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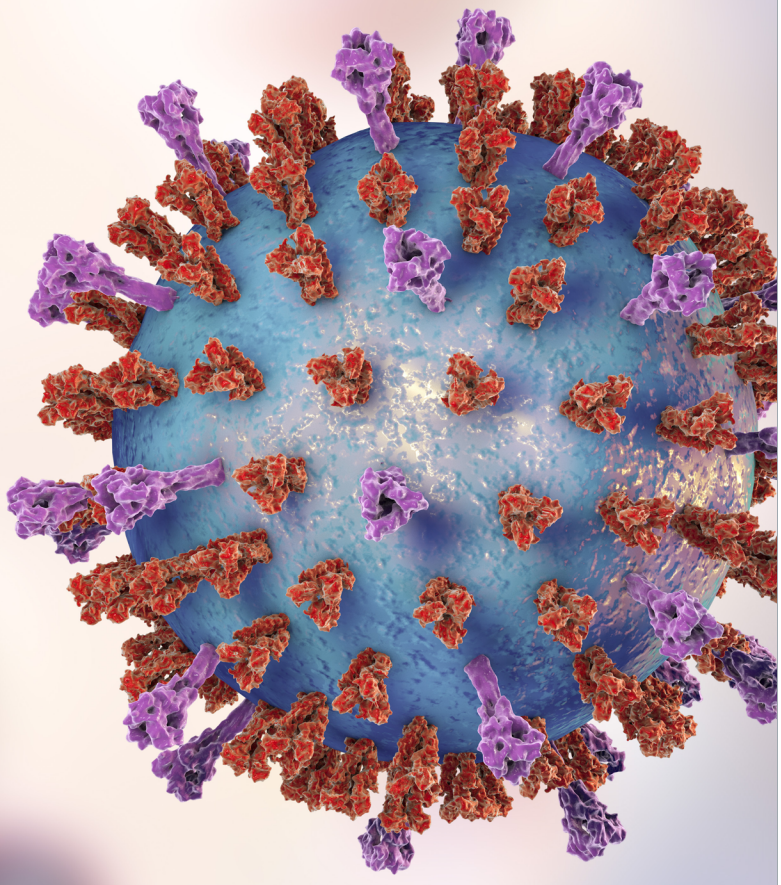
RESPIRATORY SYNCYTIAL VIRUS (RSV)



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The cover of this issue shows the respiratory syncytial virus (RSV) with two types of viral surface spikes. RSV causes the common cold. (https://www.shutterstock.com/image-photo/structure-medical-researches-quality-blurred-background-1350333653)

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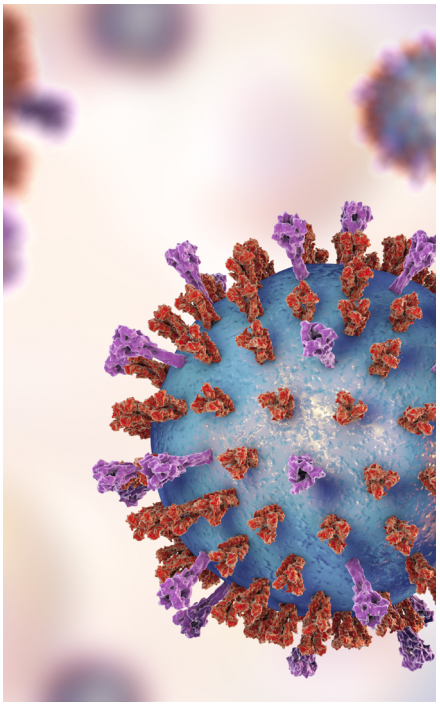

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RESEARCH

Overview of the respiratory syncytial virus vaccine candidate pipeline in Canada

April Killikelly[1], Matthew Tunis[1], Althea House[1], Caroline Quach[2], Wendy Vaudry[3], Dorothy Moore[4]

Abstract

A vaccine for respiratory syncytial virus (RSV) has been actively sought for over 60 years due to the health impacts of RSV disease in infants, but currently the only available preventive measure in Canada and elsewhere is limited to passive immunization for high-risk infants and children with a monoclonal antibody.

RSV vaccine development has faced many challenges, including vaccine-induced enhancement of RSV disease in infants. Several key developments in the last decade in the fields of cellular immunology and protein structure have led to new products entering late-stage clinical development. As of July 2019, RSV vaccine development is being pursued by 16 organizations in 121 clinical trials. Five technologies dominate the field of RSV vaccine development, four active immunizing agents (live-attenuated, particle-based, subunit-based and vector-based vaccines) and one new passive immunizing agent (monoclonal antibody). Phase 3 clinical trials of vaccine candidates for pregnant women, infants, children and older adults are under way. The next decade will see a dramatic transformation of the RSV prevention landscape.

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Keywords: vaccine, National Advisory Committee on Immunization, NACI, immunization, RSV, respiratory syncytial virus

Introduction

Respiratory syncytial virus (RSV) infection represents a large burden of disease in Canada and worldwide. The age distribution of RSV disease burden is bimodal, with the greatest impact felt in the first two years of life and in older adults. Annually, RSV disease is estimated to cause 3.4 million hospitalizations and 100,000 deaths globally (1). In Canada, the burden of RSV disease and hospitalizations are captured by various surveillance systems. Although preventive and supportive medical interventions exist to prevent or treat RSV, vaccination holds hope as a method to reduce the health and economic burden of RSV.

RSV is an orthopneumovirus in the Pneumoviridae family. It is a negative-sense, single-stranded RNA virus that has 11 proteins (2). The F protein on the surface of the viral membrane mediates fusion between the virus and the host cell. Two conformations of F have been defined, prefusion and postfusion. Some neutralizing epitopes are present on both conformations, notably site II targeted by palivizumab. Other neutralizing epitopes are present only on prefusion F, including the sites V (targeted by suptavumab) and ø (targeted by nirsevimab). Without specific stabilization or modification, the F protein will exist in a spectrum of conformations, which will have different antigenic and neutralization profiles. Without stabilization, this immunogen will settle into a postfusion conformation over time.

Two subtypes of RSV have been defined, RSV/A and RSV/B. Subtype A is more prevalent than subtype B (3). RSV infects cells in the human airway, including polarized, differentiated, ciliated epithelial cells, and causes infection of the upper and lower airways. Severe disease clinically manifests as influenza-like illnesses and lower respiratory tract infection (LRTI), with bronchiolitis the most common severe presentation in young children. Primary RSV infections can result in symptomatic LRTI, a minority of which require hospitalization. Canadian surveillance to capture the RSV burden in different populations is under way.

The only countermeasure currently available for RSV is palivizumab, a monoclonal antibody administered prophylactically to infants and children under two years of age at higher risk for severe infection.

A vaccine against RSV has been sought after for over 60 years for its potential impacts on the health outcomes for various age groups. A shadow was cast over vaccine development in the 1960s when a formalin-inactivated RSV (FI-RSV) vaccine was tested in seronegative children, that is, they were naive to RSV antigens. Instead of inducing protection, immunization resulted in enhanced respiratory disease (ERD) upon subsequent RSV infection, leading to two deaths (4–7).

Recently, RSV vaccine development has leveraged advances in understanding of T-cell biology and protein structure as well as a better delineation of different populations at risk for RSV. As of July 2019, 16 organizations were undertaking RSV vaccine development in 121 clinical trials. Vaccine candidates are in development for children, older adults and pregnant women. Phase 3 clinical trials that target pediatric, older adult and maternal populations are under way.

Five technologies dominate the field of RSV vaccine development: four active immunizing agents (live-attenuated, particle-based, subunit-based and vector-based vaccines) and one new passive immunizing agent (i.e. monoclonal antibody). Other trials are in late preclinical and early clinical stages.

The objective of this overview is to summarize the vaccine candidates in the five different vaccine technologies for three target populations and to identify current challenges to developing a vaccine for RSV.

Key Findings

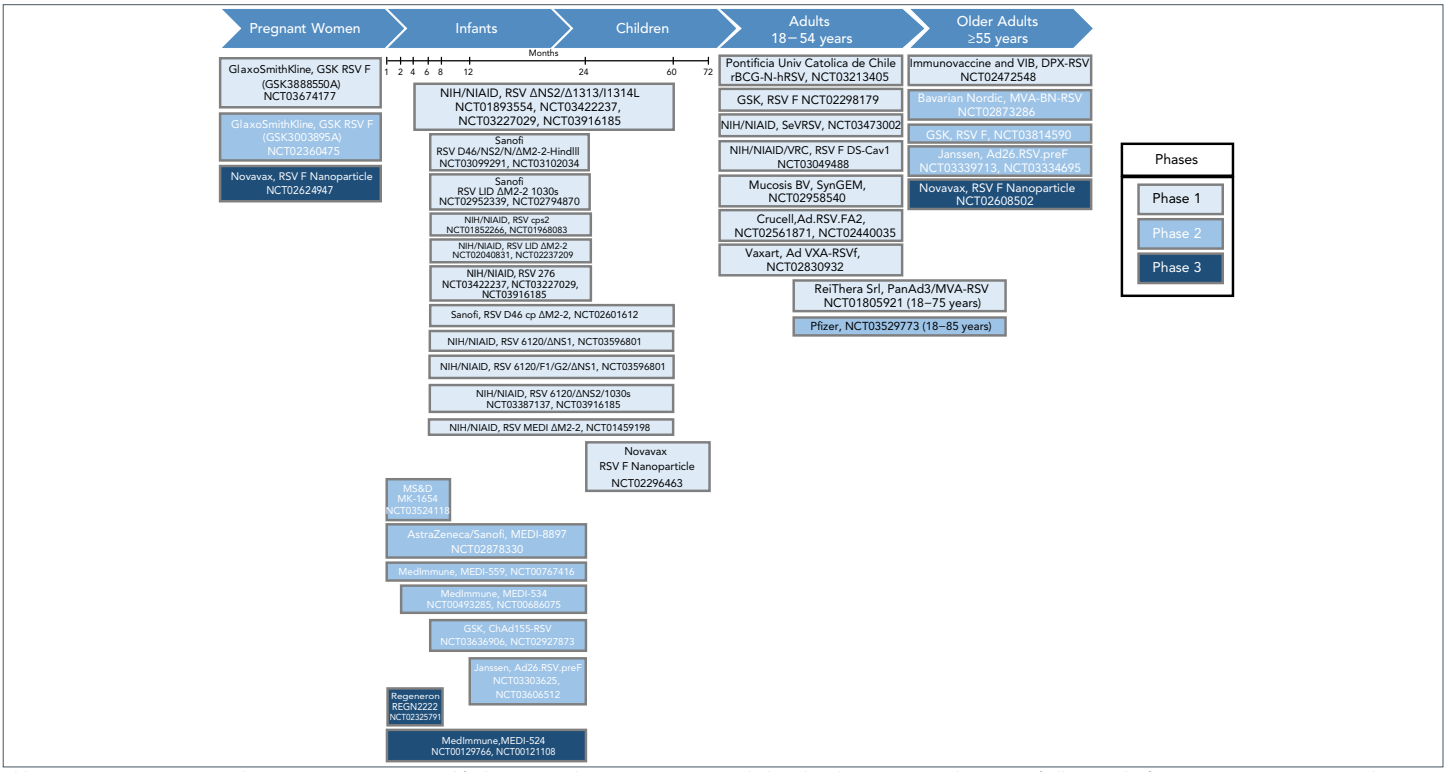
Immunization technologies and strategies

Clinical trials are under way for maternal, pediatric and older adult populations. Based on data collected through July 1, 2019, **Figure 1** represents the RSV vaccine products in development for each target population at risk for RSV. Phase 3 clinical trials that target maternal, senior adult and pediatric populations are under way. Below we summarize the developments for each vaccine candidate type, with an emphasis on products in later stages of clinical development (Stage 2 or 3 clinical trials).

Live-attenuated vaccines

Live-attenuated vaccines are versions of RSV that are able to replicate but have been modified to discourage severe disease. They can be created by traditional techniques (i.e. temperature or chemical sensitivity) or by reverse genetics to create an attenuated-replication competent vaccine. The challenge of this technique is to decrease the pathogenicity of the virus but to maintain the replicative function to stimulate immune responses. One of the key downsides, however, is the possibility of partial reversion to wild-type virus (9).

Figure 1: Summary of RSV vaccine target populations



Abbreviations: BN, Bavarian Nordic; DPX, DepoVax; MVA, modified Vaccinia Ankara virus; NCT, National Clinical Trial; NIAD, National Institute of Allergy and Infectious Diseases; NIH, National Institutes of Health; RSV, respiratory syncytial virus; SeVRSV, Sendai virus vectored respiratory syncytial virus; VRC, Vaccine Research Center
Note: Each box (listing the developing organization and the NCT number) represents a vaccine candidate in a phase of clinical development. As the phase of development increases the colour of the box becomes darker. These boxes are organized by the target population that closely aligns with the populations at risk for severe disease. As with other vaccines in development, early Phase 1 clinical trials that assess safety are done in healthy adults and later stages of clinical trials (Phases 2 and 3) are done in the target population of interest to assess efficacy and effectiveness
Adapted from: Graham (2019) (8)

This technique represents several advantages: possible needle-free delivery by intranasal administration; lack of enhanced disease (10); in the case of intranasal vaccines, replication in the presence of maternal antibodies (11); and stimulation of cellular and humoral immunity systemically and locally (12). No vaccine candidates of this type have progressed beyond Phase 2 clinical trials. The replicative nature of this type of vaccine and the reduced danger of ERD makes it an attractive strategy for seronegative infants.

Vector-based vaccines

Vector-based vaccines are created from components of the RSV virus inserted into a carrier vector, to create a chimeric vector. This chimeric vector replicates according to the carrier vector properties and induces immune responses to both the insert and carrier sequences. The intent is for the carrier vector to enhance responses to the RSV components. This platform is attractive for both pediatric and older adult populations due to the reduced risk of ERD. Unlike live-attenuated vaccines, the chimeric nature of these vectors means there is no risk of reversion to wild-type RSV. In addition, replicating vectors are able to boost the immune responses to the inserted sequences. Several companies are using variations of this platform as RSV vaccine candidates. (See infographic for an overview of the products from each manufacture).

- Bavarian Nordic (BN) is developing a vector from modified Vaccinia Ankara (MVA) virus, based on the orthopox virus used as a vaccine against smallpox. This vector is used to express several RSV antigens, including wild-type F, G, N, M2-1, and potentially other proteins. This candidate is in the Phase 2 clinical trials of MVA-BN-RSV in older adults [National Clinical Trial (NCT)02873286] for either a one or two-dose strategy via intramuscular route of administration. This trial has demonstrated that this vaccine induces both B and T-cell responses and neutralizing antibodies.
- GlaxoSmithKline (GSK) is developing a nonreplicating vector from Chimpanzee Adenovirus 155 (ChAd155), a simian adenovirus engineered by GSK to produce F, N and M2-1. The version of RSV F protein inserted into this vector lacked the transmembrane domain and the conformation of F is unknown. In adults, this intramuscular vaccine was safe and well-tolerated and induced cellular and humoral immune responses. This vaccine is currently in Phase 2 clinical trials in seropositive infants aged six months and older (NCT03636906). Phase 2 clinical trials in seronegative infants (aged 6–11 months) are in progress.
- Janssen is developing a vector from Adenovirus 26 (Ad26), a human adenovirus, as a carrier vector for prefusion F protein antigens. This vector is being assessed in older adults and infants in Phase 2 clinical trials (NCT03606512; NCT03982199). In seniors, this vector is being assessed alone and in conjunction with a subunit protein (NCT03502707).

Subunit-based vaccines

Subunit-based vaccines are composed of purified viral proteins. They are administered alone or with adjuvant, often as an aqueous solution or emulsion, depending on the route of administration or the adjuvant to boost immune responses. This type of vaccine is expected to predominately induce humoral responses and CD4+ T-cell activation (13). The lack of CD8+ T-cell responses and the history of ERD necessitates caution in the use of this type of vaccine in seronegative infants. In seropositive populations, including older adults and pregnant women, these types of vaccines represent the opportunity to boost protective antibody responses. Fusion protein or prefusion protein-based vaccines may or may not be synonymous based on their antigenicity profiles and/or features of their high-resolution structures.

- GSK is developing a stabilized prefusion protein vaccine candidate. It is in development for maternal populations and in Phase 2 for older adults (NCT03814590). In Phase 1 testing, the alum adjuvant had no effect on neutralizing antibody responses (NCT02298179). The unadjuvanted product was intended for Phase 2 clinical trial in pregnant women, but it was withdrawn due to issues with protein stability during manufacturing (NCT03191383).
- Janssen is developing a subunit vaccine candidate that is being assessed with and without an adenovirus vaccine. This protein is reported to be in the prefusion conformation. A new candidate of the fusion protein stabilized in its prefusion conformation is now in Phase 2 trials for both the older adult and maternal populations. This program is currently in Phase 1/2 clinical trials (NCT03502707).

Particle-based vaccines

Particle-based vaccines are composed of synthesized nanoscopic particles that present multiple copies of a selected antigen to the immune system. The intent is to boost immunological responses to immunogens by the high copy number and the immune-boosting properties of the particle matrix.

- Novavax developed a recombinant fusion protein particle vaccine with polysorbate 80, ResVax. The conformation of this immunogen was a singly cleaved prefusogenic form (14). In Phase 1 clinical trials in older populations and pregnant women, ResVax was safe and produced palivizumab competing antibodies (15). However, in Phase 3 clinical trials in older populations, this candidate did not meet the primary outcome (preventing RSV-associated moderate–severe lower respiratory tract disease) or the secondary outcome (reduce all symptomatic respiratory disease due to RSV) (NCT02608502). Currently, a Phase 2 trial is planned to evaluate a reformulation. In Phase 3 clinical trials in pregnant women, this vaccine did not meet its primary objective (prevention of medically significant RSV-related LRTI in young infants) but still demonstrated 39% efficacy in reducing RSV-induced LRTI within the first 90 days of life and in reducing hospitalization by 44%, with the most protection seen if the vaccine was delivered before 33 weeks gestation (NCT02624947).

Monoclonal antibodies

Monoclonal antibodies against RSV have been used as passive immunizing agents. Even once vaccine programs exist, monoclonal antibodies may continue to provide prophylaxis in populations where active immunization will not be effective, such as immunocompromised individuals, or to severely premature infants who receive little or no maternal antibodies. The downside to this technology is that passive antibodies are only protective for as long as they remain in circulation. The passive protection of the passive monoclonal antibody currently available, palivizumab, lasts about a month. New monoclonal antibodies are being developed that could have a higher potency and longer duration of activity.

- AstraZeneca/Sanofi Pasteur is developing nirsevimab (MEDI8897), a recombinant human anti-RSV monoclonal antibody that has been engineered with a triple amino acid substitution in the constant domain to increase its serum half-life. This antibody targets neutralization-sensitive site ø at the apex of the prefusion F protein. One dose of this product could be effective for up to 5–6 months and provide protection for a whole RSV season due to increased potency and increased half-life (16). The increased period of effectiveness for this product could particularly serve to benefit rural and remote communities with reduced access to health care resources and where monthly travel is currently required to obtain palivizumab.
- Regeneron was developing REGN2222 (suptavumab), a monoclonal antibody. This product was fast-tracked from Phase 1 to Phase 3 clinical trials by the Food and Drug Administration in October 2015, but did not meet its primary endpoint of preventing medically attended RSV infection within the first 150 days of life (NCT02325791).

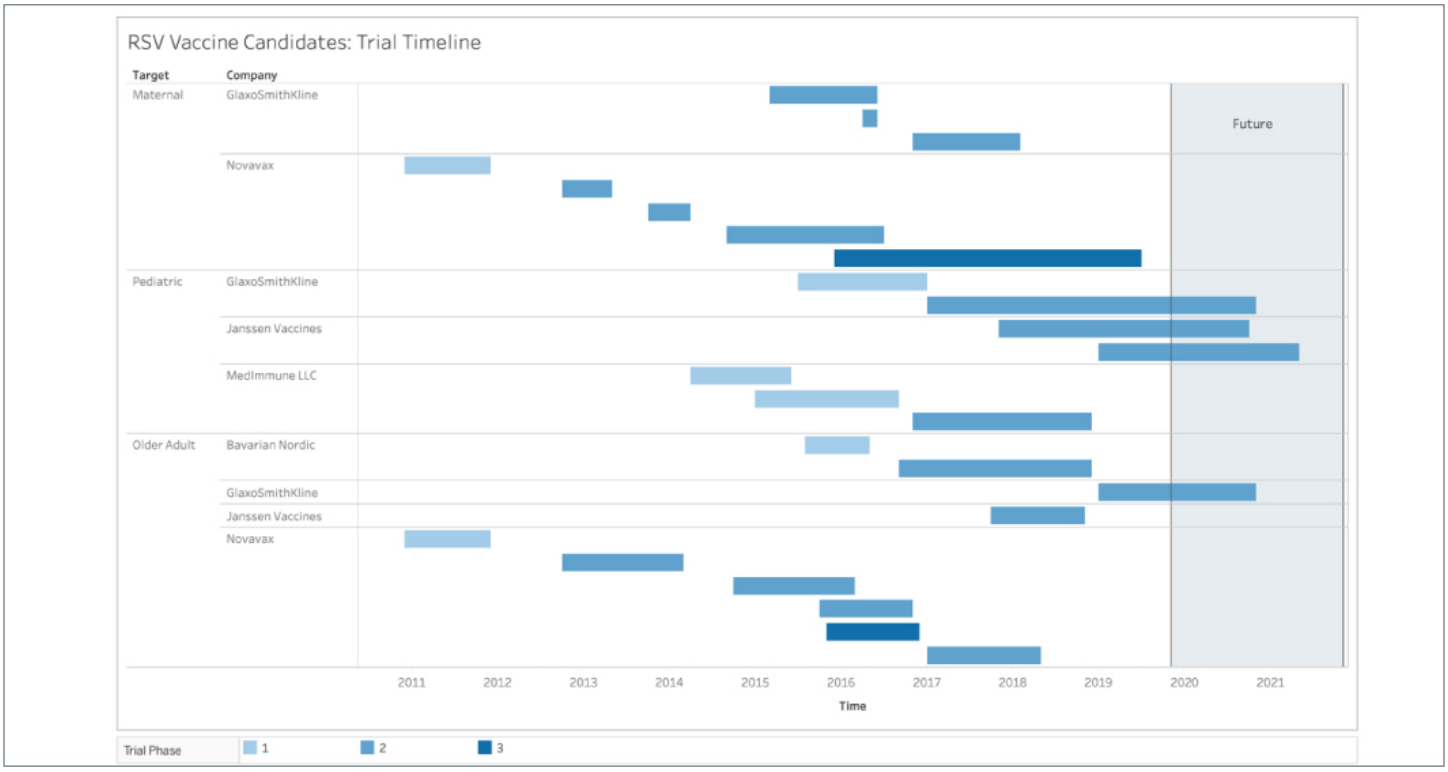
In summary, five different strategies are being pursued to address the challenges of vaccine development for RSV infection. Over 100 trials have been conducted on 38 candidates, and eight new trials were initiated last year alone. Based on data collected through July 1, 2019, **Figure 2** describes the timeline of the clinical testing of products in late-stage clinical development. This RSV product development pipeline is becoming increasingly crowded, and it is possible that new vaccines for RSV may be introduced into the Canadian market in the next 2–5 years.

Challenges to RSV vaccine development

Antigen diversity

A successful vaccine candidate will account for the diversity of antigens presented by RSV in the form of the structural variability of the proteins on the surface of the virus. The protective, neutralizing antibody response to RSV is dominated by antibodies targeting the prefusion F protein on the surface of RSV (17,18). Although the genetic sequence of F does not vary substantially between strains of RSV [89% of its sequence

Figure 2: Summary of RSV vaccine products timeline[a]



Abbreviation: RSV, respiratory syncytial virus

[a] Based on data collected through July 1, 2019, this figure describes the timeline of the clinical testing of products in late-stage clinical development. Each box represents a product in a phase of clinical development. As the phase of development increases the colour of the box becomes darker

is identical in both A and B strains (19)], amino acids do vary in prefusion specific epitopes. As new products are authorized and make it into broad usage, it will be critical to understand the sero-epidemiological responses at a population level to understand whether prefusion or postfusion antibodies are dominant responses, and whether these demonstrate equivalent protection against both RSV type A and B.

RSV infection dampens the immune response

The second major challenge of RSV vaccine development implicates the cellular and humoral immune responses: RSV infection dampens immune responses. RSV surface and internal proteins can trigger cellular immune responses and antibody-dependant cellular cytotoxicity alongside humoral immune responses. However, several viral mechanisms act to diminish virus-specific proliferative and effector responses (20). Even when cellular responses are not dampened by viral mechanisms, they may or may not offer protection. The CD8 T-cell mediated response to RSV is complex and has been associated with both viral clearance and disease pathology, depending on the type and location of the cells (21,22). The response mediated by CD4+ T-cells is also not straightforward as helper T-cell subset 2 biased CD4 responses have been associated with adverse vaccine reactions, yet are needed to induce antibody-mediated responses and other cellular responses, including T-follicular helper cells and effector cells (23,24). The key for vaccine development is to bolster immune responses, despite the dampening effect of RSV, to achieve the aims of the vaccine program: humoral responses may be targeted to prevent infection and cellular responses may be augmented to prevent severe disease (25). Clear definitions of correlates of protection for each of these immune responses are needed to ensure that seroconversion during trials translates to vaccine efficacy.

There are no clear correlates of protection

The third major challenge is the lack of clear correlates of protection for at-risk populations. Natural infection does not induce protection, as evidenced by the fact that 100% of children are infected by age two years but RSV disease recurs across age demographics. Longitudinal studies have demonstrated that children can be naturally reinfected with the same strain of virus, but that the second and subsequent infections are less severe (26,27), and there have been similar findings in adults (28). Why this is unclear; it may be a combination of low viral immunogenicity or hampered immunological boosting by recurrent infections (29). Current biological markers of protection are humoral, as measured by assays that determine antibody specificity (including the palivizumab-competition assay) and function (neutralization assays). However, this may not be sufficient, as illustrated by the late-stage failure of a monoclonal antibody from Regeneron (suptavumab).

Different correlates of protection may be needed for the two populations at risk for severe RSV disease: infants and older adults. Infants pose a challenge for vaccination as they have underdeveloped immune capabilities. This population may be susceptible to vaccine-induced ERD, as observed in the formalin-inactivated RSV trials. ERD has been attributed to low antibody efficacy (30) and Th2-biased CD4 immune responses (31–33). The aims of direct and indirect immunization programs for infants includes protection of infection, severe disease and hospitalization (34). Discussions are underway in some jurisdictions to define the thresholds of protection in multiple humoral and cellular correlates of protection needed before advancing clinical trials into seronegative populations (35).

Older adults face a different challenge in that the immune responses they have developed are waning due to immunosenescence. Immunization in older adults may have different aims and different correlates of protection depending on the health priorities of the jurisdiction (34). To prevent infection, humoral correlates of protection may be monitored. To prevent severe disease, cellular correlates of protection may be monitored. These two aims are not mutually exclusive, but a vaccine candidate may be better suited at achieving one of the aims over the other. To create a vaccine that is both efficacious and effective, vaccine manufacturers need to consider the public health goals of the vaccine programs and use correlates of protection in preclinical and clinical phases of development that align with these goals.

Discussion

The key to vaccine development will be eliciting an age-appropriate immune response in each target population. Current vaccine strategies are mindful of the history of ERD and the unique immunological characteristics and vulnerability of seronegative children. Live-attenuated and virus-vectored vaccines are two vaccination strategies that are appealing for infants and children, as replicating vaccines do not prime vaccine-enhanced RSV disease (10,36,37). Neonates can also acquire immunity against RSV from their mothers. Active transplacental antibody transfer begins at 28–30 weeks gestation, and maternal vaccination to boost anti-RSV response is intended to confer increased infant protection postpartum (38). Maternal and infant immunization strategies are being pursued to indirectly and directly target the infant population.

Older adults face different challenges in that they are already seropositive but face immunosenescence. To boost the immunological repertoire of this at-risk population, direct and indirect immunization strategies, such as vaccination of children (as with Rotavirus) (39), may be pursued.

The field of vaccine development for respiratory viruses is rapidly expanding. Technologies tested and proved effective in one field elicit development across the board. Structure-based immunogen design, spurred from publication of the pre-F

structure in 2013 (40), has bolstered the development of new RSV vaccines across multiple vaccine platforms (see Figure 2). Technologies to identify and isolate B cells with receptors of interest is enabling the identification of monoclonal antibodies with useful characteristics. Regulatory and production timelines for these products may be faster than for traditional vaccines, putting pressure on expert groups to create guidance within shorter timeframes. mRNA-based vaccines may shorten production timelines further.

Conclusion

Substantial progress has been made in the RSV vaccine development field. Federal, provincial and territorial public health departments in Canada and abroad need to be aware of new products as they are closer to market—how they have addressed the key challenges in RSV vaccine development and how they work to achieve the public health goals for RSV in each jurisdiction.

Authors' statement

AK — Writing–original draft, project administration, conceptualization
MT — Writing–reviewing & editing, conceptualization, supervision
AH — Writing–reviewing & editing, conceptualization, supervision
CQ — Writing–reviewing & editing, conceptualization, supervision
WV — Writing–reviewing & editing, conceptualization, supervision
DM — Writing–reviewing & editing, conceptualization, supervision

Conflict of interest

None.

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RESEARCH

Gap analyses to assess Canadian readiness for respiratory syncytial virus vaccines: Report from an expert retreat

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Abstract

Respiratory syncytial virus (RSV) can cause severe disease in infants and older adults. Various vaccine candidates are in development and may become authorized for use in Canada within the next 2–5 years. The Public Health Agency of Canada sought to enhance preparedness for RSV vaccine and passive immunization candidates by organizing an expert retreat to identify knowledge gaps in surveillance and research and development in the context of provincial and territorial RSV public health priorities.

We determined that RSV candidate vaccines in development directly address four out of five identified public health priorities, and identified remaining data gaps around vaccine efficacy and effectiveness. We determined that limited or sufficient surveillance data is available to support decision-making for four out of five RSV public health priorities and identified data gaps for several key populations: (i) for RSV cases under 17 years of age, gaps remain for denominator data to calculate incidence and data on medically attended outpatient visits; (ii) for RSV cases in Indigenous and remote communities, gaps remain for data on incidence, prevalence, specific risk factors, feasibility and acceptability; and (iii) for RSV cases in older adults, gaps remain for data on incidence. This process demonstrated the feasibility of, and stakeholder support for, gap analyses in surveillance data to support decisions about prospective vaccines and immune products.

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Keywords: vaccine, National Advisory Committee on Immunization, NACI, immunization, RSV, respiratory syncytial virus

Introduction

The National Advisory Committee on Immunization (NACI) is Canada's National Immunization Technical Advisory Group (NITAG) and is mandated to provide the Public Health Agency of Canada (PHAC) with technical guidance for vaccine use. When issuing guidance, NACI considers a broad range of evidence, including the vaccine characteristics, the burden of illness and the ethics, equity, feasibility and acceptability of immunization programs. These factors have all been identified as important drivers for Canadian provincial and territorial (P/T) decision-makers (1).

As many respiratory syncytial virus (RSV) vaccines are in clinical development, NACI needs data on RSV epidemiology and the cost of new vaccine candidates to provide comprehensive guidance addressing these decision drivers. Due to the public health need and the expedited timelines for new vaccine recommendations, PHAC seized the opportunity to enhance RSV vaccine preparedness by hosting an expert gap-analysis retreat to understand the current and future needs of vaccine decision-makers. The NACI secretariat, alongside a technical advisory committee (i) coordinated the identification of P/T RSV public health priorities; (ii) selected participants based on their expertise in the fields of RSV surveillance, research, economics, pediatric health and immunization as well as representation from key groups inside and outside of government (see **Appendix 1**); and (iii) selected industry manufacturers to present on the progress

of late-stage (Phase 2 or higher) human clinical trials. Industry representatives were invited to present data via teleconference and retreat participants participated in confidential discussions.

Background

RSV infection represents a large burden of disease in Canada and worldwide. The age distribution of RSV disease burden is bimodal, where the greatest impact is felt in the first two years of life and in older adults. Published Canadian data are lacking, but data from other high-income countries show the following bimodal trend for RSV hospitalization rates per 1,000 people: 26.3 (0–5 months), 11.3 (6–11 months), 1.4 (12–59 months), 1.0 (older than or 65 years) (2,3).

Vaccines targeting maternal, infant or older adult populations have different impacts on RSV prevention in diverse populations. To perform a gap analysis, we first needed to identify and understand the public health priorities (PHPs) for RSV prevention. While vaccine procurement happens federally, vaccine program decision-making and implementation falls within the P/T mandate. To ensure our analysis was relevant and useful for Canadian immunization programs, we focused our attention on alignment with P/T public health priorities. In consultation with members of the F/P/T Canadian Immunization Committee and Council of Chief Medical Officers of Health, we developed the following list of the P/T public health priorities for RSV vaccine programs:

1. PHP-1: Preventing hospitalization and death in infants
2. PHP-2: Preventing hospitalization and death in high-risk infants
3. PHP-3: Preventing infection in children living in remote settings
4. PHP-4: Preventing hospitalization and death in children
5. PHP-5: Preventing hospitalization and death in older adults

These PHPs for RSV guided the subsequent gap analysis and could enable the creation of vaccine guidance that would suit the needs of P/Ts.

The objective of the paper is to summarize expert discussion around two topics to inform Canadian RSV vaccine readiness: (i) research and development of vaccine candidates; and (ii) existing public health surveillance. For each of these topics, the alignment with respect to the PHPs was discussed and a gap analysis was performed. The intent of this process is to provide expert rationale for further research and surveillance system development to enhance Canadian RSV vaccine readiness.

Key findings: Research and development of RSV vaccine candidates

Alignment of vaccine candidates with public health priorities

To align RSV vaccine candidates in development with P/T public health priorities, we considered the different outcomes of the PHPs: prevention of infection versus prevention of hospitalization or death.

Different vaccine candidate development strategies boost protective immunological responses to either prevent infection, severe disease and/or transmission (4). For vaccine guidance, distinction between these three outcomes is essential. Data that demonstrate that a vaccine prevents severe disease or death may form the evidence base of a recommendation targeting individuals (i.e. clinicians, vaccine recipients). Data that demonstrate that a vaccine prevents infection and/or transmission may form the evidence base of a recommendation targeting the population. These two types of recommendations could potentially have very different funding prioritizations and mechanisms within P/T vaccine programs, impacting who has access to these vaccines and when.

There is a strong foundation of evidence that vaccines that induce protective antibody levels (including subunit vaccines, particle-based vaccines and monoclonal antibodies) prevent severe disease in infants. Vaccines that boost cellular responses (including live attenuated and vectored vaccines) may reduce severe disease as well as viral transmission due to boosting mechanisms related to CD8-mediated viral clearance and shedding.

A population-level vaccine recommendation is supported by an evidence base demonstrating that protective humoral and cellular responses prevent infection and/or transmission on a population-wide level. Otherwise, it may be reasonable to consider indirect evidence from other vaccines that have had an unexpected effect on population-wide transmission. For example, rotavirus vaccine is indicated for the prevention of acute gastroenteritis in children younger than two years old; however, since the vaccine's introduction, rotavirus infection rates in nonvaccinated children and adults have also decreased substantially (5).

We determined that vaccine candidates in development directly address four out of five P/T public health priorities (see **Table 1**).

Preventing hospitalization and death in infants (PHP-1), high-risk infants (PHP-2) and children (PHP-4): Janssen, GSK and Novavax are developing vaccine candidates that target infant populations either directly or through maternal immunization. AstraZeneca/Sanofi Pasteur is developing a monoclonal antibody to address the burden of RSV disease in

Table 1: Vaccine candidate gap analysis

PHP	Provincial/ territorial PHPs for RSV	RSV vaccine candidate in development to address priority
1	Preventing hospitalization and death in infants	Janssen Junior, GSK Maternal and Pediatric, Novavax Maternal, AstraZeneca/Sanofi Pasteur[a]
2	Preventing hospitalization and death in high-risk infants	Janssen Juniors, GSK Maternal and Pediatric, Novavax Maternal, AstraZeneca/Sanofi Pasteur[a]
3	Preventing infection in children living in remote settings	AstraZeneca/Sanofi Pasteur[b]
4	Preventing hospitalization and death in children	AstraZeneca/Sanofi Pasteur[a]
5	Preventing hospitalization and death in older adults	Janssen Senior, GSK Older Adult, Novavax Older Adult, Bavarian Nordic[a]

Abbreviations: PHP, public health priority; RSV, respiratory syncytial virus
[a] RSV candidate directly addresses public health priority
[b] RSV candidate partially addresses public health priority

infants at high risk of severe disease. These vaccine candidates are in Phases 2 and 3 of clinical development for healthy infants; infants at higher risk due to comorbid conditions; and healthy children. These three PHPs are being directly targeted by several vaccine candidates in late-stage clinical development.

Preventing infection in children living in remote settings (PHP-3): Both vaccines and immune products targeting RSV could address this PHP. Palivizumab is the only product currently available. It is only given to infants at high risk of severe RSV disease or, in the case of a specific pilot project in Nunavik, to all term infants living in remote northern communities (6). The duration of palivizumab activity is approximately one month. The next generation monoclonal antibody products, including the product in development from AstraZeneca/Sanofi Pasteur, may have longer periods of effectiveness (possibility more than five months). This could increase the ease of use of these products in regions with decreased access to health care systems, including remote communities.

Palivizumab and other monoclonal antibodies are expected to prevent severe RSV disease, but it is not known if these products would also reduce RSV infection. Additional research is needed on feasibility and acceptability for RSV vaccine programs in Canadian remote communities. Work is underway in Nunavik, northern Quebec, to assess the impact of expanding access to palivizumab for all infants younger than three months old (6). Although the results of this study will inform decision-making around the use of multidose palivizumab in northern and remote communities, these data may not be directly applicable to new monoclonal antibodies given the potential increase in the duration of protection. Additional studies may be needed to directly address this PHP.

Preventing hospitalization and death in older adults (PHP-5): Janssen, GSK, Novavax and Bavarian Nordic are developing vaccines that target healthy older adults as well as older adults with comorbid conditions, including chronic obstructive pulmonary disease. This PHP is being directly targeted by several vaccine candidates in late-stage clinical development. In addition, this population may be protected by immunization of younger cohorts via herd immunity, similar to rotavirus or pneumococcal disease (5).

Gaps identified for vaccine candidate research and development

Alongside the gap analysis of P/T priorities and vaccine candidates, vaccine manufacturers with late-stage clinical trial programs for a vaccine or immune product targeting RSV were invited to present their data on vaccine effectiveness, safety, immunogenicity and other relevant topics (4). Based on those confidential discussions, we identified areas where additional research or analysis is needed to fully understand the potential efficacy and effectiveness of vaccine candidates in development:

I. **Co-administration of RSV vaccines.** The antigens presented by multiple candidate vaccines may be the same antigens that are targeted by anti-RSV monoclonal antibodies, including palivizumab. The safety and efficacy of co-administration of vaccines and monoclonal antibodies targeting RSV has not been evaluated.

II. **Consistent case definition**. Case definitions for RSV outcomes vary across clinical trials. This may limit the head-to-head comparisons of data necessary for guidance synthesis. A consistent and specific RSV-associated illness definition is necessary to be able to compare the efficacy and effectiveness of different RSV candidate vaccines.

III. **Protection against RSV/A and RSV/B strains**. RSV/A and RSV/B strains are typed on their G surface proteins. Vaccines may have differential efficacy against these strains. Antigenic sites targeted by some of the RSV vaccine candidates are on the F surface protein, specifically antigenic sites ø and V, which differ between strains A and B (7). Additional research is necessary to confirm the protective efficacy of these vaccines against both RSV strains.

IV. **Impact of pre-existing immunity to adenovirus on vaccine efficacy**. Several RSV candidates use vectors from human or chimpanzee adenoviruses to deliver RSV antigens. These vectors may elicit their own immune responses that could dampen or augment immune response to RSV antigens, change the efficacy of the vaccine and/or change the safety profile of the vaccine in previously immune people. Evidence is necessary to determine the prevalence and effect of adenovirus immunity.

V. **Impact of potential escape mutants**. Palivizumab targets conserved site II on the RSV F protein. Nirsevimab, a novel monoclonal antibody being developed by AstraZeneca/ Sanofi Pasteur and currently in Phase 3 clinical trials, targets site ø on RSV F protein (4). Under conditions of selection pressure, viral variants could change the presentation of

these antigenic sites (by changing the protein sequence and/or glycosylation patterns) to the degree where these monoclonal antibodies are no longer effective. Surveillance systems would need to be in place to detect these escape mutations in breakthrough infections of monoclonal therapy recipients.

Key findings: Public health surveillance

Alignment of surveillance with public health priorities

The surveillance data that inform most PHPs are available from two sources in Canada: an active sentinel hospital surveillance system, the Immunization Monitoring Program ACTive (IMPACT) (8), and a hospital administrative database, the Canadian Institute for Health Information's (CIHI) hospital morbidity database (9). **Table 2** shows the extent to which existing national surveillance systems and/or data sources provide evidence for the P/T-defined RSV public health priorities.

Table 2: Extent of available surveillance data to assess effectiveness of RSV vaccine for public health priorities by target groups

Public health priority	Public health parameters Measures used by NACI to assess burden of illness				
	Incidence	Study setting[a]	Virus strain	High risk populations[b]	
Infant hospitalization	IMPACT[c] CIHI[c]	IMPACT[c] CIHI[c]	IMPACT[d]	IMPACT[d]	CIHI[c]
Infant death	IMPACT[c] CIHI[c]	IMPACT[c] CIHI[c]	IMPACT[d]	IMPACT[d]	CIHI[c]
Infection in remote communities (child)	IMPACT[c] CIHI[c]	IMPACT[c] CIHI[c]	IMPACT[c]	IMPACT[c] CIHI[c]	
Child hospitalization	IMPACT[c] CIHI[c]	IMPACT[c] CIHI[c]	IMPACT[d]	IMPACT[d]	CIHI[c]
Child death	IMPACT[c] CIHI[c]	IMPACT[c] CIHI[c]	IMPACT[d]	IMPACT[d]	CIHI[c]
Senior hospitalization	CIHI[c]	CIHI[c]	ND[e]	CIHI[c]	
Senior death	CIHI[c]	CIHI[c]	ND[e]	CIHI[c]	

Abbreviations: CIHI, Canadian Institute for Health Information; IMPACT, Immunization Monitoring Program ACTive; NACI, National Advisory Committee on Immunization; ND, no data; RSV, respiratory syncytial virus
[a] Study settings may include: community, primary care, hospital, nosocomial
[b] High risk populations for RSV include: infants, children and seniors with underlying medical conditions
[c] Limited data - yellow
[d] Sufficient data - grey
[e] No data - pink

Three PHAC surveillance experts jointly conducted a subjective assessment of each system/data source to determine whether adequate, limited or no data exist to support decision-making. IMPACT was able to provide sufficient data on viral strain characteristics and high-risk pediatric populations (infants and children hospitalized with RSV in IMPACT centres). IMPACT was able to provide limited data on incidence and infection in remote communities, and no data on RSV-associated illness not requiring hospitalization. Incidence rates are difficult to calculate for some sites because the site catchment areas do not align with population statistics (see **Table 3** for more information). As there are no IMPACT sites in the three territories or northern areas of affected provinces, RSV cases in these communities would only be captured if patients were transferred to an IMPACT hospital. Study setting is limited to hospital wards and intensive care units.

Table 3: Overview of surveillance gaps in assessing data available for priority populations

Priority population	Data gap	Proposed gap-filling strategy
Cases under 17 years of age	Denominator data	Hospital-level linkage of IMPACT centres with CIHI
	Non-medically attended RSV infection data	None proposed
Cases in Indigenous and remote communities	Incidence, prevalence or specific risk factor data	Surveillance pilot projects may clarify the burden of disease, acceptability and feasibility of vaccine programs in these at-risk communities
Cases in older adults	Incidence, prevalence, strain or specific risk factor data	Retrospective cohort study of laboratory-confirmed RSV by CIRN-SOS Prospective surveillance through a sentinel surveillance network

Abbreviations: CIHI, Canadian Institute for Health Information; CIRN-SOS, Canadian Immunization Research Network Severe Outcome Surveillance; IMPACT, Immunization Monitoring Program ACTive; RSV, respiratory syncytial virus

CIHI was able to provide limited data on hospitalizations for all public health parameters, across all ages, but not viral strain characteristics. The extent of data availability through CIHI was assessed as limited because viral testing is not always performed at acute care hospitals (9), and modelling is required to estimate hospitalizations due to RSV. Data for high-risk populations are also available from CIHI, but these data are limited by the way in which comorbid conditions are captured in administrative databases. The most responsible diagnosis and 24 other diagnosis fields can be scanned for comorbid conditions, but the use of these fields is variable based on clinical need.

Data gaps within three priority populations

The retreat participants identified three priority populations for which more data are needed (see Table 3).

I. Under 17 years of age:

a. Lack of denominator data: The IMPACT system aims to provide data on RSV hospitalizations of children aged 16 years and younger. However, it is a sentinel (and not population-based) surveillance system, and catchment areas for some sites are not aligned with available population data. Therefore, current data from this system are limited to the number of health events (e.g. number of

admissions, number of deaths, number of intensive care unit admissions). Interpretation of these indicators without the context of the population from which these are derived is difficult and would be improved with calculation of population-based indicators. Hospital-level linkage of IMPACT centres with hospital administrative data from CIHI may be explored to conduct trend validation, compare patient numbers captured by different data sources, examine representativeness/comprehensiveness of this sentinel networks and ascertain denominator data.

b. Lack of non-medically attended RSV infection data: No data are available for non-medically attended RSV infection, as would be needed for RSV transmission models and cost-effectiveness studies. No gap-filling strategy was proposed at the retreat.

II. Indigenous and remote communities: Indigenous and remote communities face additional barriers to accessing healthcare and are underrepresented in current national surveillance systems. Estimates of the incidence, prevalence or specific risk factors are not systematically available for Indigenous communities. The IMPACT system captures patients from Indigenous and remote communities who are hospitalized or transferred to an IMPACT site, but these data do not reflect the true burden of illness in this community. Surveillance pilot projects are under way in Quebec in some remote Indigenous communities to determine the burden of disease, acceptability and feasibility of vaccination programs (6). The changing landscape of vaccine products available to prevent RSV represents opportunities for longer-lasting and more durable products. Further study is needed to ascertain the needs of Indigenous and remote communities.

III. Older adults: National data on RSV infection in older adults are limited to hospital administrative data from CIHI. Evidence suggests that crude RSV counts and rates derived from hospital administrative data in Canada underestimate the burden of illness in older adults because of incompleteness of viral testing in this age group (10). Despite limitations of missing data, administrative data remain an important source of data. Primary data collection of epidemiology and burden of disease inputs is warranted for evaluations in older adults. Two strategies to address this need were proposed during the discussions:

a. A retrospective cohort study of laboratory-confirmed RSV in patients 65 years and older hospitalized for influenza-like illnesses (ILI) is underway via the Canadian Immunization Research Network Severe Outcome Surveillance network (11). The ability of this dataset to fill existing data gaps for older adults could be explored.

b. The feasibility of establishing prospective surveillance for RSV in older adults through a sentinel surveillance network could be explored.

Additional surveillance systems limitations were discussed:

- Understanding the long-term sequelae of RSV helps in the development of vaccination programs and economic models. Current data about the role of RSV in the development of chronic obstructive pulmonary disorder or asthma are inconclusive. Additional studies are needed to further understand this link and the long-term burden of RSV illness.
- Some respiratory and RSV surveillance systems use case definitions of ILI to define their target populations. The drivers for this are often either opportunistic (RSV systems leverage existing influenza surveillance infrastructure and ILI definitions to identify suspect cases) or practical (individuals selected for specimen collection are based on existing clinical testing algorithms or standards of care). The inclusion of fever in the ILI case definition may result in missed RSV cases; however, there is no standard syndromic case definition for RSV infection. To address this issue, PHAC participated in an international World Health Organization-led collaboration to develop an RSV surveillance case definition and will endeavour to apply this case definition in PHAC-led surveillance initiatives or analyses (12).Current surveillance systems are based on passive surveillance of those seeking medical attention for RSV. To estimate the burden of non-medically attended RSV, an active surveillance strategy would be needed. Although the feasibility of this approach is complex, these data are essential to build accurate RSV transmission and economic models.

Strengths and limitations

Although the above analyses provide expert rationale for future study and pursuit of gap-filling strategies, there are some caveats to our approach. First, the analyses are limited by the expertise of the participants in the room. The number of participants was incomplete due to the feasibility of hosting an in-person, roundtable discussion. As a result, these analyses do not represent an exhaustive analysis of the field as a whole.

Second, the PHPs identified in collaboration with P/Ts are representative of a spectrum of regional needs. Although consensus was achieved in advance of the retreat, we recognize that these priorities do not represent each community, province or territory and these analyses should be considered a rough estimate rather than a precise fit.

Finally, the field of RSV vaccine and monoclonal antibody development is moving at such a fast pace that this report will be out-of-date before it goes to press. However, even as vaccine candidate development is proceeding, the discussion of alignment with PHPs and identification of data gaps will guide the field towards more efficacious and effective vaccines.

Conclusion

This retreat demonstrated the feasibility and stakeholder appetite for discussing prospective vaccines. This retreat has provided valuable insight into what public health parameters are

important to consider for RSV prevention, what surveillance is currently underway and what questions remain to be addressed.

Authors' statement

AK — Writing–original draft, project administration, conceptualization
AS — Writing–reviewing & editing, conceptualization, supervision
MWY — Writing–reviewing & editing, conceptualization
MT — Writing–reviewing & editing, conceptualization, supervision
CB — Writing–reviewing & editing, conceptualization, supervision
AH — Writing–reviewing & editing, conceptualization, supervision
WV — Writing–reviewing & editing, conceptualization, supervision
DM — Writing–reviewing & editing, conceptualization, supervision
CQ — Writing–reviewing & editing, conceptualization, supervision

Conflict of interest

None.

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Appendix 1: RSV Vaccine Readiness Retreat participant list

Name	Professional affiliation
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Sarah Buchan	Public Health Ontario
Natasha Crowcroft	Public Health Ontario
Gaston De Serres	Institut national de santé publique du Québec (INSPQ)
Shelley Deeks	Public Health Ontario
Nick Gnidziejko	Canadian Institute for Health Information (CIHI)
Joanne Langley	Dalhousie University and the Canadian Immunization Research Network (CIRN)
Jason LeBlanc	Nova Scotia Health Authority
Dorothy Moore	McGill University
Monika Naus	British Columbia Centre for Disease Control (BCCDC)
Jesse Papenburg	McGill University
Ellen Rafferty	University of Alberta
Beate Sander	Toronto Health Economics and Technology Assessment (THETA)
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Robert Pless	Health Canada, Biological and Genetic Therapies Directorate (BGTD)
Guillaume Poliquin	National Microbiology Laboratory (NML)
Simran Sandhu	CIRID, SED
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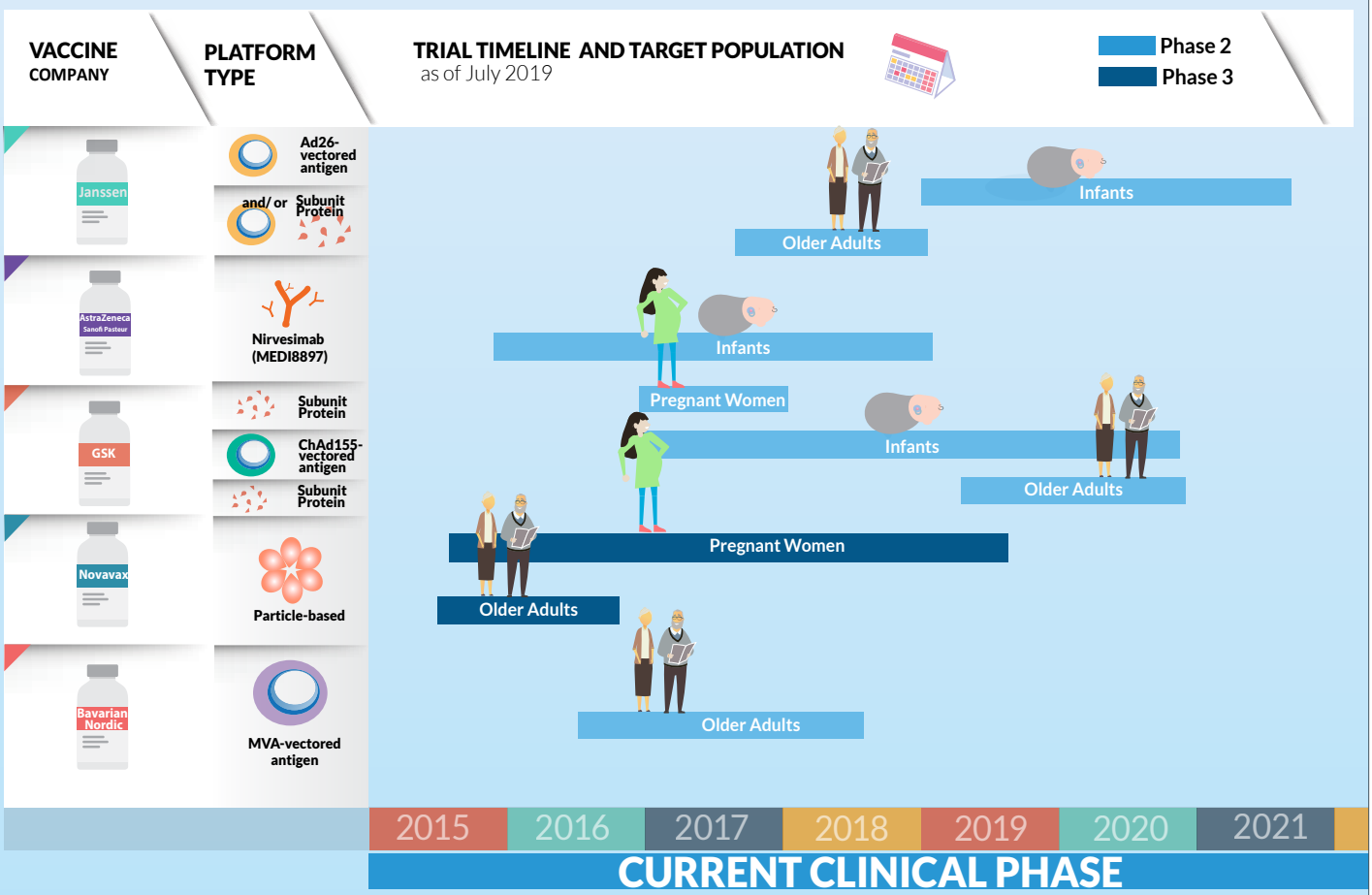
Veeran-Anne Singh	FNIHB
Matthew Tunis	CIRID, NACI Secretariat
Man Wah Yeung	CIRID, NACI Secretariat

Summary of RSV Vaccine Products in Late-Stage Development



Large community mumps outbreak in Manitoba, Canada, September 2016–December 2018

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Abstract

Background: After routine mumps immunization programs were implemented in Manitoba in the 1980s, incidence was low, with 0–9 cases of disease annually. In September 2016, a mumps outbreak began in fully vaccinated university students in Winnipeg, Manitoba.

Objective: We describe the investigation of this province-wide mumps outbreak, which lasted between September 2016 and December 2018. We present the details of public health measures implemented and challenges encountered. Possible contributing factors to the sustained transmission are also provided.

Methods: Probable and confirmed cases of mumps were investigated by public health departments using the investigation form developed for this outbreak. Confirmed mumps cases were linked to the provincial immunization registry. An outbreak response team planned and implemented control measures across the province.

Results: The outbreak began in vaccinated university students in September 2016 and spread across the province. Activity was high and prolonged in the northern remote areas. By the end of 2018, 2,223 cases had been confirmed. All age groups were affected, and incidence was highest among people aged 18–29 years. Two-dose coverage of mumps-containing vaccine in confirmed cases was close to 70%.

Conclusion: This prolonged outbreak revealed a large vulnerable population likely resulting from under-vaccination and waning vaccine-induced immunity in the absence of natural boosting from exposure to mumps virus. It is important to maintain high two-dose coverage with mumps-containing vaccines. A third dose of mumps-containing vaccine in future outbreaks may be considered.

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Keywords: mumps, outbreak, incidence, vaccination, MMR vaccine, investigation, immunity, Manitoba

Introduction

Mumps is an illness caused by the mumps virus, of the Paramyxoviridae family. Symptoms of mumps infection include fever, headache and the characteristic swelling and tenderness of the parotid or other salivary glands. Aseptic meningitis, encephalitis, orchitis, oophoritis, deafness and pancreatitis are some rare complications due to mumps infection (1–3). In Manitoba, laboratory-confirmed and probable cases are required to be reported to Manitoba Health, Seniors and Active Living (MHSAL) under *The Manitoba Public Health Act* (4).

A single dose of the measles–mumps–rubella (MMR) vaccine, at 12 months of age, was added to the routine childhood immunization schedule in Manitoba in 1983. A second dose of the MMR vaccine, for children aged 4–6 years, was added to the routine schedule in 1996 (5). This is consistent with the most recent recommendation of 2007, from the National Advisory Committee on Immunization (NACI) for mumps-containing vaccine. After reviewing mumps outbreaks in Canada and internationally, NACI recommended two-dose routine mumps immunization in infants and children as well as in certain high-risk adult groups including secondary and postsecondary students, military personnel and health care workers (6).

Historically, the incidence of mumps has been continually low in Manitoba, with 0–9 cases each year between 2000 and 2015 or 0.3 cases per 100,000 population, on average (7). Disease is

most common in people aged 18–45 years. In recent years, the average incidence rate of mumps in Canada was 0.3 cases per 100,000 population from 2011 to 2015 (8).

On October 18, 2016, routine surveillance detected a cluster of six cases of mumps with symptom onset between September 25 and October 12, 2016, in Winnipeg, the capital city of Manitoba. All six were University of Manitoba students aged 18–24 years; three were on university athletic teams. All had documented receipt of two doses of MMR vaccine in childhood. MHSAL declared a mumps outbreak and established an outbreak response team on the same day. Five regional health authorities deliver publicly funded health services in five geographic regions in Manitoba: one urban region, the Winnipeg Regional Health Authority, and four rural regions, Interlake–Eastern Regional Health Authority, Southern Health–Santé Sud, Prairie Mountain Health and Northern Regional Health (9). All regional health authorities participated on the response team.

In this report, we describe the investigation of this province-wide mumps outbreak between September 2016 and December 2018. We also present the details of public health measures implemented and challenges encountered. Possible contributing factors to the sustained transmission are also provided.

Methods

A provincial outbreak of mumps was declared on October 18, 2016, and was confirmed over on December 31, 2018, when activity level returned to baseline. This outbreak originated in a university population, but spread quickly, evolving into a large and sustained outbreak across the entire province. The outbreak response team planned and implemented control measures including prompt contact tracing, recommendations of self-isolation after symptom onset, communication (including dissemination of educational materials) and the offer of MMR vaccine to susceptible contacts.

Epidemiologic investigation

Case definitions were derived from the provincial communicable disease management protocol for mumps (10). A probable case was defined as the occurrence of symptoms compatible with mumps (acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland) that lasted two days or more, on or after September 1, 2016. A confirmed case was defined as a laboratory confirmation of recent mumps infection in a probable case or a probable case with an epidemiologic link to a laboratory-confirmed case and in the absence of recent vaccination with mumps-containing vaccines. The MHSAL's Communicable Disease Management Protocol recommends that investigators consult the current Canadian Immunization Guide for information on age-specific reactions and timeframes when determining if symptoms were possibly due to a recent dose of mumps-containing vaccine.

An outbreak investigation form was developed to collect information on demographics, occupation, symptoms, complications and severity, vaccination status and activities during the incubation period (12–25 days before the onset of parotitis) and communicability period (seven days before until five days after the onset of parotitis). Regional health authorities implemented outbreak investigation and control measures immediately. Regional public health nurses interviewed cases and completed investigation forms before submitting to MHSAL.

MHSAL coordinated data collection and data entry. General information about all mumps reports were captured in the routine surveillance database. An outbreak-specific database was implemented to capture information from the outbreak investigation forms. Due to the high volume of mumps reports, only confirmed cases were entered into the outbreak investigation database. Confirmed cases were linked to the provincial immunization registry to calculate vaccination coverage rates. We conducted descriptive analyses to identify the epidemiologic and geographic characteristics of the outbreak. Data linkage and analysis were conducted using SAS Enterprise Guide, version 7.1 [SAS Institute Inc., Cary, North Carolina, United States (US)].

Laboratory investigation

The Cadham Provincial Laboratory in Winnipeg performed standard laboratory testing on specimens, including tests to detect mumps virus immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies in acute and convalescent serum specimens approximately 7–10 days apart; tests for mumps virus RNA through reverse transcription polymerase chain reaction (RT-PCR); and attempts to isolate mumps virus in culture. Samples of positive cultures were sent to the National Microbiology Laboratory (NML) for viral genotyping.

Vaccination coverage

Vaccinations for cases were extracted from the population-based provincial immunization registry within the Public Health Information Management System (PHIMS). The registry was implemented in 1988 to record vaccinations for those born in Manitoba on or after January 1, 1980. Vaccinations received outside of Manitoba are not entered without an official document. As a result, vaccination records are generally more complete for people younger than 30 years or born after 1986 who grew up in Manitoba.

Interventions

Control measures included prompt contact tracing, with regional public health nurses conducting case and contact management. Self-isolation for five days after symptom onset was recommended to symptomatic cases. Contacts who might have been exposed during the period of communicability were notified. They also received mumps-related education, including information about early signs and symptoms, and were advised to see a health care provider if they developed symptoms.

MMR vaccines were offered to susceptible contacts (people with zero documented doses of mumps-containing vaccine born between 1970 and 1984 and those with less than two documented doses born after 1984), based on Manitoba's eligibility criteria (11) and the most recent NACI recommendation (6). Health care facilities were encouraged to ensure that all staff were vaccinated. In correctional facilities with cases, vaccination clinics were held to offer vaccines to susceptible staff and inmates.

MHSAL disseminated educational materials to universities, schools and the general public. A series of letters were sent to Manitoba universities, schools, daycare centres and sports organizations to increase public awareness. MHSAL also responded to media requests and issued news releases to provide updates on the outbreak and emphasize the importance of vaccination. A public website maintained by MHSAL provided weekly updates. Health care providers received letters to guide prevention and control practices. MHSAL issued public health alerts through the Canadian Network for Public Health Intelligence (CNPHI) to notify other provincial and federal public health counterparts.

The outbreak response team considered the possibility of offering a third dose of MMR as an intervention in Northern Regional Health in January 2018 after the US Advisory Committee on Immunization Practices published updated recommendations (12). Northern Regional Health provides service to approximately 75,000 residents in northern Manitoba, the smallest population in five regions, but distributed across the largest geographic area. Many live in remote and isolated communities, and some communities can only be accessed by plane or boat. MHSAL decided not to recommend a third dose of MMR due to operational feasibility in northern areas. As the virus had been circulating regionally for an extended period of time, it was not possible to define an eligible population who would have benefited from a third dose.

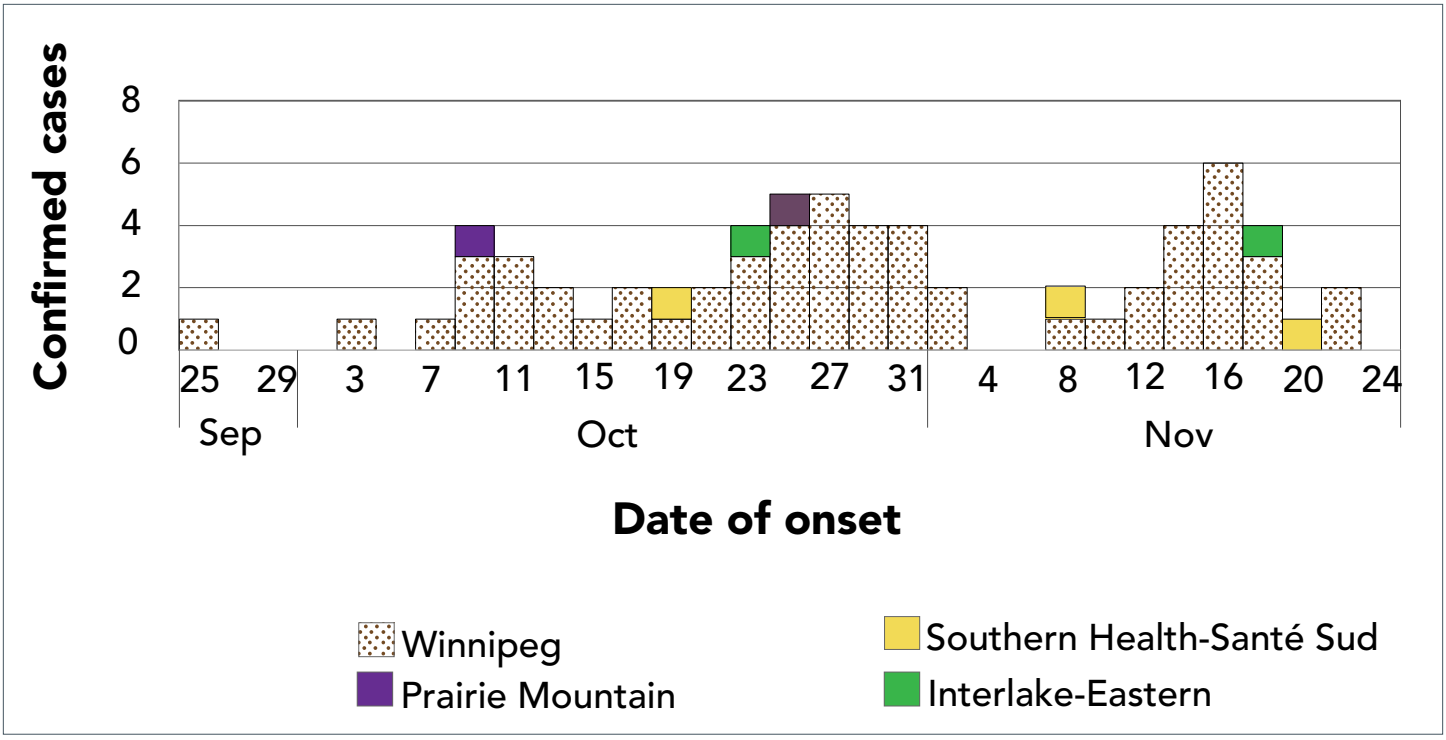
Results

Descriptive epidemiology

This mumps outbreak started among university students in the Winnipeg Regional Health Authority. This region serves approximately 57% of the 1.4 million residents of Manitoba. Three peaks in the early months of the outbreak corresponded to three important exposure events: multiple homecoming celebrations at the University of Manitoba (September 19–25, 2016); Thanksgiving weekend (October 8–10), which might have resulted in infectious people travelling; and Halloween (October 31) (**Figure 1a**). During this period, cases included young adults in Winnipeg who were linked to universities, schools, sports gatherings and/or holidays.

Over 80% of those university students who were born in Manitoba had received two doses of mumps-containing vaccines (data not shown).

Figure 1a: Confirmed cases of mumps (N=65) by date of symptom onset and health region, Manitoba, September 25–November 26, 2016



By late November 2016, mumps had spread to three rural health regions, Interlake–Eastern Regional Health, Southern Health–Santé Sud and Prairie Mountain Health, including to correctional facilities in those regions. By January 2017, mumps had spread to the most rural region, Northern Regional Health. The number of mumps cases in this region continued to increase throughout the year, peaking in mid-September 2017. Compared with the other health regions, mumps morbidity in Northern Regional Health was high and prolonged. Even with the geographic isolation of communities, mumps continued to spread throughout the region, ultimately infecting almost 2% of the regional population.

After September 2017, the number of mumps cases in Manitoba began to decline, largely driven by the decline in cases in Northern Regional Health. MHSAL declared the outbreak over at the end of 2018 when it was clear that mumps activity had returned to baseline (**Figure 1b**).

Outbreak investigation confirmed 2,223 mumps cases (1.6 cases per 1,000 population). Of the 2,223 mumps cases, 1,566 (70.4%) were reported from Northern Regional Health and 370 (16.6%) from Winnipeg Regional Health Authority. Females accounted for 48.8% (n=1,084) of all provincial cases (**Table 1**).

Overall, in Mantioba incidence was highest (3.4 cases per 1,000) in people aged 18–29 years. In Northern Regional Health (**Figure 2**), incidence in people aged 30–45 years (32.5 cases per 1,000) was similar to that in people aged 18–29 years (32.0 cases per 1,000). Incidence in Northern Regional Health (20.4 cases per 1,000) was substantially higher than in all other regions (range=0.5–0.7 cases per 1,000). MHSAL received one report of orchitis and one report of meningitis likely due to mumps infection. No deaths were reported.

Laboratory results

The majority of all confirmed cases (97.1%) were laboratory-confirmed, including 87.8% by RT-PCR testing, 9.2% by serology and 0.1% by viral culture; 2.8% of cases in symptomatic patients were confirmed by an epidemiologic link to laboratory-confirmed cases.

Initially, all samples were shipped to NML for genotyping. After the volume of samples exceeded the NML's capacity, approximately 10% of randomly selected samples were cultured and genotyped. Of these 243 samples, 229 (94.2%) were found to be genotype G, the endemic mumps virus genotype circulating in Canada and the US (12). The remaining samples could not be sequenced.

Figure 1b: Confirmed cases of mumps (N=2,223) by month of symptom onset and health region, Manitoba, September 2016–December 2018

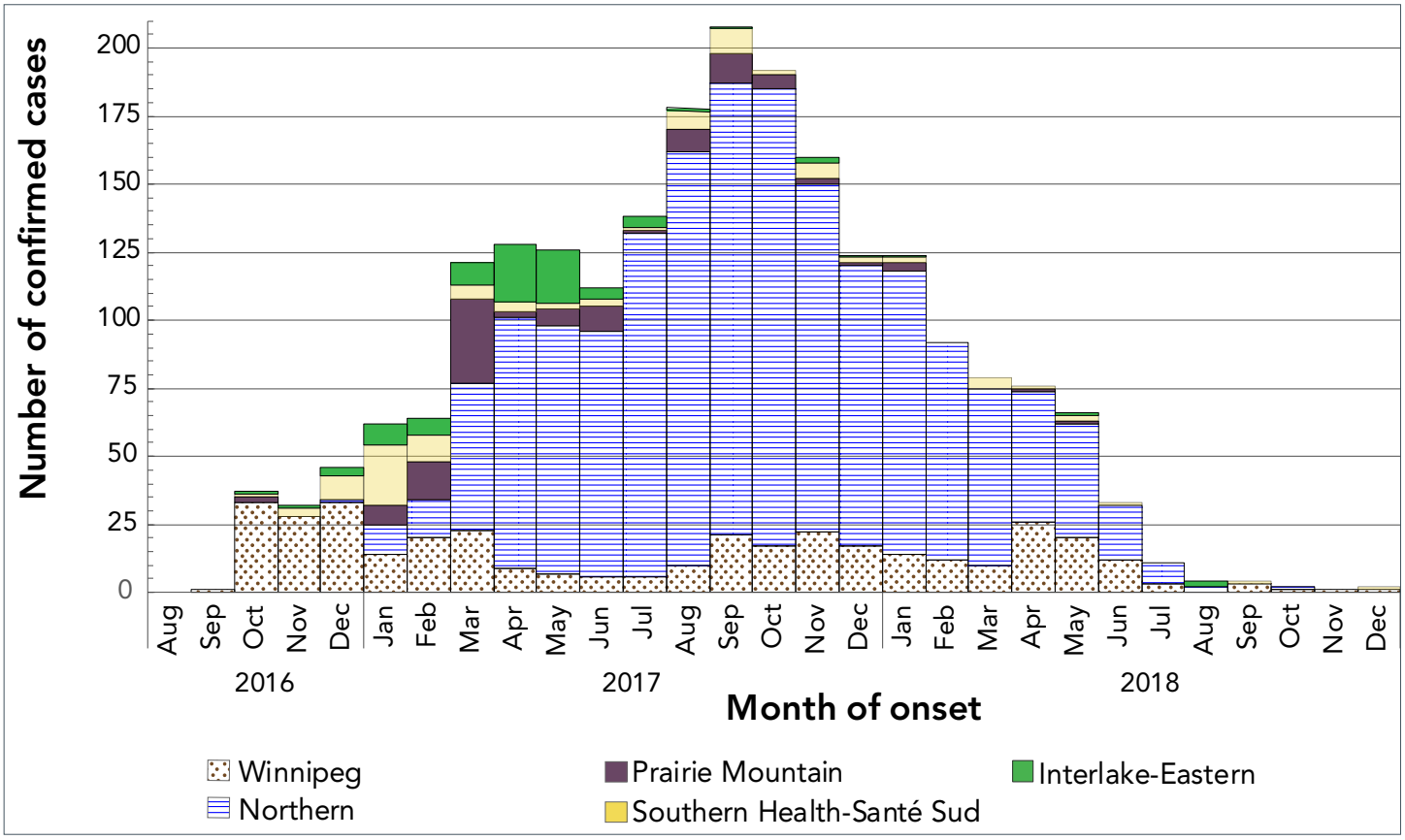
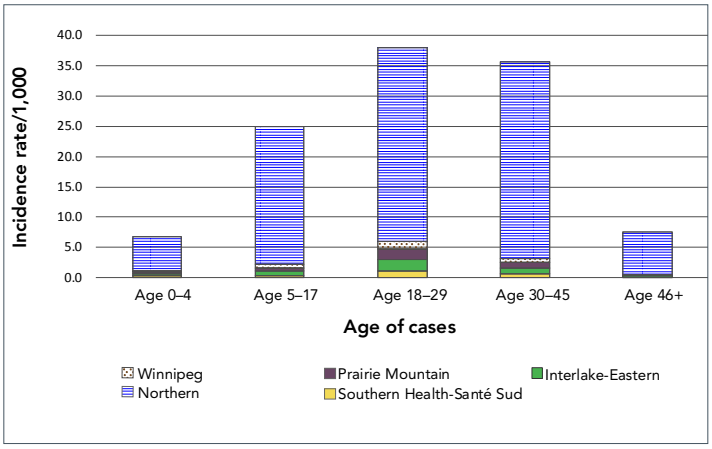


Table 1: Characteristics of confirmed mumps cases by health region, Manitoba, Canada, September 2016–December 2018

Characteristics	Regional health authority					Total
	Northern	Winnipeg	Prairie Mountain	Southern Health–Santé Sud	Interlake–Eastern	
Cumulative incidence[a]	20.4	0.5	0.6	0.5	0.7	1.6
Cases, N	1,566	370	104	98	85	2,223
Percent of total cases	70.4	16.6	4.7	4.4	3.8	100
Female, N	809	164	40	28	43	1,084
Percent	51.7	44.3	38.5	28.6	50.6	48.8
Median age, years	26	24	26	24	27	25
Quartile 1	15	18	19	18	18	17
Quartile 3	36	33	36	38	40	36
Unvaccinated[b], N	51	20	3	5	4	83
Percent	5.9	11.4	6.4	10.9	8.3	7.0
Partially vaccinated[c], N	200	42	10	9	17	278
Percent	23.1	24.0	21.3	19.6	35.4	23.5
Fully vaccinated[d], N	616	113	34	32	27	822
Percent	71.0	64.6	72.3	69.6	56.3	69.5

[a] Cases per 1,000 population
[b] Zero doses of measles–mumps–rubella (MMR) or measles–mumps–rubella–varicella (MMRV) vaccine in patients aged 5–29 years and who registered with Manitoba Health, Seniors and Active Living (MHSAL) at age younger than two months
[c] One dose of MMR or MMRV in patients aged 5–29 years and who registered with MHSAL at age younger than two months
[d] Two or more doses of MMR or MMRV in patients aged 5–29 years and who registered with MHSAL at age younger than two months

Figure 2: Cumulative incidence rate per 1,000 of mumps cases by age group and health region, Manitoba, Canada, September 2016–December 2018



Vaccination status

The vaccination history for cases younger than 30 years who had lived in Manitoba since birth was available from the population-based provincial immunization registry. Based on the registry, of the 1,183 (53.2%) cases aged 5–29 years who were eligible for two doses of mumps-containing vaccines in Manitoba and were registered with MHSAL at age younger than two months, 822 (69.5%) had received at least two doses (Table 1). Two-dose mumps vaccination coverage among mumps cases ranged from 56.3% in the Interlake–Eastern region to 72.3% in the Prairie Mountain region. Of the 822 cases vaccinated with at least two doses of mumps-containing vaccine, the median interval between receipt of the last dose and symptom onset was 11.3 years.

Discussion

MHSAL led an outbreak investigation during a provincial mumps outbreak that continued from September 2016 to December 2018. According to the Surveillance and Epidemiology Division at the Public Health Agency of Canada, as of January 2019 the magnitude of this outbreak was the largest in Canada in the last 20 years, based on reported cases. This outbreak began in university students with high two-dose mumps vaccination coverage and spread to other communities across Manitoba, likely facilitated by social events. The activity level was especially high and prolonged in Northern Regional Health, the most rural region of Manitoba with a large number of isolated communities.

This outbreak revealed a large susceptible population, despite the availability of publicly funded mumps vaccinations for 30 years. Low mumps vaccination coverage probably contributed to this outbreak, though the contribution varied by geographic region. Mumps vaccination coverage in Manitoba has remained below the estimated 92% needed to achieve and sustain herd immunity (13). In 2017, 90% of those aged 17 years who had lived continuously in Manitoba since birth had two doses of mumps-containing vaccines recorded in the provincial immunization registry compared to 31% of those aged 17 years who had not lived continuously in Manitoba since birth, partially due to incomplete records in the registry for residents not born in Manitoba (14).

Cases included young, vaccinated adults, indicating that waning vaccine-induced immunity was probably a more important contributor to this outbreak (3). Almost three-quarters (70%) of cases with records in the provincial registry were fully immunized. However, of cases vaccinated with at least two documented doses of mumps-containing vaccine, a median of more than 11 years had elapsed since receipt of the most recent dose. This is consistent with other reports of waning vaccine-induced immunity against mumps disease (15–17).

This waning immunity might be attributable to the absence of boosting from natural exposure to wild-type mumps virus (18,19). Unlike other Canadian provinces and territories that have reported smaller mumps outbreaks since the 1980s, mumps reports were historically rare in Manitoba (7). In northern Manitoba, where the population density is low and vaccination

coverage is high, natural boosting from disease exposure is even less likely than in the other areas in Manitoba.

In addition, the mumps strain in the North American (Jeryl-Lynn) vaccine is genotype A. The replacement of the genotype A mumps virus from the prevaccine era with the genotype G mumps virus currently endemic in Canada and the US may also contribute to waning immunity (20).

The number of reported mumps-associated complications in this outbreak was low, which might reflect gaps in public health surveillance as case investigation might have been conducted before complications developed. It is possible that previous mumps vaccination conferred some protection against severe disease (21,22). Because complications were infrequently reported, analysis of vaccine effectiveness against severe mumps complications was not possible.

Limitations

The vaccination history for some cases was not available in the provincial immunization registry; therefore, coverage among cases might have been higher. If so, low coverage might have contributed even less to this outbreak than waning vaccine-induced immunity. In a future study, this research team plans to explore the relationship between time since the last dose of mumps-containing vaccine and mumps disease.

Conclusion

A substantial and sustained public health effort was required during this outbreak, which originated among university students and spread throughout the province. This highlights the importance of achieving and maintaining high two-dose coverage of mumps-containing vaccines in the population. Due to waning of vaccine-induced immunity, a large cohort of susceptible people may remain in the population; a third dose of mumps-containing vaccine may be considered in future outbreaks to boost vaccine-induced immunity if warranted by epidemiologic data.

Authors' statement

YW — Conceptualization, methodology, investigation, formal analysis, writing–original draft, writing–review & editing
KW — Conceptualization, methodology, writing–review & editing
RR — Methodology, writing – review & editing
KK — Methodology, writing – review & editing
CL — Supervision, writing – review & editing

Conflict of interest

No potential conflicts of interest were disclosed.

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Measles surveillance in Canada: 2018

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Abstract

Background: Measles has been eliminated in Canada since 1998. Every year, the Public Health Agency of Canada presents epidemiologic evidence to the Pan American Health Organization (PAHO) to verify that measles continues to be eliminated in Canada. The objectives of this article are to: provide an epidemiologic summary of measles activity reported in 2018 in Canada, and provide documented evidence to support the continued verification of measles elimination status in Canada.

Methods: Measles surveillance data were captured by the Canadian Measles and Rubella Surveillance System (CMRSS) and descriptive analyses of demographics and risk factors were performed. Outbreak characteristics were summarized and genotypic analyses conducted. Surveillance data for 2018 were evaluated against PAHO's essential criteria for measles elimination status.

Results: In 2018, 29 measles cases were reported across five provinces in Canada, an incidence rate of 0.8 cases per 1,000,000 population. Of these 29 cases, 16 were imported and five resulted in further transmission within Canada. The age-specific incidence rate was highest among those aged younger than one year (10.2 cases per 1,000,000 population, n=4). Only nine cases were considered up-to-date for measles vaccination, and 11 cases were hospitalized. Genotype information was available for most of the measles cases (n=27); they were all found to be genotypes that circulated globally in 2018. Canada met or partially met three out of four of PAHO's criteria for verification of measles elimination.

Conclusion: Although importations and areas of low vaccination coverage continue to challenge Canada's elimination status, there is no evidence that endemic transmission of the measles virus has been re-established. Canada maintains its measles elimination status.

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

Introduction

Measles, one of the most contagious human infectious diseases, was responsible for an estimated 2.6 million deaths per year before the introduction of the measles vaccine in 1963 (1). Measles has been eliminated in Canada since 1998 (2). The World Health Organization (WHO) defines elimination as the absence of endemic measles transmission for at least 12 months in a defined geographic area with a well-performing surveillance system, which includes genotyping of the virus identified in confirmed cases of measles (3).

Nevertheless, measles continues to be an important public health issue globally. In 2018, there were about 9.8 million measles cases and over 140,000 measles-related deaths worldwide (4). This represents an increase in the global number of measles cases of over 40% and an increase in the global number of measles-related deaths of almost 30% compared to 2017 (5). Most measles-related deaths occurred in children under five years of age (1).

As measles continues to circulate internationally, the risk of importing measles into Canada persists. The estimated first dose measles-containing vaccine coverage rate is 90% among two year olds, which is below the minimum 95% vaccination coverage for all population cohorts needed to prevent sustained measles transmission (2,6). Timely and enhanced national surveillance of measles is necessary in order to rapidly detect cases and

outbreaks and put into effect public health action that stops further transmission. Enhanced surveillance is conducted through the Canadian Measles and Rubella Surveillance System (CMRSS), which is coordinated by the Public Health Agency of Canada's (PHAC) Centre for Immunization and Respiratory Infectious Diseases and the National Microbiology Laboratory (NML). This surveillance involves weekly collection of data on confirmed measles cases (7) from all 13 provinces and territories (8).

Canada continues to be committed to measles elimination and has set vaccination coverage goals and vaccine-preventable disease reduction targets based on international standards and best practices as part of the National Immunization Strategy objectives for 2016–2021 (9). These national goals and targets are consistent with commitment to WHO disease elimination targets and the Global Vaccine Action Plan, within the Canadian context. Under the Strategy, Canada targets 95% coverage (and hence measles elimination) with one dose of the measles–mumps–rubella (MMR) vaccine by two years of age and 95% coverage with two doses of MMR by seven years of age. All the provinces and territories recommend the first dose of measles-containing vaccine at 12 months of age and the second dose between 18 months and six years of age (10). All provinces and territories, which are responsible for delivering health services including vaccination programs, have endorsed the national goals and targets.

The objectives of this surveillance report are to provide an epidemiologic summary of measles activity reported in Canada for 2018; and provide documented evidence to support the continued verification of measles elimination status in Canada.

Methods

Surveillance data

Confirmed cases of measles meeting the national case definition (7) were reported weekly to PHAC by provinces and territories through CMRSS. All confirmed cases of measles with rash onset between January 1, 2018, and December 31, 2018, were included in this report. Epidemiologic weeks of rash onset are assigned by the Centre for Immunization and Respiratory Infectious Diseases with week one ending on the first Saturday of the year. A data validation process was conducted with all provinces and territories, which 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.

Genotyping

Virus genotyping is routinely performed at NML for all confirmed cases in Canada for which viral specimens are available. Genotyping is conducted by sequencing of specific measles genome targets in accordance with WHO guidelines (11,12). Measles viral sequences are deposited in the WHO Measles Nucleotide Surveillance (MeaNS) database and compared to designated named strains and to sequences deposited by other members of the global measles laboratory network (12,13).

Analysis

Descriptive epidemiologic analyses were performed based on available fields in the CMRSS database (7). Subgroup analysis was precluded by the small number of measles cases reported in 2018.

Cases aged 1–6 years with at least one documented dose of measles-containing vaccine were classified as up-to-date in terms of measles vaccination. Those aged seven years or over and born after 1970 were classified as up-to-date for measles vaccination if they had two documented doses of measles-containing vaccine and were classified as under-vaccinated if they had only one documented dose. An adult born before 1970 was presumed to have acquired natural immunity and was considered up-to-date in terms of measles vaccination (9,14). A child under one year of age was classified as up-to-date for measles vaccination status regardless of vaccination status unless the child travels outside of North America, in which case the vaccine can be given after six months of age (15).

A case was considered to be hospitalized only if admitted to hospital due to measles or due to disease complications; if only seen in the emergency department, the case was not considered hospitalized.

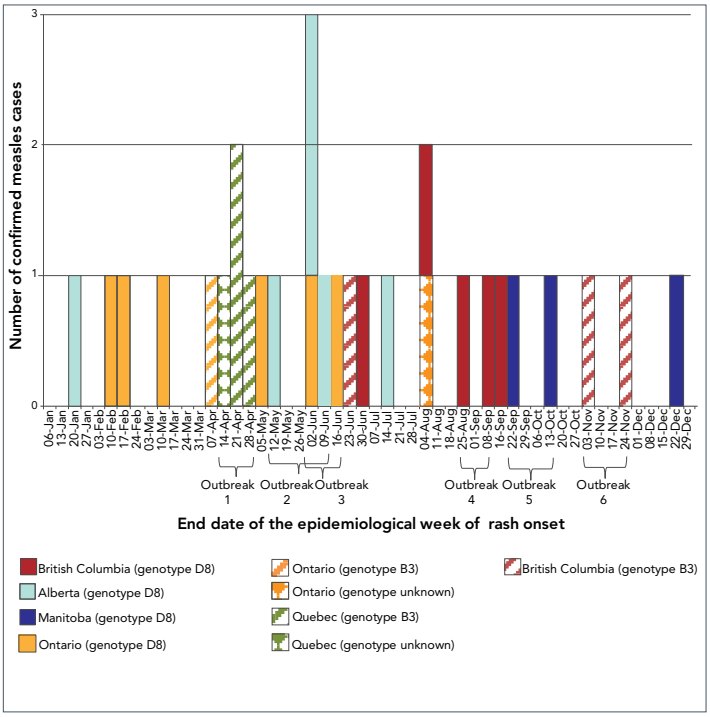
The source of exposure was identified by the reporting province or territory in the course of the public health investigation. The sources of exposure were classified as outside Canada (imported); within Canada and linked to an imported case (import-related); within Canada and linked to a case of unknown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

Measles outbreaks, defined as two or more confirmed cases linked either epidemiologically, virologically or both, were described based on available information (14). Incidence rates were calculated using Statistics Canada population estimates for July 1, 2018.

Results

A total of 29 confirmed measles cases (incidence rate of 0.8 cases per 1,000,000 population) in five provinces were reported in Canada in 2018. Of these 29 confirmed cases, 27 were genotyped. The genotypes detected were B3 (n=7) and D8 (n=20), both of which circulated globally in 2018 (4). **Figure 1** shows the distribution of measles cases by epidemiologic week of rash onset, outbreak number, genotype and reporting province or territory. Altogether, 28 cases were laboratory-confirmed and one case was epidemiologically linked to a laboratory-confirmed case.

Figure 1: Number of reported measles cases (N=29), by epidemiologic week of rash onset, outbreak number, genotype and reporting province or territory, Canada, 2018



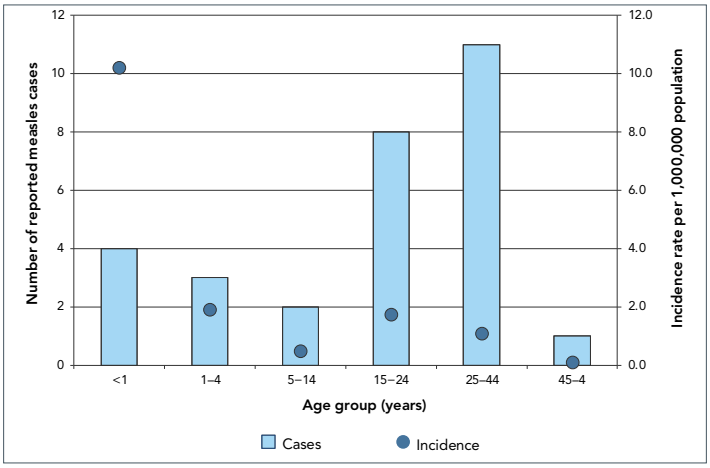
Information on age, sex and province or territory of residence was available for all measles cases reported in 2018. The cases ranged from younger than one to 53 years old, with a median age of 21 years. The most frequently reported age group was 25–44 years (n=11), with the next most frequently reported aged 15–24 years (n=8). The highest incidence rate was reported in infants younger than one year of age, at 10.2 cases per 1,000,000 population (**Figure 2**). Three-quarters of cases (n=22) were female.

Five Canadian provinces reported measles cases in 2018: Ontario (n=9, which included one visitor to Ontario); British Columbia (n=8); Alberta (n=6); Quebec (n=4); and Manitoba (n=2). Incidence rates ranged from 0.5 to 1.6 cases per 1,000,000 population in the provinces that reported measles cases.

Vaccination

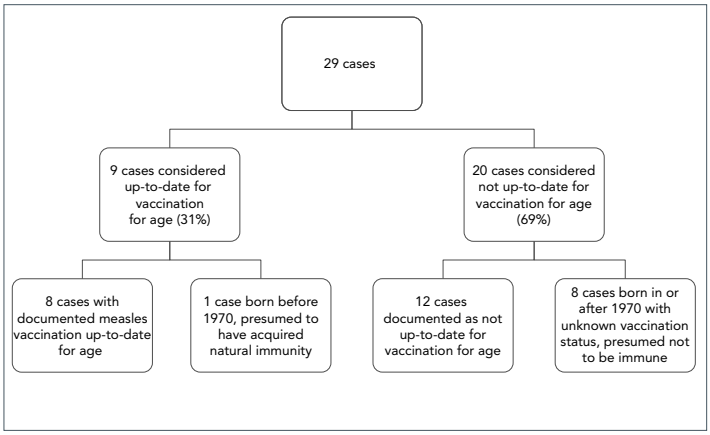
Of the 29 measles cases reported in 2018, two-thirds (n=20) were considered not up-to-date for measles vaccination for age. Of these 20 cases, 12 were documented as being not up-to-date for vaccination for age. Eight cases had unknown or missing vaccination history, but were born after 1970 and were therefore presumed not to have acquired natural immunity (15,16). Of the 12 cases documented as being not up-to-date for vaccination for age, three cases were between six months and one year of age and had travelled outside of North America without receiving the first dose of measles-containing vaccine as indicated in current vaccine recommendations (15).

Figure 2: Confirmed measles cases (N=29) and incidence rates (per 1,000,000 population) by age group, Canada, 2018



Of the 29 measles cases reported in 2018, nine were considered up-to-date for measles vaccination for age, with eight documented as having received appropriate measles vaccination for age (including one infant younger than one year of age who was unvaccinated and had not travelled outside of North America) (**Figure 3**). One case with unknown vaccination history had been born before 1970 (and was therefore considered up-to-date for measles immunization) and had not travelled outside of North America (15).

Figure 3: Vaccination status of confirmed measles cases (N=29), Canada, 2018



Hospitalization

Of the 29 cases reported in 2018, 24 had hospitalization information. In total, 11 cases were hospitalized, a measles-specific hospitalization rate of 0.3 per 1,000,000 population. The median age of hospitalized cases was 15 years (range: 4–51 years). Of the 11 hospitalized cases, eight had vaccination information available. Of these eight cases, six had no documented doses of measles-containing vaccine but two were considered fully vaccinated.

Sources of exposure

Of the 29 confirmed cases of measles in 2018, 16 were imported into Canada after exposure to measles during travel to the following countries or regions: India (n=7); Ukraine (n=4); Brazil (n=1); the Philippines (n=1); Romania (n=1); Southeast Asia (not including India, n=1); and Uganda (n=1). Fourteen of the imported cases were genotyped, and the genotypes were consistent with those known to be endemic in the source country or reported to the WHO MeaNS database as detected in the source country (13).

Of the 16 imported cases, five transmitted the disease within Canada, resulting in a further seven import-related cases. In total, imported and import-related cases accounted for three-quarters (n=23) of cases in 2018. Of the cases that were neither imported nor import-related (n=6), four had no recent history of travel or known links to other confirmed measles cases, one was exposed in Canada to a case of unknown origin and one cannot be assigned as imported or non-imported because the exposure period occurred both in another country with known measles activity and within Canada. All six of these remaining cases were genotyped and the genotypes were D8 (n=5) and B3 (n=1), both of which were circulating globally.

Outbreaks

Six measles outbreaks were identified in Canada in 2018 (details are provided in **Table 1**). All outbreaks were small (2–4 cases per outbreak) and transmission was limited to household contacts or other close contacts of the index case. No outbreak went beyond the second generation. For all outbreaks combined, the median time interval between the rash onsets of the index case and the secondary cases was 13 days, with a range of 9 to 27 days. Only one case had an incubation period that was outside the expected range of 7 to 21 days; this case had received immune globulin shortly after exposure, which may have delayed but not prevented disease onset. Of the 29 cases reported in 2018, 14 were outbreak-related.

Table 1: Summary of measles outbreaks in Canada (N=6), by earliest date of rash onset, 2018

Outbreak number	Province/ territory	Number of cases	End date of epidemiologic week of rash onset of index case	Genotype (Strain)[a]	Description
1	Quebec	4	April 15	B3 (MVs/ Dublin. IRL/8.16/)	The index case reported travel to Romania during the exposure period. Three secondary cases among family contacts of the index case were subsequently reported. All of the cases were unvaccinated.
2	Alberta	2	May 13	D8	The index case reported travel to India during the exposure period. One secondary case, a close contact of the index case, was subsequently reported. The vaccination history of the index case was unknown. The secondary case was unvaccinated.
3	Ontario	2	June 3	D8 (MVs/ Gir Somnath. IND/42.16/)	The index case reported travel to Ukraine during the exposure period. One secondary case, a close contact of the index case, was subsequently reported. The vaccination history of the index case was unknown. The secondary case was unvaccinated.
4	British Columbia	2	August 26	D8 (MVs/ Osaka. JPN/29.15/)	The index case did not report travel outside of Canada during the exposure period, but was potentially exposed to an international measles case at a Canadian port. One secondary case, a contact of the index case, was subsequently reported. Both cases were fully vaccinated.
5	Manitoba	2	September 9	D8 (MVs/ Samut Sakhon. THA/49.16)	The index case reported travel to Southeast Asia during the exposure period. One secondary case, a close contact of the index case, was subsequently reported. The index case was unvaccinated. The secondary case was fully vaccinated.
6	British Columbia	2	November 4	B3	The index case reported travel to the Philippines. One secondary case, a contact of the index case, was subsequently reported. The vaccination history of the index case was unknown. The secondary case was fully vaccinated.

[a] World Health Organization (WHO)-named strain, in brackets, if applicable. WHO-named strains represent a system to reflect currently circulating epidemiologically significant lineages of measles viruses within the existing genotype classification system. This enables tracking of global transmission pathways (12). The strains are defined within the Measles Nucleotide Surveillance (MeaNS) database and represent a lineage, a precisely defined virus strain, that has been frequently detected within a two-year period in multiple countries. GenBank accession numbers for the named strains are KY013331, KY120864, LC072667 and MK079566

Discussion

Epidemiology of measles in Canada, 2018

In 2018, 29 confirmed cases of measles were reported in Canada. This is below the median number of cases reported since the beginning of enhanced surveillance in 1998 (median of 35 cases per year). This decrease in the number of cases was in contrast to a trend of increasing rates of measles globally. In the United States, the number of measles cases and outbreaks in 2018 increased compared to 2017 (5,17). Of the 16 measles cases imported into Canada in 2018, only five resulted in secondary transmission, demonstrating that sustained transmission was not observed.

Imported and import-related cases accounted for the large majority of measles cases in 2018, underscoring the ongoing risk that international travel places on the spread of measles in Canada. This was reflected by the genotype data of the cases that identified the two main genotypes, B3 and D8, both of which were circulating globally in 2018. These genotypes were also circulating globally in 2017 and were detected in Canada (18). However, the genotypes capture genetically related sequences, and multiple strains are contained within the genotypes. For measles molecular epidemiology, strains are informative. The strains detected in 2017, with the exception of the genotype B3 named strain MVs/Dublin.IRL/8.16/, were not detected in 2018.

Over two-thirds of the measles cases reported in 2018 were not up-to-date for measles vaccination for age. This highlights the importance of adhering to vaccine recommendations. The seven cases of breakthrough disease that developed measles despite being fully vaccinated may have failed to develop an appropriate immune response. Alternatively, vaccine-induced immunity may have waned to non-protective levels or the vaccine was stored, handled or administered improperly (19,20). Two of these seven cases had documented doses of measles vaccination outside of Canada, where vaccine storage and administration guidelines may be different.

Over one-third (11/29) of the cases required hospitalization, supporting previously published evidence that measles infection can lead to serious illness (1).

Verification of measles elimination through national and international goals and targets

The Pan American Health Organization (PAHO) set out four criteria for the ongoing verification of measles elimination (21). Canada met or partially met three of the four criteria in 2018 (**Table 2**). Since the criteria are based on investigation of measles-like illnesses (i.e. suspected cases), whereas only confirmed cases are nationally notifiable in Canada, the data presented in this article can only indirectly address the PAHO criteria. Canada's national surveillance system for measles performs well, being able to detect imported and import-related cases, as well as cases with unknown sources of exposure. By ensuring measles elimination according to internationally accepted criteria, Canada also meets its established national goals and targets.

Table 2: Pan American Health Organization essential criteria for the verification of measles elimination

Criterion	Indicator	Description
Verify the interruption of endemic measles cases for a period of at least three years from the last known endemic case, in the presence of high-quality surveillance.	Zero cases of endemic transmission.	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 (3,18,21,22).
Maintain high-quality surveillance, sensitive enough to detect imported and import-related cases.	>2 suspect cases per 100,000 population adequately investigated.	Criterion partially met. CMRSS allows the identification of imported and import-related cases that are confirmed to meet the case definition, but not suspected cases.
Verify the absence of endemic measles virus strains through viral surveillance.	Measles genotype assessed in 80% of outbreaks.	Criterion met. Genotype information was available for 6/6 of outbreaks reported in 2018. Genotype information was also available for 100% of sporadic (non-outbreak related) measles cases.
Verify adequate immunization in the population.	95% of population cohorts aged 1–40 years have received a measles-containing vaccine.	Criterion not met. Canada currently measures (biennially) measles vaccination coverage rates at two and seven 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% (6).

Abbreviation: CMRSS, Canadian Measles and Rubella Surveillance System

Canada falls short on 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%, below the PAHO indicator of 95% (6). 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.

Limitations

Only measles cases that interact with the Canadian health system are captured in enhanced measles surveillance, and therefore visitors to Canada who do not seek healthcare may not be detected. However, most chains of transmission did result from known imported cases in 2018.

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.

Conclusion

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. Although importation of measles and areas of low vaccination coverage continue to challenge Canada's elimination status, there is no evidence that endemic transmission of the measles virus has been re-established. This is supported by high overall vaccination coverage rates, the small number of secondary cases that resulted from imported cases and the available laboratory information that indicates that cases resulted from measles strains circulating internationally in 2018.

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
DM — Conceptualization, methodology, writing-review and editing, project administration

Conflict of interest

None.

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Risk factors for drug-resistant tuberculosis at a referral centre in Toronto, Ontario, Canada: 2010–2016

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Abstract

Background: Drug-resistant tuberculosis (TB) poses a major public health concern worldwide. However, no studies have addressed risk factors for drug resistance in Ontario, which has its own unique profile of immigrants. We evaluated demographic and clinical risk factors for drug-resistant TB among patients treated at West Park Healthcare Centre, located in Toronto, Ontario (Canada).

Methods: All patients who were diagnosed with TB and treated at West Park Healthcare Centre between January 2010 and December 2016 were included in this retrospective cohort study. Characteristics of patients with isoniazid mono-resistant (INH-R) TB and multidrug resistant (MDR) TB were compared to patients with drug-susceptible TB with bivariate and multivariable logistic regression.

Results: Risk factors for INH-R TB included younger age (younger than 35 years), prior TB treatment, non-diabetic and birth in a non-South-East Asian country, but only the latter two factors were significant in multivariable analysis. On the other hand, we found younger generation (younger than 65 years), birth in European region, recent arrival to Canada (fewer than 120 months), prior treatment and human immunodeficiency virus (HIV) infection were associated with MDR-TB, among which younger age (younger than 35 years), more recent immigration (fewer than 24 months), prior treatment and HIV infection were significant in multivariable analysis.

Conclusion: These findings may be of use to TB clinicians in the province by informing the initial empiric antibiotic regimen prescribed while awaiting phenotypic drug susceptibility testing and assisting in decisions regarding whether to request rapid molecular drug susceptibility testing.

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Keywords: tuberculosis, *Mycobacterium tuberculosis*, drug susceptibility test, isoniazid-resistant, multidrug-resistant

Introduction

Drug-resistant tuberculosis (TB) poses a major public health concern worldwide. The two most common, clinically important forms of drug-resistant TB include isoniazid (INH) mono-resistant (INH-R) (resistant to INH) and multidrug-resistant (MDR) TB (resistant to at least INH and rifampin, RMP) (1,2). Drug resistance is identified either by genotypic methods or phenotypic culture-based drug susceptibility testing (DST), the latter being considered the gold standard (3). Identification of drug resistance is critical to guide appropriate selection of anti-mycobacterial drugs and to prevent further drug resistance. However, phenotypic DST can take weeks to report, and not all clinical settings perform rapid molecular DST routinely. Therefore, clinicians often start empiric TB treatment prior to the availability of phenotypic DST results, and may expand the initial empiric regimen, or may request rapid molecular DST, based upon an individual patient's risk factors for drug resistance.

Few studies have described risk factors for drug resistance in Canada. In British Columbia, age, foreign-born status, ethnicity, prior treatment, diagnosis outside of Canada and certain

birth country regions were associated with drug resistance from 1990–2001 (4). In Alberta from 1982–2011, age (younger than 65 years), prior treatment, arrival to Canada from 2002–2011, and recent emigration from Philippines and Vietnam were risk factors for MDR-TB in foreign-born persons (5). A national surveillance study found that age, foreign-born status, prior treatment, and certain World Health Organization epidemiological regions-of-birth were associated with drug resistance on a national level from 1997 to 2008 (1). However, no studies have addressed risk factors for drug resistance in Ontario, which has its own unique profile of immigrants (6) and has the highest burden of drug-resistant TB cases in Canada (7,8). There is also a need for more contemporary data, because risk factors may differ as immigration patterns change and as rates of drug-resistant TB, including primary MDR-TB, change world-wide.

The principal objective of this study was to evaluate possible demographic and clinical risk factors for drug-resistant TB among patients treated at West Park Healthcare Centre (WPHC) and to compare risk factors for INH-R TB against risk factors for MDR-TB. Additionally, the enrolled TB patients were reviewed according to the recent American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention (ATS/IDSA/CDC) statement (3), recommending rapid molecular testing for RMP +/- INH resistance be performed in the following patient sub-groups: 1) previous treatment; 2) born or lived for one or more years in a country with TB incidence of greater or equal to 20/100,000 or primary MDR prevalence of greater or equal to 2%; 3) contact with MDR; and 4) human immunodeficiency virus (HIV) infection.

Methods

The TB program at WPHC, located in Toronto, Ontario, is recognized as a referral centre for drug-resistant TB, and sees the majority of MDR-TB cases in the province (84% between 2000 and 2011) (9). All patients who were diagnosed with TB and treated at WPHC between January 2010 and December 2016 were included in this retrospective cohort study. Chart review was used to identify patients for inclusion and to extract demographic and clinical characteristics. The study protocol was approved by the Joint Bridgepoint/West Park Healthcare Research Ethics Board. In light of the retrospective design, the requirement of informed consent was waived.

Throughout the study period, all drug susceptibility testing was consistently performed at the Public Health Ontario TB and Mycobacteria Laboratory (Toronto, Ontario). The DST was performed according to Clinical Laboratory Standards Institute testing standards recommended methods (as available), using radiometric broth [BACTEC 460; Becton, Dickinson and Co., Franklin Lakes, New Jersey, United States (US)] until October 1, 2010, and nonradiometric broth (MGIT 960; Becton, Dickinson and Co.) thereafter (10,11). The first culture of *Mycobacterium tuberculosis* complex isolated from a patient was routinely tested for susceptibility to the four first-line drugs: INH; RMP; ethambutol; and pyrazinamide. Isolates resistant to INH at 0.1 mg/L were considered "resistant" herein, but were also tested at 0.4 mg/L and underwent moxifloxacin testing. Any isolate found resistant to RMP or any two of the first line drugs underwent DST to second line drugs. Second line susceptibility testing for the following drugs was performed during the study time period: rifabutin; amikacin; streptomycin; kanamycin; capreomycin; ofloxacin; ethionamide; and *p*-aminosalicylic acid. The DST for clofazimine was performed until October 1, 2010 and DST for moxifloxacin and linezolid started on October 1, 2010.

Characteristics of patients with INH-R TB and MDR-TB were compared with those patients with drug-susceptible (DS) TB (i.e. susceptible to the four first line drugs) using bivariate and multivariable logistic regression models. Statistical analyses were performed using GraphPad Prism 6.0 (GraphPad Software; La Jolla, California, US), StatPlus:macLE (AnalystSoft; Walnut, California, US) and Jamovi (Version 0.9, retrieved from https://www.jamovi.org). In bivariate analyses, many demographic characteristics (age, sex, birth country region and time from arrival in Canada) and clinical characteristics (known TB risk factors, location of TB and microbiologic results) were analysed for their possible association with drug-resistant TB, to be thorough and exploratory. Variables with a *p*-value less than 0.05 in bivariate analysis, and variables considered *a priori* to be clinically important (age, sex, birth country region, time from arrival in Canada and history of TB treatment) were selected for inclusion in the multivariable models. The multivariable models were restricted to foreign-born patients so that the association between time in Canada and drug resistance would be accurately studied. Patients were also divided into slightly different groups by DST (drug susceptible, non-MDR drug resistance and MDR/RMP resistance) to evaluate the recent recommendations for rapid molecular DST for rifampin put forth by the ATS/IDSA/CDC (3).

Results

Between 2010 and 2016, 485 patients with active TB were seen at WPHC, representing 11.1% of the total of 4,384 seen in Ontario (12). Among these WPHC patients, DST results were available in 82.9% (n=402/485) (**Table 1**). The other 83 patients (17.1%) did not have a phenotypic DST performed in Ontario (due to lack of culture confirmation or to a diagnosis made outside of Ontario), and were excluded from further risk factor analyses. The TB strains susceptible to the four first-line drugs accounted for 76.1% (n=306/402), strains INH-R accounted for 10.9% (n=44/402) and strains resistant to both INH and RMP +/- other drugs (MDR) accounted for 11.4% (n=46/402). Only four patients had mono-resistance to drugs other than INH (one to RMP and three to pyrazinamide), and two had poly-resistance to the first line drugs (but not MDR); six patients were excluded

from risk factor analyses. Extensively drug resistant TB (MDR with additional resistance to a fluoroquinolone and a second line injectable) was also rare at 1.0% (n=4/402).

Table 1: Phenotypic drug susceptibility test results among patients enrolled in the study

Drug susceptibility	n/N	%
Drug susceptibility test for first-line drug (n=402 with DST available)		
Sensitive to first-line four drugs	306/402	76.1
Mono-resistance to INH	44/402	10.9
Mono-resistance to RMP	1/402	0.2
Mono-resistance to EMB	0/402	0.0
Mono-resistance to PZA	3/402	0.7
Poly-resistance to first-line drugs	2/402	0.5
Multidrug resistance (INH and RMP)	46/402	11.4
Extensively drug-resistance	4/402	1.0
Any resistance to INH	92/402	22.9
Any resistance to RMP	47/402	11.7
Any resistance to EMB	21/402	5.2
Any resistance to PZA	24/402	6.0
Drug susceptibility test for second-line drug (n=46 with MDR-TB)		
Any resistance to EMB	20/46	43.5
Any resistance to PZA	20/46	43.5
Any resistance to RFB	41/46	89.1
Any resistance to AMK	3/45	6.7
Any resistance to SM	29/46	63.0
Any resistance to KM	6/41	14.6
Any resistance to CM	6/46	13.0
Any resistance to MXF	5/41	12.2
Any resistance to OFX	8/46	17.4
Any resistance to ETA	13/46	28.3
Any resistance to PAS	5/46	10.9
Any resistance to LZD	0/41	0.0
Any resistance to CLO	0/5	0.0

Abbreviations: AMK, amikacin; CLO, clofazimine; CM, capreomycin; DST, drug susceptibility test; EMB, ethambutol; ETA, ethionamide; INH, isoniazid; KM, kanamycin; LZD, linezolid; MDR, multidrug-resistant; MXF, moxifloxacin; OFX, ofloxacin; PAS, *p*-aminosalicylic acid; PZA, pyrazinamide; RFB, rifabutin; RMP, rifampin; SM streptomycin; TB, tuberculosis

The TB patients were divided into three groups based on DST: DS-TB (n=306); INH-R (n=44); and MDR (n=46) and their demographic characteristics are shown in **Table 2** and clinical characteristics in **Table 3**. Compared with patients with DS-TB (Table 2), in unadjusted analyses, patients with INH-R TB were significantly younger; odds ratio (OR) for age younger than 35 years=2.58, 95% CI 1.06–6.30, with reference age older than 65 years, and less likely to have been born in South-East Asia (OR 0.157, 95% CI 0.03–0.91). Patients with INH-R TB (Table 3) were also more likely to have been previously treated (OR 2.39, 95% CI 1.01–5.68), and less likely to have diabetes (OR 0.26, 95% CI 0.08–0.87) in unadjusted analyses. Compared with DS-TB patients, in unadjusted analyses, patients with MDR-TB (Table 2) were also significantly younger (younger than 35 years, OR 15.2, 95% CI 3.49–66.1) and more likely to have been born in Europe (OR 15.6, 95% CI 1.66–146.4) and had a significantly shorter time from arrival to Canada to TB diagnosis. These patients (Table 3) were more likely to have been previously treated (OR 5.74, 95% CI 2.77–11.9), more likely to have HIV infection (OR 4.76, 95% CI 1.29–17.5) and more likely to have only pulmonary TB and less likely to have pulmonary and extrapulmonary TB.

In multivariable analysis restricted to foreign born patients (**Table 4**), patients with INH-R TB were less likely to be from South-East Asia than DS-TB patients (OR 0.10, 95% CI 0.01–0.73), and less likely to have diabetes (OR 0.18, 95% CI 0.04–0.81). Risk factors for MDR-TB in multivariable analysis restricted to foreign born patients included age younger than 35 years old (OR 8.11, 95% CI 1.43–45.7), TB diagnosis less than 24 months after arrival in Canada (OR 4.11, 95% CI 1.21–13.9), history of TB treatment (OR 3.78, 95% CI 1.58–9.05) and HIV infection (OR 10.95, 95% CI 1.90–62.9).

In our evaluation of the 2017 ATS/IDSA/CDC recommendations for rapid molecular DST for rifampin, we found that patients with MDR/RMP resistance were significantly more likely to have had previous TB treatment (OR 5.39, 95% CI 2.57–11.3) and HIV infection (OR 4.26, 95% CI 1.06–17.0) than DS-TB patients in multivariable analysis (**Table 5**).

Table 2: Demographic characteristics of all TB patients enrolled into the study

Demographic characteristic	All TB patients		DS-TB		INH-R TB		INH-R TB vs DS-TB			MDR-TB		MDR-TB vs DS-TB		
	(n=485)	%	(n=306)	%	(n=44)	%	OR	(95% CI)	*p*-value	(n=46)	%	OR	(95% CI)	*p*-value
Age, years														
Younger than 35 years	146	30.1	79	25.8	17	38.6	2.58	(1.06–6.30)	0.037	25	54.3	15.1	(3.49–66.11)	0.01
35–65 years	212	43.7	131	42.8	19	43.2	1.74	(0.73–4.14)	0.210	19	41.3	6.96	(1.58–30.6)	<0.001
Older than 65 years	127	26.2	96	31.4	8	18.2	1.0	reference[a]	N/A	2	4.3	1.0	reference[a]	N/A
Gender														
Sex, female	215	44.3	120	39.2	24	54.5	1.86	(0.99–3.51)	0.056	24	52.2	1.69	(0.91–3.15)	0.098
Country of birth														
Foreign-born	450	92.8	280	91.5	40	90.9	0.93	(0.31–2.80)	0.895	45	97.8	4.18	(0.56–31.53)	0.166
Canadian-born	35	7.2	26	8.5	4	9.1	1.0	reference[a]	N/A	1	2.2	1.0	reference[a]	N/A
Birth country WHO region														
African Region	43	8.9	27	8.8	3	6.8	0.72	(0.15–3.54)	0.688	2	4.3	1.92	(0.16–22.5)	0.602
Region of the Americas[b]	27	5.6	18	5.9	3	6.8	1.08	(0.22–5.44)	0.923	0	0.0	N/A	reference[a]	N/A
Eastern Mediterranean Region	49	10.1	29	9.5	5	11.4	1.12	(0.27–4.62)	0.875	2	4.3	1.79	(0.15–20.9)	0.641
European Region	21	4.3	10	3.3	0	0.0	1.0	reference[a]	N/A	6	13.0	15.6	(1.66–146.4)	0.016
South-East Asia Region	124	25.6	83	27.1	2	4.5	0.157	(0.03–0.91)	0.038	14	30.4	4.38	(0.55–34.9)	0.163
Western Pacific Region	186	38.4	113	36.9	27	61.4	1.55	(0.50–4.82)	0.446	21	45.7	4.83	(0.62–37.5)	0.132
Canada	35	7.2	26	8.5	4	9.1	1.0	reference[a]	N/A	1	2.2	1.0	reference[a]	N/A
Months from arrival to TB diagnosis[c]														
Less than 24 months	93	19.2	45	14.7	6	13.6	1.13	(0.42–3.01)	0.813	18	39.1	7.60	(3.09–18.6)	<0.001
24–120 months	141	29.0	80	26.1	16	36.4	1.69	(0.82–3.50)	0.157	19	41.3	4.51	(1.89–10.7)	<0.001
More than 120 months	213	43.9	152	49.7	18	40.9	1.0	reference[a]	N/A	8	17.4	1.0	reference[a]	N/A

Abbreviation: DS, drug susceptible; INH-R, isoniazid mono-resistant; MDR, multidrug resistant; N/A, not applicable; TB, tuberculosis; WHO, World Health Organization
[a] Reference means the control group which all other groups are compared to
[b] Excluded Canada
[c] Foreign-born only, three patients missing the date of arrival

Table 3: Clinical characteristics of all TB patients enrolled into the study

Clinical characteristics	All TB patients		DS-TB		INH-R TB		INH-R TB vs DS-TB			MDR-TB		MDR-TB vs DS-TB		
	(n=485)	%	(n=306)	%	(n=44)	%	OR	(95% CI)	*p*-value	(n=46)	%	OR	(95% CI)	*p*-value
TB risk factor														
History of TB treatment	70	14.4	26	8.5	8	18.2	2.39	(1.01–5.68)	0.048	16	34.8	5.74	(2.77–11.89)	<0.001
History of TB contact	102	21.0	64	20.9	7	15.9	0.72	(0.31–1.6)	0.442	9	19.6	0.92	(0.42–2.00)	0.833
History of known/ suspected DR-TB contact	4	0.8	1	0.3	1	2.3	7.09	(0.44–115.5)	0.169	1	2.2	6.77	(0.41–111.2)	0.179
Travel to high-incidence region	165	34.0	105	34.3	13	29.5	0.80	(0.40–1.60)	0.532	14	30.4	0.84	(0.42–1.63)	0.604
Resided in refugee camp	26	5.4	19	6.2	0	0.0	N/A	N/A	N/A	2	4.3	0.65	(0.14–2.87)	0.57
Homeless/ incarcerated	44	9.1	33	10.8	3	6.8	0.61	(0.18–2.96)	0.422	2	4.3	0.37	(0.08–1.62)	0.19
Illicit drug use	31	6.4	22	7.2	6	13.6	2.04	(0.78–5.35)	0.148	1	2.2	0.28	(0.03–2.18)	0.287
Regular alcohol consumption	172	35.5	117	38.2	13	29.5	0.68	(0.34–1.35)	0.267	17	37.0	0.95	(0.49–1.79)	0.868
Smoking (current/ previous)	145	29.9	98	32.0	15	34.1	1.10	(0.56–2.14)	0.784	16	34.8	1.13	(0.58–2.17)	0.71
Active malignancy	21	4.3	12	3.9	1	2.3	0.57	(0.07–4.50)	0.593	3	6.5	1.71	(0.46–6.30)	0.421
Immunosuppressive therapy	14	2.9	9	2.9	1	2.3	0.77	(0.95–6.21)	0.804	2	4.3	1.50	(0.031–7.17)	0.611
Diabetes	85	17.5	67	21.9	3	6.8	0.26	(0.08–0.87)	0.029	8	17.4	0.75	(0.33–1.68)	0.488
HIV infection	10	2.1	6	2.0	0	0.0	N/A	N/A	N/A	3	6.5	4.76	(1.29–17.5)	0.019
Distribution of TB														
Only pulmonary TB	280	57.7	176	57.5	28	63.6	1.29	(0.67–2.49)	0.442	34	73.9	2.09	(1.04–4.19)	0.038
Pulmonary + extrapulmonary TB	103	21.2	75	24.5	11	25.0	1.02	(0.49–2.13)	0.944	5	10.9	0.37	(0.14–0.98)	0.047
Only extrapulmonary TB	102	21.0	55	18.0	5	11.4	0.59	(0.22–1.55)	0.282	7	15.2	0.82	(0.34–1.92)	0.648
Cavity on chest radiograph	98	20.2	72	23.5	9	20.5	0.84	(0.38–1.82)	0.651	9	19.6	0.79	(0.36–1.71)	0.552
AFB test														
AFB positive smear in sputum	191	39.4	155	50.7	25	56.8	1.60	(0.80–3.20)	0.179	17	37.0	0.57	(0.29–1.08)	0.089

Abbreviations: AFB, acid-fast bacilli; DR, drug-resistant; DST, drug susceptibility test; INH, isoniazid; N/A: not applicable; MDR, multdrug resistant; WHO, World Health Organization

Table 4: Risk factors associated with isoniazid mono-resistant tuberculosis and multidrug resistant tuberculosis at West Park Healthcare Centre in foreign born patients

Risk factors	INH-R vs DS-TB			MDR vs DS-TB		
	OR	(95% CI)	p-value	OR	(95% CI)	*p*-value
Age, years						
Younger than 35 years	1.69	(0.54–5.26)	0.365	8.11	(1.43–45.7)	0.018
35–65 years	1.16	(0.44–3.06)	0.76	4.84	(0.94–24.7)	0.058
Older than 65 years	1.0	reference[a]	N/A	1.0	reference[a]	N/A
Gender						
Sex, female	1.36	(0.65–2.88)	0.408	1.57	(0.71–3.47)	0.265
Birth country WHO region						
African Region	0.46	(0.08–2.64)	0.384	0.45	(0.05–3.86)	0.468
Region of the Americas	1.0	reference[a]	N/A	N/A	N/A	N/A
Eastern Mediterranean Region[b]	0.90	(0.17–4.81)	0.909	1.0	reference[a]	N/A
European Region	N/A	N/A	N/A	4.29	(0.54–33.7)	0.166
South-East Asia Region	0.10	(0.01–0.73)	0.023	1.31	(0.25–6.95)	0.744
Western Pacific Region	1.50	(0.38–5.83)	0.558	1.97	(0.38–10.2)	0.415
Median month from arrival to TB diagnosis[c]						
Less than 24 months	1.10	(0.34–3.52)	0.861	4.11	(1.21–13.9)	0.023
24–120 months	1.26	(0.53–3.00)	0.588	2.48	(0.83–7.35)	0.101
More than 120 months	1.0	reference[a]	N/A	1.0	reference[a]	N/A
TB risk factor						
History of TB treatment	2.21	(0.73–6.15)	0.163	3.78	(1.58–9.05)	0.003
Diabetes	0.18	(0.04–0.81)	0.026	N/A	N/A	N/A
HIV infection	N/A	N/A	N/A	10.95	(1.90–62.9)	0.007
Distribution of TB						
Only pulmonary TB	N/A	N/A	N/A	2.76	(0.92–8.19)	0.067
Pulmonary and extrapulmonary TB	N/A	N/A	N/A	0.70	(0.17–2.77)	0.617

Abbreviations: DS, drug susceptible; HIV, human immunodeficiency virus; INH-R, isoniazid mono-resistance; MDR, multidrug resistant; N/A, not applicable; TB, tuberculosis; WHO, World Health Organization

[a] Reference means the control group which all other groups are compared to

[b] The reference group for this analysis was patients from the Eastern Mediterranean Region because no patients with MDR-TB were from the Region of the Americas

[c] Three patients missing the date of arrival

Table 5: Criteria recommended by 2017 ATS Guidelines for rapid molecular drug susceptibility testing for rifampin[a]

Criteria	All TB patients[b]		DS-TB		Non-MDR/ RMP drug resistance		MDR/RMP-R TB		MDR/RMP-R TB vs DS-TB			MDR/RMP-R TB vs non-MDR/RMP drug resistance		
	(n=485)	%	(n=306)	%	(n=49)	%	(n=47)	%	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Previous TB treatment	70	14.4	26	8.5	9	18.4	16	34.0	5.39	(2.57–11.3)	<0.001	2.21	(0.83–5.90)	0.112
Born or lived less than one year in higher risk country	428	88.2	264	86.3	43	87.8	45	95.7	2.72	(0.62–11.2)	0.184	3.02	(0.56–16.2)	0.197
Contact of MDR-TB	4	0.8	1	0.3	2	4.1	1	2.1	9.04	(0.54–148.7)	0.123	0.46	(0.03–5.60)	0.548
HIV infection	10	2.1	6	2.0	0	0.0	4	8.5	4.26	(1.06–17.0)	0.04	N/A	N/A	N/A

Abbreviations: ATS, American Thoracic Society; DS, drug-susceptible; HIV, human immunodeficiency virus; MDR, multidrug resistant; N/A, not applicable; R, resistance, RMP, rifampin; TB, tuberculosis
[a] Rapid molecular drug susceptibility testing for rifampin by drug resistance pattern (A) and multivariable analyses comparing MDR/RMP-R TB with drug susceptible TB (B) and non-MDR/RMP drug resistant TB (C)
[b] TB incidence of ≥20/100,000 or primary MDR prevalence of ≥2%

Discussion

We identified several risk factors for drug resistance among TB patients seen at our institution in Toronto, Ontario. Regarding INH-R TB, we found that young age (younger than 35 years), prior TB treatment, lack of diabetes and birth in a non-South-East Asian country were risk factors in bivariate (unadjusted) analysis, but only the latter two were significant in multivariable analysis. Prior TB treatment has been previously reported as a risk factor for INH-R TB, even after adjustment for possible confounders (13). Somewhat surprisingly, we found a significant association between diabetes and INH-R TB in both bivariate and multivariable analysis, with the former appearing "protective" against the latter. Most previous studies have not included diabetes in their assessment of risk factors for drug resistance; and a study from British Columbia did not find an association between the two variables (4). Additionally, some reports, including a recent meta-analysis, have described a positive association between diabetes and MDR-TB (14). Given that no prior studies reported a negative association between INH-R TB and diabetes, and the lack of a plausible biologic explanation for this finding, we suspect that this association might be spurious. While we did control for age in our multivariable model, there could be residual confounding by age, as INH-R TB was more common in younger patients, who generally have a lower prevalence of diabetes. This association could also have been found by chance, and may be related to multiple testing; future study on this association is needed. Interestingly, in our population, foreign birth (OR 0.93 95% CI 0.31–2.80) was not associated with INH-R TB. Although other North American studies have found foreign birth to be a risk factor for INH-R or mono-resistant TB (1,4,13), only one of these studies adjusted for potential confounders and no association was found (13).

We found several risk factors for MDR-TB in our population that have been described previously in North America, including younger generation, prior treatment (5), more recent arrival to Canada (1) and HIV infection. HIV infection is controversial; a meta-analysis found that most North American studies reported an association. There was no significant association for MDR-TB overall when studies from all world regions were included; yet there was an association with primary MDR-TB (15). In the bivariate analysis, we also found that patients with only pulmonary TB were more likely to have MDR-TB, but patients with pulmonary and extra-pulmonary were less likely. It is possible that the distribution of TB was confounded by the time when they were diagnosed, as patients with MDR-TB were more likely to have recently arrived to Canada and, therefore, may have had less advanced disease. In fact, the overall fraction of pulmonary involvement (pulmonary plus pulmonary and extra-pulmonary) was similar among DST categories (DS 82.0% (n=251/306), INH-R 88.6% (n=39/44) and MDR 84.8% (n=39/46)).

Regarding regions of birth, there was no significant association in multivariable analysis, but birth in Europe (OR 15.6, 95% CI 1.66–146.4) was a risk factor for MDR-TB in bivariate analysis, and the lack of significance in multivariable analysis in our study could have been due to the small numbers of cases analysed.

Given the growing number of immigrants in Canada (5.5 million in 2000 to 7.9 million in 2017) (16,17) and the worldwide epidemic of DR-TB, the prevalence of DR-TB in Canada has the potential to increase (8). One of the many challenges posed by DR-TB in low burden countries is the delay between TB diagnosis and culture-based DST, which can prolong the time to appropriate treatment initiation, increase morbidity and prolong infectiousness. However, in such regions, universal rapid molecular testing may not be cost-effective, and may lead to high numbers of false positives (18). Therefore, targeted testing, based on risk factors, is often used. The most recent ATS/IDSA/CDC guidelines for TB diagnosis (3) suggest that rapid molecular testing for RMP +/- INH resistance be performed in the following

patient sub-groups: 1) previously treated; 2) born or lived for at least one year in a country with TB incidence of greater or equal to 20/100,000 or primary MDR prevalence of at least 2%; 3) contact with MDR; and 4) HIV infection. Our results support the application of these guidelines in Ontario regarding patient sub-groups (patient subgroups 1 and 4).

While we did not find a significant association between RMP-resistance and a history of contact with MDR-TB (patient sub-group 3), the OR was high and our numbers were small, and it seems logical that these patients may be at risk and should be tested. However, our data raises questions about the potential benefits and costs of "targeted" testing for patients in sub-group 2 in a geographical region such as ours (Toronto, Ontario) where the majority of TB patients are immigrants. Perhaps in Ontario and similar regions, this criterion could be modified such that only patients from a higher risk country, who are also of younger age and/or have recently immigrated, would be tested. Targeted testing for patients from very high-risk countries (i.e. European Region) may also be considered.

Strengths and limitations

Given WPHC's status as a referral center for complicated and drug-resistant TB cases in Ontario, it is not surprising that our proportions of drug-resistant cases (10.9% INH-R and 11.4% MDR) were higher than provincial (8.5%/1.4%) (7) and national (6.2%/1.2%) (18) rates in 2016. Our higher than average population of drug-resistant cases presented an opportunity to study patient characteristics in detail; however, the number of drug resistant cases in our study was still relatively low. Furthermore, we may not have had the power to detect a significant association between some true risk factors and drug resistant TB. Additionally, there could be selection bias in our study population, since DS-TB cases with less severe TB disease or with fewer comorbidities might have been less likely to be referred to our specialized center. Another potential limitation to our study is that it is representative of patients in the Toronto region (which sees the majority of TB in the province; 76% in 2016) (19), and may not represent the characteristics of patients from other Ontario cities, who may be less likely to be referred to our institution. Additionally, we did not have detailed information regarding all countries where an individual resided in before coming to Canada. Finally, we tested many patient characteristics for their association with drug resistant TB, and we may have found associations that were spurious due to multiple testing.

Conclusion

We summarize risk factors for INH-R and MDR-TB among patients seen at our institution in Toronto, Ontario. These findings may be of use to TB clinicians throughout the province by informing the initial empiric antibiotic regimen they prescribe while awaiting phenotypic DST, and by assisting them in their decision regarding whether to request rapid molecular DST. These findings may also guide policy makers and laboratory personnel regarding targeted application of molecular DST in the province.

Authors' statement

TH — Data collection, statistical analysis, writing original draft, review and editing
NS, PD, JM and HS — Data collection
TM and SB — Data collection, statistical analysis, writing original draft, review and editing

Conflict of interest

None.

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Motivational interviewing: A powerful tool to address vaccine hesitancy

Arnaud Gagneur[1,2]*

Abstract

According to the World Health Organization, vaccine hesitancy is among the top threats to global health and few effective strategies address this growing problem. In Canada, approximatively 20% of parents/caregivers are concerned about their children receiving vaccines. Trying to convince them by simply providing the facts about vaccination may backfire and make parents/caregivers even more hesitant. In this context, how can health care providers overcome the challenge of parental decision-making needs regarding vaccination of their children?

Motivational interviewing aims to support decision making by eliciting and strengthening a person's motivation to change their behaviour based on their own arguments for change. This approach is based on three main components: the spirit to cultivate a culture of partnership and compassion; the processes to foster engagement in the relationship and focus the discussion on the target of change; and the skills that enable health care providers to understand and address the parent/caregiver's real concerns.

With regard to immunization, the motivational interviewing approach aims to inform parents/caregivers about vaccinations, according to their specific needs and their individual level of knowledge, with respectful acceptance of their beliefs. The use of motivational interviewing calls for a respectful and empathetic discussion of vaccination and helps to build a strong relationship.

Numerous studies in Canada, including multicentre randomized controlled trials, have proven the effectiveness of the motivational interviewing approach. Since 2018, the PromoVac strategy, an educational intervention based on the motivational interviewing approach, has been implemented as a new practice of care in maternity wards across the province of Quebec through the Entretien Motivationnel en Maternité pour l'Immunisation des Enfants (EMMIE) program.

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Introduction

Trying to convince vaccine-hesitant parents/caregivers to vaccinate their infants by simply providing the facts about vaccinations may backfire and make them even more hesitant (1). A Cochrane review by Kaufman *et al.* concluded that a face-to-face intervention that is strictly based on providing practical and logistical information regarding vaccination but does not take into consideration parents' beliefs is likely to be ineffective (2). However, another Cochrane review that assessed parents' and caregivers' views and experiences with communication about routine childhood vaccination found that parents did want more information compared to what they were receiving, but they were looking for simple, context-specific facts provided in a timely manner by a trusted health care provider (3).

The take-home message, according to the literature, is that while parents/caregivers want more information, traditional educational methods fail to meet their needs. This being the case, how should we provide parents/caregivers with facts about vaccination? This is of critical importance as, according to the World Health Organization, vaccine hesitancy is among the top 10 threats to global health (4). Until recently, few strategies have been found to effectively address the growing problem

of vaccine hesitancy (i.e. the reluctance or refusal to vaccinate despite the availability of vaccines) (1).

The motivational interviewing (MI) technique is one of the few strategies that has resulted in an increase in infants' vaccine coverage and a decrease in parents' vaccine hesitancy (5–10). MI is a person-centred communication style used to enhance internal motivation for attitudinal change by exploring and solving inherent ambivalences (11). It has been described as a promising tool in health promotion (12), and the National Advisory Committee on Immunization (NACI) currently recommends its use for vaccination (13).

Evidence for the effectiveness of MI on vaccine hesitancy is strong. Gagneur and other researchers developed an educational intervention based on the MI approach for parents in maternity wards during their postpartum stay (the PromoVac strategy) (5–8). A regional pilot study found that this strategy led to a 15% increase in mothers' intention to vaccinate, a 7% increase in infants' vaccine coverage at seven months, and a 9% greater chance of a complete immunization status among children two years or younger if their parents received the intervention in the maternity ward (6–8). A provincial randomized controlled trial found that vaccine hesitancy scores were reduced by 40% (5,6). Vaccine-hesitant mothers benefited the most from the intervention, with 97% reporting that they were satisfied with the intervention and would recommend it to all parents (7).

Dempsey *et al.* also demonstrated the effectiveness of a vaccination promotion strategy that used MI to increase human papillomavirus (HPV) vaccine uptake among adolescents (10).

In 2018, the PromoVac strategy was implemented in all maternity wards in Quebec through a provincial public health program called EMMIE (Entretien Motivationnel en Maternité pour l'Immunisation des Enfants). With an increase of 11% in vaccination intention and a decrease of 30% in vaccine hesitancy score, the preliminary results of the evaluation of the PromoVac strategy confirmed findings of previous studies (14).

The objective of this article is to define motivational interviewing and to show how it could be helpful against vaccine hesitancy. This article highlights the impact of this approach on vaccine hesitancy and vaccine coverage, and its use in a public health program in maternity wards in the province of Quebec (12).

This is the third of a series of articles produced by the Canadian Vaccination Evidence Resource and Exchange Centre (CANVax) (15). This centre includes a group of multidisciplinary professionals that identify and create useful resources to foster vaccine uptake (16).

Best practices for motivational interviewing

MI is an interviewing technique that aims to reinforce the motivation and commitment of the person being interviewed. It is less about the health care professional talking to the patient/caregiver and more about working with them. It is designed to strengthen personal motivation for and commitment to a specific goal by eliciting and exploring the person's own reasons for change within an atmosphere of acceptance and compassion (11).

MI is based on three main components: the spirit to cultivate a culture of partnership and compassion; the processes to foster engagement in the relationship and focus the discussion on the target of change; and the skills that allow health care providers to understand and address individual patient/caregiver's real concerns.

1. Cultivate a culture of partnership and empathy

The four elements of the spirit of MI enable health care providers to provide a respectful relationship with empathy:

- Partnership — Achieving equality, strengthening collaboration
- Acceptance — A positive, empathic attitude that reinforces autonomy
- Evocation — Having the individual verbalize the change
- Compassion/altruism — Acting in a caring way

2. Foster engagement in the relationship and target the goal of the intervention

Four successive MI processes enable engaging in a relationship with the patient/caregiver and moving towards a goal of change within the patient/caregiver's abilities (**Table 1**).

Table 1: The four successive processes of motivational interviewing

Processes	Objectives	Questions to address
Engaging	Strengthen the link, show empathy and interest	What is the actual reality of the individual?
Focusing	Define and focus the discussion on the target of change	What should we address as a target of change?
Evoking	Objective 1: Reasons and abilities to change (the importance of change) Objective 2: Change talk (the confidence to change)	How relevant would it be to go towards change? What abilities, strengths does the individual have to get there?
Planning	Engagement talk. How to change	How will the individual get there?

These are not linear processes or a step-by-step guide to MI. Engaging in the relationship comes first because engagement is necessary prior to having a conversation about change. If at any point engagement is lost, the health care provider steps back to the engaging process to re-engage the client.

3. Understand the patient/caregiver and adapt to their specific needs

The health care provider identifies and understands the patient/caregiver's real concerns and can strengthen their motivation to change through the use of MI skills. MI skills include asking open-ended questions, using reflective listening, and affirming and reiterating statements back to the interviewee (**Table 2**). Such skills are used in a dynamic where the health care provider actively listens to the patient/caregiver and then repackages their statements back to them while highlighting what they have done well. This way, the patient/caregiver's confidence can improve with regard to change.

Table 2: Motivational interviewing skills

Skills	Objectives	Examples
Open questions	To evoke responses and avoid doubts	Open-ended questions: ("What did you understand?"/"What do you think?") Closed questions: ("Did you understand?"/"Do you think it's important?")
Affirmation	To encourage the individual and highlight their strengths	"The health and safety of your children are important to you." "You already have a lot of knowledge."
Reflective listening/ summaries	To allow the individual to add nuance to and correct what they have just said Simple reflection: what the individual says Complex reflection: what the individual means	"You have read articles about the relationships between vaccines and disorders such as autism." "What matters most to you is that your child is as healthy as possible."
Elicit–Share–Elicit	How to give information/ advice: ELICIT = ask what the parent/caregiver knows and ask permission to complete their knowledge SHARE = provide the information /advice on the subject ELICIT = verify what the parent/caregiver has understood and what they will do with this information	"What do you know about ...?" "If you agree, I could complete ..." "Does this new information make sense?"

Why motivational interviewing works with a vaccine-hesitant parent/caregiver

Using MI in an educational session fosters a patient/caregiver-oriented relationship and, importantly, a tailored session that welcomes parents at their individual level of knowledge while remaining respectful of their beliefs (5–8). The use of the MI approach calls for a respectful and empathetic discussion about vaccination and helps build a strong relationship between the patient/caregiver and the health care practitioner (9). Parents can freely discuss their concerns and ask questions about vaccination without feeling judged (6,9). Health care practitioners can then identify and target parental concerns or misconceptions about vaccination and provide tailored information (6).

Targeting concerns and tailoring information are the most prominent distinguishing features of this approach compared to currently available interventions in the field of vaccination promotion. This distinguishing feature may explain why the MI technique has had such positive results in curbing vaccine hesitancy and improving vaccine coverage (5–8). The educational session with MI is adapted to parents/caregivers' individual needs and their concerns and questions about vaccinating their child. Using MI techniques, health care professionals help individuals explore their own ambivalence, find their own arguments for change and make their own informed decision about vaccinating their child. In a study on parents/caregivers' decisional process in vaccination, Paulussen *et al*. showed that most parents/caregivers did not actively process the information provided on benefits and drawbacks prior to deciding whether to have their child vaccinated (17). A parent's attitude towards vaccination and high vaccination intention may, therefore, be susceptible to uninformed and informed counterarguments. By eliciting and exploring a parent's personal reasons for vaccination, the MI approach enhances their personal motivation to vaccinate via a robust decisional process. Moreover, MI is a short intervention and could easily be integrated into the usual vaccination consultation once health care practitioners are trained.

Table 3 shows a case example of how vaccine education between a health care provider and a parent could occur with the traditional versus motivational interviewing approach.

Table 3: Example of traditional approach and use of motivational interviewing in a dialogue about immunization

Traditional approach based on education and counselling	Motivational interviewing approach
HCP: It's important to immunize your child. If not, you're putting him in danger. Do you know there are still cases of measles in Canada? This disease could be very dangerous. And what about meningitis? It could be fatal, you know? You should update your child's vaccinations as he is already late according to the schedule. We could do that now if you want. **Mother:** I don't see the urgency. And autism is worse than measles! There are more problems than solutions with this vaccine. Moreover, it's completely unbelievable to give so many vaccines at the same time!	**HCP:** What do you think about the advantages of vaccination? [Open-ended question] **Mother:** Well, I know that vaccines protect children against several diseases that we don't see anymore. My child received all his first vaccines but I'm worried that the measles vaccine could cause autism. For other vaccines, I have fewer doubts but I'm still hesitating.

Table 3: Example of traditional approach and use of motivational interviewing in a dialogue about immunization (*continued*)

Traditional approach based on education and counselling	Motivational interviewing approach
HCP: Studies have demonstrated that there is no link between autism and the measles vaccine. The vaccine is safe, I assure you. You should be aware of the information that you could find on the Internet. Giving several vaccines at the same time is safe and is not associated with more pain. We should update his vaccines now. **Mother:** I've heard something else and not only on the Internet. I've read a lot, and vaccination is not mandatory, I can do what I want.	**HCP:** As you said, vaccines have reduced diseases in such an important way that they are now much less frequent. It's why you have vaccinated your child when he was a baby. If I understood you correctly, with the exception of measles vaccine, other vaccines seem safe to you. [Summary; Complex Reflection] **Mother:** Yes, I know it's a good thing to prevent those infections. But about measles, I'm conflicted. You know, I've read a lot of books and articles. Lots of people are worried about the link between the measles vaccine and autism.
HCP: Yes, you're right, it's not mandatory, but you're putting him and other children who cannot receive vaccines in danger. The risks of diseases are much higher than the risks of vaccines. If I take this time to speak with you, it's because it's very important. **Mother:** It's easy for you! Quick, quick! But what if he gets autism? I'm worried about the risk of the vaccines but you don't seem to be worried about the health of my child.	**HCP:** So, you find that it's important to protect your child against diseases when the vaccines are safe, but you're worried about what you've heard regarding autism and measles vaccine. [Summary] I see that you've done a lot of research about the subject. [Affirmation] If you agree, I could give you some additional information for studies on autism and measles. [Elicit] **Mother:** Sure! I want to know exactly what happened.
HCP: Of course I am! And I'm worried about the fact that he could get diseases that could be prevented by vaccines. **Mother:** I think we do not understand each other. Let's talk about this another time.	**HCP:** In fact, you're right. One study had hypothesized a link between measles vaccine and autism, but this study was fake and the author lost his medical licence. More than 500 additional studies around the world have demonstrated that there is no link between the vaccine and autism. The frequency of autism is the same in vaccinated children as in nonvaccinated children. [Share] What do you think? [Elicit, last step of Elicit–Share–Elicit] **Mother:** Well, so I'm not crazy to be worried about that? **HCP**: Of course not, you're totally right. [Affirmation] **Mother:** Thank you for taking the time to understand my concerns. I think it's a bit clearer now.
Summary: The HCP adopted the role of the expert and used a directive intervention approach based on argumentation and righting reflex. This type of intervention led to an opposition.	**Summary:** MI allowed the mother, in a nonjudgmental way, to express her concerns and her ambivalence. Using an Elicit–Share–Elicit method allowed the HCP to give solicited information that could be accepted by the mother.

Abbreviations: HCP, health care provider; MI, motivational interviewing

Conclusion

MI is a powerful tool that has been shown to be effective at increasing vaccine acceptance and curbing vaccine hesitancy (18,19). It is a new best practice that the World Health Organization recommends integrating into the training of immunization providers and health care providers involved in immunization counselling (20). The several available workshop or academic training materials on applying motivational interviewing to immunization could be very helpful in assisting health care providers in integrating motivational interviewing into their daily practice (18–22).

Author's statement

AG — Writing–original draft, review and editing

Conflict of interest

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UPDATE

Coronavirus disease (COVID-19)

Source: Government of Canada. Coronavirus disease (COVID-19): For health professionals. Government of Canada; 2020. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals.html

What health professionals need to know

Health professionals in Canada have a critical role to play in identifying, reporting and managing potential cases of COVID-19.

Coronaviruses are a large family of viruses, some of which infect only animals, and others that can infect humans. Seven strains of coronavirus are now known to cause illness in humans.

The strain of coronavirus found in Wuhan is the most recent of 7 known strains. Of the 6 others, 4 cause only minor respiratory symptoms similar to those of a cold, and 2, severe acute respiratory syndrome (SARS CoV) and Middle East respiratory syndrome (MERS CoV), have been associated with more serious and life-threatening diseases.

Those who are infected with COVID-19 may have little to no symptoms. Symptoms, similar to a cold or flu, may take up to 14 days to appear after exposure to COVID-19. Current studies are investigating if the virus can be transmitted to others if someone is not showing symptoms. Symptoms include:

- cough
- fever
- difficulty breathing
- pneumonia in both lungs

In severe cases, infection can lead to death.

The World Health Organization (WHO) is actively monitoring the situation and has issued updated information on the outbreak, including a risk assessment, advice on public health measures and infection prevention and control, and enhanced surveillance.

The Public Health Agency of Canada (PHAC) is also monitoring the COVID-19 situation closely and providing updates as new information becomes available.

Transmission

Current epidemiologic information suggests that human-to-human transmission of COVID-19 can occur when an individual is in close contact with a symptomatic case. Human coronaviruses are most commonly spread from an infected person through: respiratory droplets; close, prolonged personal contact; and touching an infected area, then touching mouth, nose or eyes before washing hands.

Leadership. Surveillance. FluWatch.

FluWatch is Canada's national surveillance system that monitors the spread of influenza and influenza-like-illnesses (ILI).

It relies on data from physicians, nurse practitioners, and registered nurses involved with primary care.

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