columbia (n=5), Québec (n=4) and Ontario (n=2). Six of these cases were female and five were male. Ten of these 11 cases were genotyped; in seven cases, the genotype D8 MVs/Gir Somnath.IND/42.16/ named strain was detected, which was circulating globally in 2019. Three distinct genotype B3 strains (sequence IDs 5230, 5654 and 5800) were identified in the remaining three cases, two of which were not detected in any other measles case genotyped in 2019 (5230 and 5800) (**Figure 3**, Table 3).

Figure 3: Maximum parsimony phylogenetic tree of measles N-450 sequences identified in Canada in 2019 (n=73) prepared using MEGA X software[a]



Abbreviations: ID, identifier; MeaNS, Measles Nucleotide Surveillance; WHO, World Health Organization

[a] Genotype B3 sequences are shown in the orange shading and genotype D8 sequences in the blue shading. WHO genotype B3 and D8 reference sequences are included, along with their GenBank accession numbers, and can be identified with the starting text "B3" or "D8". The four WHO-named strains that match Canadian sequences are included and begin with an asterisk (MVs/Gir Somnath.IND/42.16, MVs/Dagon Seikkan.MMR/5.18, MVi/Gombak.MYS/40.15 and MVi/Marikina City.PHL/10.18/). Canadian sequences are identified by their WHO name, which indicates province and week of rash onset (by number in the year, as assigned in accordance with WHO guidelines). Distinct sequence IDs, as identified and assigned by MeaNS, the WHO measles sequence database, are shown in brackets (4-digit number). Travel history is indicated where applicable with "ex:<country name>." Outbreaks are represented by a single sequence. These sequences are tagged with their outbreak number in accordance with Table 1 and with the number of identical sequences identified in the outbreak in brackets. The remaining sequences (without an outbreak number listed) are from non-outbreak-related cases (n=35). The scale bar indicates number of nucleotide differences between branches

Outbreaks

Ten measles outbreaks were identified for a total of 74 cases (**Table 4**). Seven of the 10 outbreaks were small (from 2 to 3 cases per outbreak), with limited transmission to household contacts or other close contacts of the index case. Three outbreaks were larger (from 12 to 34 cases per outbreak), with community-level transmission.

The WHO-named strain MVs/Gir Somnath.IND/42.16 was the most frequently detected in 2019. In total, 46 measles cases were identified with this strain (41% of all cases), and these cases were associated with six distinct outbreaks and 14 sporadic cases for a total of 20 chains of transmission. In the longest sustained outbreak associated with this strain, Outbreak 10, illness onset occurred during the week ending June 15 in the earliest case and during the week ending August 24 in the last case.

Table 4: Summary of measles outbreaks in Canada (N=10), by earliest date of rash onset, 2019

Outbreak number	Province/ territory	Number of cases (number of generations)	End date of the epidemiologic week of rash onset of index case	Genotype (WHO-named strain, if applicable, MeaNS Distinct Sequence ID)[a]	Description
1	British Columbia	13 (n=5)	February 2	D8 (MVs/Gir Somnath.IND/42.16, 4683)	• Three co-index cases reported travel to Viet Nam • 10 subsequent cases were reported later • Primary exposure occurred in two schools • Four of the 13 cases (31%) had at least one documented dose of measles-containing vaccine
2	Northwest Territories	2 (n=2)	February 16	B3 (MVi/Marikina City.PHL/10.18, 5306)	• The index case reported travel to the Philippines • The secondary case was a contact of the index case • The index case was unvaccinated • The secondary case had two documented doses of measles-containing vaccine prior to exposure

Table 4: Summary of measles outbreaks in Canada (N=10), by earliest date of rash onset, 2019 (*continued*)

Outbreak number	Province/ territory	Number of cases (number of generations)	End date of the epidemiologic week of rash onset of index case	Genotype (WHO-named strain, if applicable, MeaNS Distinct Sequence ID)[a]	Description
3	British Columbia	2 (n=2)	March 9	D8 (MVs/Dagon Seikkan.MMR/5.18, 5551)	• The index case reported travel to the US • The secondary case was a family contact of the index case • The index case was unvaccinated • The secondary case had two documented doses of measles-containing vaccine prior to exposure
4	British Columbia	2 (n=2)	March 9	D8 (MVs/Gir Somnath.IND/42.16, 4683)	• The index case reported travel to Viet Nam • The secondary case was a family contact of the index case • The index case was unvaccinated • The secondary case had one documented dose of measles-containing vaccine prior to exposure
5	Ontario	2 (n=2)	March 23	B3 (N/A, 5622)	• The index case reported travel to Bangladesh • The secondary case was a household contact of the index case • The index case was unvaccinated • The secondary case had one documented dose of measles-containing vaccine
6	New Brunswick	12 (n=3)	April 27	D8 (MVs/Gir Somnath.IND/42.16, 4683)	• The index case reported travel to various countries in Europe • The secondary case was a healthcare contact of the index case • 10 tertiary cases followed after exposures in a school and in the community • The index case was unvaccinated • 10 of the 11 subsequent cases had at least one documented dose of measles-containing vaccine • Nine of the cases (75%) in this outbreak had two documented doses of measles-containing vaccine
7	Québec	3 (n=2)	May 4	B3 (N/A, 5852)	• The index case reported travel to France • Two secondary cases were contacts of the index case • The index case was unvaccinated • One of the secondary cases was unvaccinated, while the other had two documented doses of measles-containing vaccine
8	Alberta	2 (n=2)	May 18	D8 (MVs/Gir Somnath.IND/42.16, 4683)	• The index case reported travel to Viet Nam and Thailand • The secondary case was a workplace contact • Neither case had any documented doses of measles-containing vaccine
9	Ontario	2 (n=2)	June 1	D8 (MVs/Gir Somnath.IND/42.16, 4683)	• The index case did not report travel outside of Canada during the exposure period • The secondary case was a household contact • Neither case had any documented doses of measles-containing vaccine
10	Québec	34 (unknown)	June 15	D8 (MVs/Gir Somnath.IND/42.16, 4683)	• The index case reported travel to an area of heightened measles activity in the US • Several generations of transmission were linked to a shopping mall and a non-vaccinating community in the Montréal area • 32 cases, including the index case, were unvaccinated • Two cases had at least one documented dose of a measles-containing vaccine

Abbreviations: ID, identifier; MeaNS, Measles Nucleotide Surveillance; US, United States; WHO, World Health Organization

[a] GenBank accession number for the listed named strains are KY120864, MN602382 and MN602384

Verification of measles elimination through national and international goals and targets

The data in this report are provided as evidence in support of the ongoing verification of measles elimination in Canada, for which the PAHO has set out four essential criteria (9). Based on the information available, Canada met or partially met three of the four criteria in 2019 (**Table 5**).

Table 5: Pan American Health Organization essential criteria for the verification of measles elimination

Criterion	Indicator
Verify the interruption of endemic measles cases for a period of at least 3 years from the last known endemic case, in the presence of high-quality surveillance	Criterion met Canada achieved measles elimination status in 1998. Since then, molecular and epidemiologic data continue to demonstrate that no viral strain has circulated for a period of ≥1 year (Figure 4) (4,16–19)
Maintain high-quality surveillance sensitive enough to detect imported and import-related cases	Criterion partially met In Canada, national measles surveillance conducted through CMRSS consists of confirmed case surveillance and does not capture the number of clinical or suspect cases investigated, which are investigated at the provincial and territorial levels. However, based on data obtained by the Measles and Rubella Surveillance Pilot Project (which does not include all provinces and territories), the national rate of suspected case investigations has been previously estimated to be between 12 and 19 per 100,000 population (17). Although the indicator cannot be met, the criterion has been met as the epidemiologic and laboratory evidence provided in this report indicates that Canada's measles surveillance capacity is sufficiently sensitive to detect imported and import-related cases and conduct case investigations
Verify the absence of endemic measles virus strains through viral surveillance	Criterion met Genotype information was available for 10/10 of outbreaks reported in 2019. Genotype information was also available for 90% of non-outbreak-related measles cases (35 genotyped of 39 cases)
Verify adequate immunization in the population	Criterion not met Canada currently measures (biennially) measles vaccination coverage rates at 2 and 7 years of age, and therefore is unable to assess measles vaccination coverage for all ages 1–40 years. The 2017 childhood National Immunization Coverage Survey estimated first dose measles-containing vaccine coverage in two year olds to be 90%, and two-dose measles-containing vaccine coverage in seven year olds to be 86% (5)

Abbreviation: CMRSS, Canadian Measles and Rubella Surveillance System

Discussion

There were 113 confirmed cases of measles reported in Canada in 2019, the majority of which were imported or import-related (90%) and unvaccinated against measles (71%). This is higher than the median number of cases reported from 1998 to 2018 (median of 32 cases per year), and coincides with a trend of increasing rates of measles globally since 2017 (2,20–22). The United States (US) had the greatest number of measles cases since 1992 in 2019. Over 73% of cases in the US were linked to outbreaks in New York, and the majority of the cases in these outbreaks were not vaccinated against measles (23). These US outbreaks had a direct impact on measles rates in Canada, with the largest Canadian outbreak of 2019 epidemiologically linked to a large outbreak in the US. Other large outbreaks in Canada were caused by unvaccinated travellers to Viet Nam and Europe, where outbreaks were also occurring in 2019. These outbreaks underscore the ongoing risk that any international travel places on the spread of measles in Canada, and validates PHAC's 2019 broadening of its travel health notice for measles exposure risk to any international travel, and not only to certain areas (24).

Globally, only four of the 24 recognized measles genotypes continue to be detected, genotypes B3, D4, D8 and H1, as a result of elimination efforts (4), and only genotypes B3 and D8 were detected in confirmed measles cases in Canada in 2019. The genotype classification system captures viruses with similar yet distinct genetic (N-450) sequences, and for effective molecular epidemiology, additional granularity is required. The WHO global measles rubella laboratory network developed a system of "named strains" that are defined in the MeaNS database and represent a lineage, a precisely defined virus strain with a specific N-450 sequence, that has been frequently detected within a 2-year period in multiple countries (11). In addition, the MeaNS database assigns a 4-digit identifier to all distinct or unique N-450 sequences within the database. All sequences obtained from cases of measles with the same N-450 sequence will share the same distinct sequence ID. In this way, all possible genetic sequences of reported measles cases can be tracked with their distinct sequence ID and some will also be designated as belonging to a named strain lineage, representing those with broader circulation. In 2019, 19 distinct sequence IDs, including four named strains, were identified in the 73 confirmed cases of measles that were genotyped.

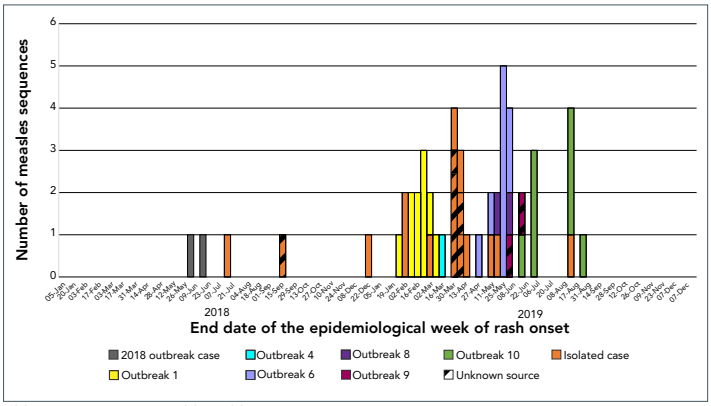
The WHO-named strain MVs/Gir Somnath.IND/42.16 was the only strain detected in 2019 that was also detected in a handful of cases in 2018 (16). This strain has been circulating globally since 2018, based on submissions to the MeaNS database, as reflected in the number of cases with travel history associated with this strain both in 2018 and 2019 (**Figure 4**). In 2018 to 2019, 51 measles cases were identified with this strain and these cases were associated with seven distinct outbreaks and 17 sporadic cases for a total of 24 chains of transmission. The time between illness onset in the first and last cases in the longest

sustained outbreak associated with this strain was 70 days, which is far short of the 12 months of ongoing transmission that would signal endemic circulation. The detection of this strain in a large number of chains of transmission over an extended time demonstrates the value of integrating laboratory and epidemiologic data and necessitates the adoption of extended genotyping methods.

Both in Canada and abroad, maintaining high vaccination coverage rate with measles-containing vaccine requires a sustained public health effort and is an essential component of a strategy for achieving and maintaining measles elimination. As in previous years, the large majority of measles cases were unvaccinated, highlighting the importance of adhering to vaccination guidelines (16,17,25–27). Only one in five measles cases in 2019 had received two doses of measles vaccination, including five cases who were aged younger than one year and not yet eligible to receive the first routine dose of measles-containing vaccine under the routine vaccination schedule (25).

The age distribution of measles cases reported in 2019 was similar to that seen in previous years, with younger age groups affected to a higher degree than older age groups (16–18). Of note, over half of the measles cases in the 15–24 year age group had received two doses of measles-containing vaccine. The majority (n=7) of the fully vaccinated cases from this age

Figure 4: Number of measles cases with genotype D8, WHO-named strain MVs/Gir Somnath.IND/42.16 detected in 2018 and 2019 (n=51), by epidemiologic week of rash onset, chain of transmission status and source of exposure, Canada[a]



Abbreviation: WHO, World Health Organization

[a] Chains of transmission (outbreak or sporadic case) are identified by colour with 2019 outbreaks numbered as per Table 4. Solid bars reflect cases with known source of exposure. Bars with diagonal stipes indicate cases with unknown source

group were related to a large outbreak in a secondary school in which many students were exposed. Given the large number of individuals exposed in this outbreak, some breakthrough cases, or cases that developed measles despite being fully vaccinated, would be expected even with high vaccine coverage. In addition, seroepidemiology conducted in the province of Ontario has found that this age group may have waning immunity to measles (28). Breakthrough cases may have either failed to develop an appropriate immune response; their immunity may have waned to non-protective levels by time of exposure; or the vaccine they were given may have been stored, handled or administered improperly (29,30).

Based on the information available, Canada met or partially met three of the four PAHO essential criteria for the verification of measles elimination in 2019. Canada falls short of the criterion regarding measles-containing vaccine coverage. Canada currently measures (biennially) measles vaccination coverage rates at 2 and 7 years of age, and therefore is unable to assess measles vaccination coverage for all ages between 1 and 40 years, as set out in the PAHO elimination framework. The 2017 estimate for two year olds receiving measles-containing vaccine is 90% and for seven year olds receiving the second dose of measles-containing vaccine is 86%, below the PAHO indicator of 95% (5). This estimate is derived from a survey that collected data from parent-held vaccination records, in which some information may be incomplete, erroneous or missing altogether. As vaccine doses with missing or invalid date are not counted in the calculation of coverage, the survey most likely underestimates coverage.

Strengths and limitations

This report has several limitations that bear consideration. Only measles cases that interact with the Canadian health system are captured in enhanced measles surveillance, and therefore cases with mild symptoms or visitors to Canada who do not seek health care may not be detected. Other federal or provincial surveillance systems may use case attribution methods that differ from CMRSS, which can cause discrepancies in annual case counts (31). Information on mortality and detailed information on morbidity (e.g. length of hospitalization, sequelae) are not currently captured by CMRSS, limiting the ability to completely describe the burden of illness due to measles. However, despite these limitations, this report serves to provide a detailed picture of measles in Canada in 2019 through an integrated analysis of both laboratory and epidemiologic case data for all reported cases.

Conclusion

The occurrence of measles cases and subsequent measles outbreaks in Canada in 2019, which were largely due to measles importations, underscore the importance of continued enhanced measles surveillance and efforts to increase vaccine uptake across the country. Although importation of measles and areas of low vaccination coverage continue to challenge Canada's elimination status, the laboratory and epidemiologic evidence provided by this report indicates that endemic transmission of the measles virus has not been re-established in Canada.

Authors' statement

CC — Methodology, software, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, visualization
FRD — Conceptualization, methodology, formal analysis, writing–original draft, writing–review and editing, project administration
JH — Methodology, validation, investigation, data curation, writing–original draft, writing–review and editing
SS — Conceptualization, methodology, writing–review and editing, project administration

Competing interests

None.

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Knowledge brokering on infectious diseases for public health

Margaret Haworth-Brockman[1,2]*, Yoav Keynan[1,2,3]

Abstract

The National Collaborating Centres (NCCs) for Public Health (NCCPH) were established in 2005 as part of the federal government's commitment to renew and strengthen public health following the severe acute respiratory syndrome (SARS) epidemic. They were set up to support knowledge translation for more timely use of scientific research and other knowledges in public health practice, programs and policies in Canada. Six centres comprise the NCCPH, including the National Collaborating Centre for Infectious Diseases (NCCID). The NCCID works with public health practitioners to find, understand and use research and evidence on infectious diseases and related determinants of health. The NCCID has a mandate to forge connections between those who generate and those who use infectious diseases knowledge.

As the first article in a series on the NCCPH, we describe our role in knowledge brokering and the numerous methods and products that we have developed. In addition, we illustrate how NCCID has been able to work with public health to generate and share knowledge during the coronavirus disease 2019 (COVID-19) pandemic.

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Keywords: public health, infectious diseases, knowledge brokering, Canada, COVID-19

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Introduction

The National Collaborating Centres (NCCs) for Public Health (NCCPH) were established in 2005 as part of the Canadian federal government's commitment to renew and strengthen public health following the severe acute respiratory syndrome (SARS) epidemic. The NCCs were set up to support knowledge translation for more timely use of scientific research and other knowledges in public health practice, programs and policies in Canada (1). Funded by the Public Health Agency of Canada (PHAC), each of the six NCCs is hosted at a university or government-based organization and focuses on a specific public health area: Determinants of Health, Environmental Health, Healthy Public Policy, Indigenous Health, Infectious Diseases and Knowledge Translation Methods and Tools (1).

The National Collaborating Centre for Infectious Diseases (NCCID) is hosted at the University of Manitoba and works with public health practitioners to find, understand and use research and evidence on infectious diseases and underlying determinants that affect disease distribution, impact and effective mitigation strategies. Our eight staff forge connections between those who generate and those who use infectious diseases knowledge related to a wide range of topics, including antimicrobial resistance and stewardship, sexually transmitted and blood-borne infections (STBBI), vaccine preventable diseases, tuberculosis (TB) and emerging infections.

As the first article in a series on the NCCPH, we describe knowledge translation role, specifically as knowledge brokers (2,3) and our numerous methods and products, and then illustrate how NCCID has been able to work with public health to nimbly and responsively mobilize knowledge during the coronavirus disease 2019 (COVID-19) pandemic.

A program science framework for knowledge brokering

Every year, NCCID undertakes a variety of projects, based on consultations with stakeholders and evidence of existing knowledge gaps. Events and resources are developed in consultation with partners across Canada, although they are often tailored for specific audiences or regional contexts. Wherever possible, we work with the other NCCs to ensure greater applicability and relevance.

The NCCID uses a program science framework to organize our work and to focus on the stages of public health interventions. Program science is a systematic application of theoretical and empirical scientific knowledge to improve the design, implementation and evaluation of public health programs (4). It enables a rigorous commitment to understanding the different

types of evidence that are needed and that can be acted upon in specific contexts (5). This framework allows us to demonstrate the interrelatedness of policy and practice-related evidence in different topic areas, while emphasizing the context and circumstances for promising practices in three areas: 1) drivers and burdens of infectious diseases—relating to the program science domain of surveillance; 2) public health responses and interventions—relating to the same domain in program science; and 3) systems and policy for monitoring infectious diseases—relating to the program science domain of monitoring and evaluation (6) (**Table 1**). In so doing, we illustrate overarching approaches that are applicable to several diseases and desired public health outcomes, especially in terms of health equity approaches for syndemics and for disadvantaged populations.

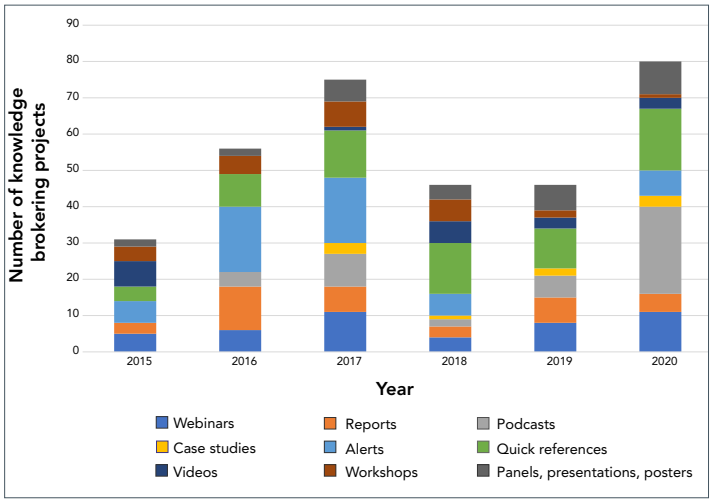
Table 1: Examples of National Collaborating Centre for Infectious Diseases' knowledge brokering topic areas within a program science framework[a]

Program science areas	Knowledge brokering topics	Intended outcomes
Drivers and burden of infectious diseases	• Drivers and burden of specific diseases • Drivers and burden in certain populations • Surveillance evidence	CHOOSE • Best strategy • Right populations • Right time
Public health responses and interventions	• Appropriate responses for TB, STBBIs, AMR, etc. • Public health for mobile populations • Promising case studies for harm reduction • Point-of-care testing • Improving vaccine confidence	DO • The right things • The right way
Monitoring and evaluation	• Uses for big data in public health • TB program performance indicators for improved equity • AMR surveillance resources	ENSURE • Appropriate scale • Efficiency • Change, when needed

Abbreviations: AMR, antimicrobial resistance; STBBIs, sexually transmitted and blood-borne infections; TB, tuberculosis
[a] Adapted from Aral and Blanchard (5)

Knowledge brokering has been defined as both a process and a product (7,8). The NCCID undertakes different types of projects within the three program science areas (**Figure 1**). The first type of project relates to creating and fostering knowledge exchange among public health personnel at all levels; convening webinars, panel presentations, workshops and gatherings. The NCCID brings together community, policy, clinical and academic experts from several jurisdictions to discuss issues and share successful (and not-so-successful) public health strategies. Facilitated conversations, enabled by NCCID, encourage thoughtful consideration of timely questions. Using newer formats, such as fishbowl discussions (9), expert commentaries, and pre-taped seminars, provides more time for presenters and participants to have lively discussions on content.The NCCID develops and disseminates new knowledge products that apply evidence

Figure 1: National Collaborating Centre for Infectious Diseases' knowledge brokering projects by type and year, 2015–2020



to specific public health practice and policy contexts. These knowledge products include podcasts, animated videos and plain-language case studies, as well as more traditional realist, scoping, and narrative reviews and journal papers. We tailor knowledge products to meet the specific needs of public health nurses, medical officers, policy analysts, students and front-line providers.

NCCID has integrated three overarching priorities across disease topics. The first priority is a focus on the mobility of populations in Canada. Earlier projects on public health approaches for refugees and asylum seekers, and on communities evacuated due to fires and floods (10), highlighted the need for knowledge brokering on the effects of migration into and within Canada. For example, collecting data on and managing TB and syphilis outbreaks are complicated when patients have to move (11), including from rural areas to cities and towns (12). Syndemics of STBBIs and TB, combined with growing epidemics of opioid and crystal methamphetamine use, are further complicated by movement, incarceration and jurisdictional divides (13,14).

The second priority for NCCID is to address inequities in public health responses to communicable diseases in rural and remote communities. While resources are strained in all public health units, this is especially true outside of the main urban centres. As well as working with public health personnel to understand the particular drivers of infectious diseases in rural, remote and northern regions—including factors associated with stigma and poor mental health—NCCID serves as a secretariat for the Rural, Remote and Northern Public Health Network of public health physicians, and partners with Indigenous scholars and health authorities on First Nations, Métis and Inuit-specific approaches to address TB, STBBIs and vector-borne illnesses.

The third priority for NCCID is to support opportunities for using big data for infectious disease surveillance, prevention, control

and monitoring. The NCCID has been at the forefront of creating opportunities for knowledge exchange between mathematical modellers and public health personnel (15,16). We recently started new collaborations with leading Canadian big data consultants to help demonstrate how big data can be used to plan and assess public health interventions.

The use of the program science framework allows NCCID to apply knowledge brokering methods and approaches across a number of topic areas. For example, NCCID is consistently explicit about which communities are disadvantaged (e.g. by geographic location, by systemic and historic racism or by inappropriate or inadequate public health and health care services) and which inequities can be mitigated to reduce disease burden. In the program science domain of public health responses, we highlight promising practices used to control one disease in a specific location that can be adapted to respond to another (e.g. providing evidence on rapid responses to curtail HIV outbreaks in Indiana that can be adapted to address rising hepatitis C in the Canadian Prairie Provinces (17). In the domain of monitoring and evaluation, NCCID projects that encourage disaggregated and cross-tabulated indicators for monitoring public health program performance (18) have been adapted to support health equity integration in public health organizations (19).

National Collaborating Centre for Infectious Diseases in the time of COVID-19

With evidence in early January 2020 of a new COVID-19 that was likely to be transmitted beyond Asia, NCCID developed a new Quick Links resource for public health personnel, collating key information from the World Health Organization, PHAC and the Centers for Disease Control and Prevention. More thorough descriptions were developed into a Disease Debrief and posted online a week later. The information summary was updated throughout 2020 to keep up with the changes in clinical and epidemiological knowledge related to the pandemic.

By late January 2020, it was clear that the new disease was going to require more attention from public health both in Canada and around the world. The NCCID rapidly initiated a series of podcasts on many significant aspects of COVID-19, providing public health audiences with brief answers to commonly asked questions, and summarizing the latest evidence from experts across Canada. There are now 20 podcast episodes available for public health physicians, nurses, field inspectors and policy analysts which have been downloaded over 1,200 times to date, and were rated among the 30 best public health podcasts series in North America by MPH Online, an independent online resource for public health students.

The flexibility of NCCID's arrangements with PHAC allowed us to offer and follow through on a number of COVID 19 projects throughout 2020. These projects included supporting knowledge brokering via new Canadian Institutes of Health Research grants (eight grants to date), creating a hub for the Canadian Public Health Laboratory Network guidelines, developing a series of webinars to introduce mathematical modelling concepts to public health audiences and to delve into how models are used to plan COVID-19-related measures (over 350 attendees). In addition, the NCCID connected Canadian modelling experts to colleagues in Medellin, Colombia to support their ongoing modelling for public health. In the winter of 2020–2021, NCCID co-hosted PHAC's information webinars on the new COVID-19 vaccines (over 5,000 attendees).

In the context of population migration and rural, remote and northern equity concerns, NCCID staff and students are conducting more long-term projects. These projects include a forthcoming analysis of equity considerations of clinical treatment decision processes and the development of new models to predict longer-term outcomes of school closures (20) and isolation measures in long-term care facilities.

Contributions to public health competencies in infectious diseases

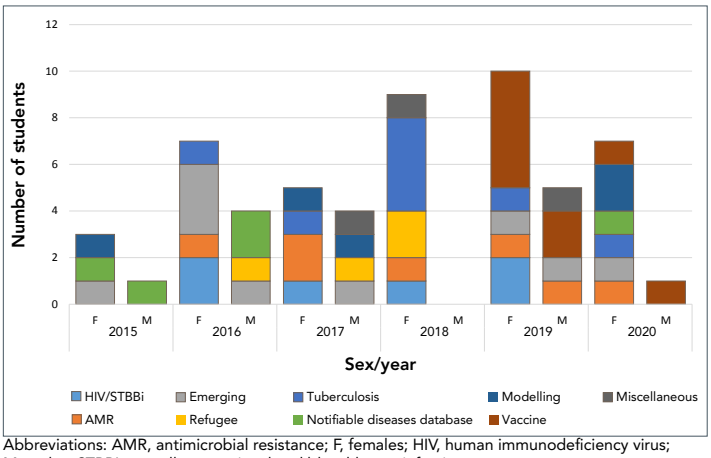
The activities of the NCCID align with key areas of focus within the Canadian public health system in several ways. The NCCID contributes to the Chief Public Health Officer's overall goal of leveling "the playing field" (21) in the prevention and control of COVID-19, TB, STBBIs and antimicrobial resistance by fostering action on the determinants of health and strengthening multi-sectoral partnerships. The NCCID encourages cross-jurisdictional sharing of tried and successful approaches to reaching underserved populations.

Our academic and public health partnerships create teaching and mentorships opportunities for students, particularly in the following core competencies (22):

- Prevention and control of infectious diseases
- Emergency responses
- Assessment, analysis and program planning

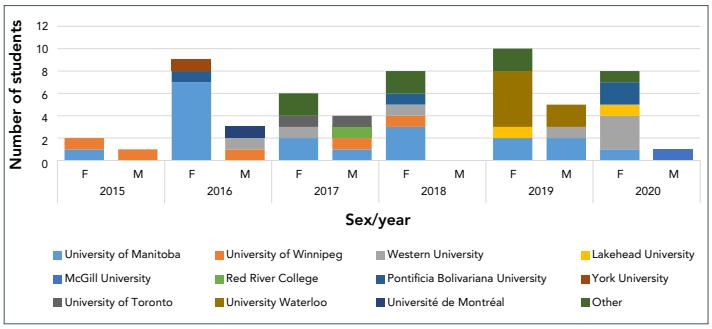
Undergraduate and post-graduate students in public health, medicine, basic sciences, nursing, communications and sociology are among the more than 40 trainees who have developed new skills in knowledge brokering at NCCID (**Figures 2** and **3**). Over time, NCCID has also drawn in participants from other sectors to encourage knowledge sharing to improve public health interventions for infectious diseases prevention and control.

Figure 2: Number of students at the National Collaborating Centre for Infectious Diseases, by research topic, by sex, and by year, 2015–2020



Abbreviations: AMR, antimicrobial resistance; F, females; HIV, human immunodeficiency virus; M, males; STBBI, sexually transmitted and blood-borne infections

Figure 3: Number of students at the National Collaborating Centre for Infectious Diseases, by home university, by sex, and by year, 2015–2020



Abbreviations: F, females; M, males

Conclusion

A knowledge broker adapts "to the social and technical affordances of each situation, and fashions a unique and relevant process to create relationships and promote learning and change" (23). This description aptly describes the role of NCCID. Analysis of the year-over-year increasing reach, uptake and impact of our activities and products confirm that our approach has value for public health audiences in Canada. By working with the other NCCs, and across disciplines, sectors and jurisdictions, NCCID optimizes the gathering and dissemination of knowledge, mobilization, facilitates development of networks and partnerships, and draws attention to knowledge gaps and issues for underserved populations. Our ability to bring to the table issues such as housing and addictions is critical for addressing determinants that often underlie disease transmission.

Authors' statement

MHB — Original concept, initial drafts, final revisions
YK — Original concept, substantive input, review of drafts

Competing interests

None.

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Designing tailored interventions to address barriers to vaccination

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Abstract

Despite efforts to promote vaccination and make vaccination services easily accessible, vaccination coverage rates remain below the target rate for many vaccines in various jurisdictions. The Tailoring Immunization Programmes (TIP) approach was developed by the World Health Organization Regional Office for Europe to support efforts of countries to achieve high and equitable vaccination uptake. In this Canadian Vaccination Evidence Resource and Exchange Centre (CANVax) series, we present key insights from the TIP planning framework to assist vaccine program planners, policy makers and vaccine providers to identify the interventions that will lead to increased vaccine uptake. The TIP is a phased approach that involves the following: 1) a clear diagnosis of the root cause of low vaccination; 2) an intervention based on this understanding; and 3) an evaluation of the implementation process and the impact of the interventions. At the provider-patient level, the approaches and insights of the TIP planning framework could inform vaccination consultation by emphasizing the importance of engaging with and listening to the patients and caregivers, and responding to their needs.

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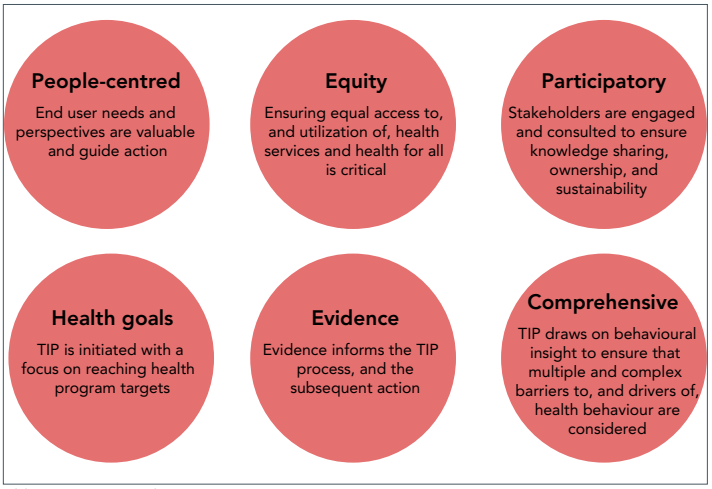
Keywords: vaccine acceptance, vaccine hesitancy, interventions, evaluation, Tailoring Immunization Programmes (TIP)

Introduction

Despite efforts to promote vaccination and make vaccination services easily accessible, vaccination coverage rates remain below the target rate for many vaccines in various jurisdictions. How can we develop effective interventions to increase vaccine acceptance and uptake? This Canadian Vaccination Evidence Resource and Exchange Centre (CANVax) series presents some insights based on the Tailoring Immunization Programmes (TIP) approach (1). The TIP approach was developed by the World Health Organization (WHO) Regional Office for Europe to support countries in their efforts to achieve high and equitable vaccination uptake. The underlying principle of this approach is that it is necessary to understand the barriers to vaccination among the population groups with suboptimal coverage before embarking on any plans for interventions. The key principles guiding TIP approach are highlighted in **Figure 1.** The TIP is a comprehensive and phased approach that requires the investment of time and resources. Even if your organization does not conduct a full TIP evaluation, the key insights provided in this article will help you to design an effective intervention to enhance vaccine acceptance and uptake.

Figure 1: Values and principles guiding Tailoring Immunization Programmes



Abbreviation: TIP, Tailoring Immunization Programmes

The TIP approach, while designed for use at the national level, is also applicable at the patient-provider level. The TIP approach and resultant insights can inform the planning of vaccine consultations in a healthcare providers' office.

The objective of this CANVax is to illustrate, through the use of a fictitious case study, how key approaches used by the TIP planning framework could assist vaccine program planners, policy makers and vaccine providers coming up with the right intervention leading to increasing vaccine uptake.

This is the eleventh in a series of articles, produced by CANVax—an online database that supports immunization program planning and delivery. This series includes both the identification of existing resources and the description of the new resources developed by a multidisciplinary group of professionals (2). The article is one of a series and shows how the various aspects of vaccine hesitancy that have been considered to date can be applied to fostering vaccine acceptance.

Canadian case study

Case study part 1:
A school-based program of vaccination against the human papillomavirus (HPV) was implemented in your jurisdiction in 2008. After the first year of the program, the vaccine coverage rate was found to be above 80%. However, in the years following the first year, the HPV vaccine coverage rates were found to be declining. To improve the vaccine coverage rate, an educational campaign targeting the parents of students was implemented last year and training sessions for school nurses were offered. Despite these interventions, the HPV vaccine uptake rates are still declining. What can be done?

The WHO TIP approach offers a method to diagnose the barriers to, and drivers of, vaccination in specific subgroups and to design appropriate interventions to address these populations. The TIP approach uses social and behavioural insight methods (i.e. people-centred research and social sciences methods) to design and evaluate interventions for behaviour change. For more information on TIP, see *TIP Tailoring Immunization Programmes (2019)* (2).

The first step in the process is to understand the problem and explore the reasons behind it to fully understand the barrier(s).

1. Tailoring Immunization Programmes insight: Diagnose the problem—do not just guess

Often, the causes of low vaccination coverage rates are not understood, and the interventions are designed based on experts' intuition rather than on actual data.

- "We have tried that in the past and it worked."
- "If only they knew how safe and effective vaccines are, they would vaccinate."

In contrast, the TIP approach emphasizes that the very first step to finding a solution is to have a good understanding of the root cause of the problem. This can do this by

- Looking at the relevant studies conducted in your jurisdiction
- Questioning front-line health providers, the students/parents/potential recipients, members of the local community and/or other key stakeholders

The aim is to identify the main barriers to, and drivers of, the intended immunization behaviour in the target group:

- Is the problem related to vaccination services? To a lack of awareness? To misinformation in social media? Only by having a good understanding of the causes of the problem will you be able to develop an effective intervention.

Case study part 2:
Interviews were conducted with school nurses and parents to assess their opinions regarding the school-based HPV vaccination program. Findings showed that an important barrier to HPV vaccination in school-based programs was related to the informed consent process. Parents reported that they did not know they needed to sign and return the form to the school nurse to have their child vaccinated. Nurses noted that the short time period between the distribution of informed consent forms to students and the vaccination day prevented them from sending reminders to parents.

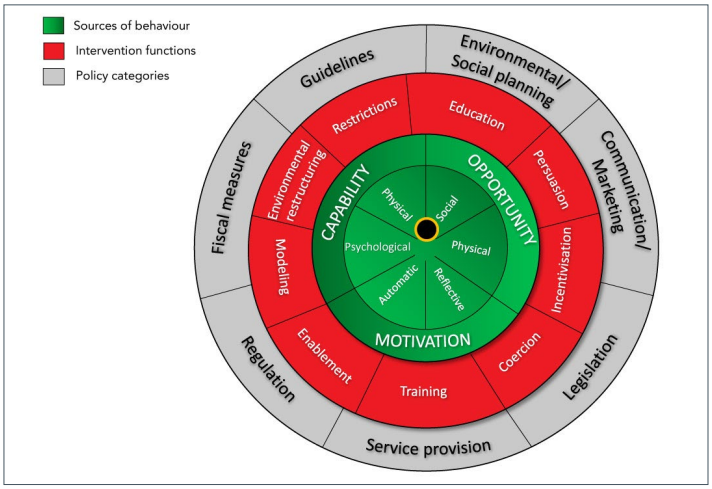
2. Tailoring Immunization Programmes insight: Design the tailored intervention

Once you have a good understanding of the root cause of the problem, the next step is to design an intervention based on both this understanding and the resources available. If the issues are about access to vaccination services, then interventions aimed to inform people about the risk and benefits of vaccines will not be effective. If lack of awareness is the main cause of under-vaccination, this needs to be addressed first.

Generally, interventions that have multiple components are more effective than single-component interventions. For example, even a simple intervention such as a change in clinic hours requires communication to the community—not just announcing the hours of change on the clinic door. The Behaviour Change Wheel model (see **Figure 2**) can help inform the design of the intervention to address health behaviours by highlighting the relevant types of interventions, depending on the barriers and drivers identified (2). The TIP approach has adapted this model for vaccination-related concerns (1). Note there are multiple components that need to be considered.

Additional information on effective interventions to increase vaccine acceptance and uptake can be found on the CANVax fact sheets (2).

Figure 2: Behaviour Change Wheel



Case study part 3:
The qualitative evaluation has identified "opportunity" barriers related to the organization of vaccination services. An intervention is then designed based on the distribution of informed consent forms to parents by teachers at the beginning of the school year; in addition, an email reminder is sent one month prior to the vaccination day to: 1) remind parents about the upcoming vaccination; 2) ask them to return the signed consent form; and 3) give the contact information of the school nurse in case parents have questions about vaccination. An evaluation of the feasibility and impact of this intervention is ongoing.

3. Tailoring Immunization Programmes insight: Implementation and Evaluation

Too often, the work of improving an immunization program stops after the interventions have been implemented. When possible, a good practice is to evaluate the implementation process and the impact of the interventions. Even if you are not conducting a large study, try to evaluate how the interventions were implemented and check whether there was an increase in vaccine uptake. This could be done using regular vaccination program monitoring activities (e.g. coverage assessment before and after the implementation of the intervention). Examples of such evaluation include formal surveys or interviews, or simply by speaking with the people involved in the process to assess the implementation so far and the successes and shortcomings experienced.

4. Tailoring Immunization Programmes insight: Approaches that healthcare providers could use to increase vaccine uptake among their patients and in their community

The driving premise of the TIP approach is that to make vaccination a possible, desirable and positive experience, it is important to engage with and listen to the patients and caregivers and to respond to their needs (1). The values and principles of TIP emphasize that end-user needs and perspectives are valued and guide actions (see Figure 1).

- Ask your patient

The underlying principle of the TIP approach is that it is necessary to understand the barriers to vaccination. In the healthcare providers office, this could simply mean exploring why the patient or caregiver is hesitant to get vaccinated. Eliciting the real reasons behind the reluctance would assist the healthcare provider to address the barrier specifically and effectively. An earlier CANVax brief on motivational interviewing provided practical tools and examples how such conversation could play out (3).

- Take the time, work as a team

The TIP approach proposes that the encounter between the patient and the healthcare provider is a critical moment in vaccination decision-making. It is often heard from both providers and patients that vaccination consultations are short and thus provide for only superficial or limited discussions. However, when applying the motivational interviewing techniques (3), it is possible to provide a short and effective counselling about vaccination. With very hesitant patients/caregivers, more time may be required, so healthcare providers should schedule more time with these patients/caregivers to fully explore barriers and drivers to vaccination.

In many clinics, there are also allied health professionals who are often a great resource as they can take the time to answer patients/caregivers' questions regarding vaccination. It is important that from the time patients enter the clinic—and meet with the office coordinator, then a nurse, then the physician—that the culture and tone is set and consistent. If all the healthcare providers are "singing from the same song sheet", it is more likely that patients/caregivers will be supportive of vaccinations.

- Provide an example to imitate

Healthcare providers demonstrating their vaccination behaviors (e.g. confirm that they vaccinated themselves/their children) and using these behaviours both to promote good vaccination practice among themselves and to set an example for their patients is a TIP recommended activity.

- Share with your peers

The TIP advocates a formal evaluation process for measuring the impact of newly developed and implemented interventions for increasing vaccine uptake. However, a formal evaluation is not possible or practical in a healthcare providers' office. Instead, taking stock, sharing your experiences with identifying specific barriers and how you addressed them and what strategies

worked for you, and learning from your colleagues' experiences, can be extremely valuable.

Conclusion

In conclusion, TIP is a valuable and effective approach to designing interventions to address barriers to vaccination. It is based on the understanding of needs and realities of individuals and communities. Even if you are not doing a formal TIP project, you can apply the key principles guiding TIP (Figure 1) to design your intervention (1).

Key approaches used by the TIP planning framework could assist vaccine program planners, policy makers, as well as vaccine providers in tailoring vaccination services to meet the needs of patients and caregivers, particular groups where increasing vaccine uptake is necessary.

Authors' statement

KH — Conceptualization, writing–review and editing
NEM — Validation, writing–review and editing
ÈD —Validation, writing–original draft, review and editing

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

Competing interests

None.

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How COVID-19 vaccines will be regulated for safety and effectiveness

Source: International Coalition of Medicines Regulatory Authorities. ICMRA statement for healthcare professionals: How COVID-19 vaccines will be regulated for safety and effectiveness. http://www.icmra.info/drupal/en/covid-19/vaccines_confidence_statement_for_hcps

Health Canada, in collaboration with members of the International Coalition of Medicines Regulatory Authorities (http://www.icmra.info/drupal/en/aboutus) (ICMRA), released a statement about confidence in COVID-19 vaccines for health care professionals (http://www.icmra.info/drupal/covid-19/vaccines_confidence_statement_for_hcps). The statement aims to inform and help health care professionals answer questions about COVID-19 vaccines. It explains how vaccines undergo robust scientific evaluation to determine their safety, efficacy and quality and how safety will continue to be closely monitored after approval.

ICMRA brings together the heads of 30 medicines regulatory authorities from every region in the world, including Health Canada, with the WHO as an observer. Medicines regulators recognise their important role in facilitating the provision of access to safe and effective high-quality medicinal products that are essential to human health and well-being. This includes ensuring that the benefits of vaccines outweigh their risks.

Information on vaccines and treatments authorized for COVID-19 can be found on Canada's COVID-19 vaccines and treatments portal (https://covid-vaccine.canada.ca/). Weekly updated information about any adverse events that individuals have experienced following COVID-19 vaccine immunization can be found in the COVID-19 Vaccine Safety Report (https://health-infobase.canada.ca/covid-19/vaccine-safety/).

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