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IMPLEMENTATION SCIENCE

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

Contact Us

ccdr-rmtc@phac-aspc.gc.ca
613.301.9930

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EDITORIAL

The emerging *Haemophilus influenzae* serotype a infection and a potential vaccine: Implementation science in action

L Barreto[1], AD Cox[1], M Ulanova[2], MG Bruce[3], RSW Tsang[4]*

Abstract

Haemophilus influenzae serotype b (Hib) was a major cause of meningitis in children until Hib conjugate vaccine was introduced into the routine infant immunization program and Hib disease in children was almost eliminated. In Alaska, northern Canada and other countries with Indigenous peoples, *H. influenzae* serotype a (Hia) has emerged as a significant cause of pneumonia, meningitis and septic arthritis especially in children under 24 months of age. A joint government initiative between the Public Health Agency of Canada (PHAC) and the National Research Council of Canada (NRC) was carried out to assess whether an Hia vaccine could be developed for the common good.

The initiative included strategic partnerships with clinician researchers in Thunder Bay, Ontario who provide health services to Indigenous people and the Artic Investigations Program (AIP) of the United States Centers for Disease Control and Prevention (CDC) in Alaska. This government initiated and funded research identified that the development of an Hia vaccine is possible and ongoing surveillance that includes strain characterization is essential to understand the potential spread of Hia in North America and around the world.

Affiliations

[1] Human Health Therapeutics Portfolio, National Research Council of Canada, Ottawa, ON

[2] Northern Ontario School of Medicine, Lakehead University, Thunder Bay, ON

[3] Arctic Investigations Program, Division of Preparedness and Emerging Infections, US Centers for Disease Control and Prevention (CDC), Anchorage, AK

[4] National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

***Correspondence:** raymond.tsang@phac-aspc.gc.ca

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Introduction

Implementation science speaks to the very reason why we do health research: to understand how things work, to test hypotheses, to develop solutions, and to assess effectiveness so we can improve individual and population health. But this process is rarely as straightforward as it seems. The conference proceedings on the *Haemophilus influenzae* serotype a (Hia) workshop in this issue of the *Canada Communicable Disease Report* (CCDR) (1) identified the many different types of evidence needed to develop a new vaccine and the challenges still ahead to convert initial research into an approved product. In this editorial, we will explain what Hia is and how it initially emerged, highlight some of the unique aspects involved in developing an Hia vaccine and underscore the importance of ongoing surveillance to observe trends in Hia infections both in North America and around the world.

Background

Haemophilus influenzae (*H. influenzae*) is a human pathogen that normally resides in the upper respiratory tract, but may occasionally be found in the urogenital mucosa leading to urinary tract, neonatal and obstetric infections (2-4). *H. influenzae* strains include those that have on their surfaces polysaccharide capsules which divide the strains antigenically into six different capsular serotypes (a to f) and those without capsules (termed non-typeable) (5). Encapsulated strains tend to cause invasive diseases such as meningitis, septicemia, bacteremic pneumonia and septic arthritis, while non-capsulated strains generally cause non-invasive infections such as otitis media, sinusitis and bronchitis.

Hib was a major cause of meningitis in children under the age of five (6,7) until Hib conjugate vaccine was introduced into the routine infant immunization program in the early 1990s. Since that point, Hib disease in children has almost been eliminated (8).

Unfortunately, the declining rates of Hib disease following infant immunization did not completely eliminate invasive *H. influenzae* disease. In the post-Hib vaccine era, non-b serotypes and non-typeable *H. influenzae* strains became more common (9-11). In Alaska, United States (US) (12), and in northern Canada (13-15), as well as in regions with a large proportion of Indigenous people (16,17), Hia has emerged as a significant cause of invasive disease, especially in children under 24 months of age (18,19). Hia causes pneumonia, meningitis and septic arthritis, and it is responsible for a considerable amount of morbidity, life-time disability and mortality (12,13,18).

Unique aspects of Hia vaccine development

In this issue of CCDR, Cox and colleagues have identified the critical evidence needed when considering the development of a new vaccine. This evidence includes: surveillance data, laboratory research, pre-clinical studies, regulatory considerations, good manufacturing practice in producing clinical vaccine lots, clinical trial capacity, best practices in public-private partnerships, and more (20). The conference proceedings highlight two unique aspects of Hia vaccine development. From the start, it has been an inter-departmental collaboration within the Government of Canada that included strategic partnerships and second, it has been government-initiated research, with internal funding for both proof-of-concept vaccine research and ongoing surveillance.

Inter-departmental collaboration

In the early 2000s, the Public Health Agency of Canada (PHAC) and the National Research Council (NRC) of Canada came together to collaborate on the general theme of "expanding vaccine development in Canada". This partnership was formed on the basis of the unique capabilities and expertise of the two different government departments in order to implement scientific solutions for the common good. At the time, laboratory surveillance activities at the National Microbiology Laboratory (NML) had identified a significant percentage of serotype a isolates that were responsible for invasive *H. influenzae* disease (20). Consultation with the Council of Provincial and Territorial Medical Officers of Health and the subsequent review of invasive Hia data from the northern Canadian territories collected via the International Circumpolar Surveillance System confirmed that Hia was a significant emerging pathogen (21,22) causing severe invasive disease for which no vaccine was currently available. Building on the success of the Hib conjugate vaccine developed in the 1980s for control of invasive Hib disease, the similarities of the biology of Hia and Hib, and the diseases they cause, research was initiated to lay the foundation for developing a Hia conjugate vaccine.

Strategic external partnerships

The Thunder Bay campus of the Northern Ontario School of Medicine at Lakehead University is situated in Northwestern Ontario and its educational and research activities are affiliated with the Thunder Bay Regional Health Sciences Centre — a 375-bed academic teaching hospital. Both the Northern Ontario School of Medicine and the teaching hospital provide a variety of health services to a population with a significant percentage of Indigenous people. The Arctic Investigations Program (AIP) of the US Centers for Disease Control and Prevention (CDC) located in Anchorage, Alaska has extensive experience in the study of invasive Hib disease beginning in the 1970s before the Hib conjugate vaccine was introduced. Investigators at the AIP had also conducted clinical trials with the Hib conjugate vaccines leading eventually to the implementation of the current Hib-OMV (PRP-OMP) vaccine specifically for American Indigenous children (23).

Each partner in this multi-disciplinary collaboration brings in unique but complementary expertise to the group. The NML of PHAC and the US CDC's AIP provide laboratory surveillance of infectious diseases in the respective countries and NML has an extensive culture collection in a bio-bank for research and development. NRC has a strong tradition in conducting microbial carbohydrate research, extensive experience in protein carbohydrate conjugation technology and has engaged with industry to develop vaccine products. The Northern Ontario School of Medicine has access to a large regional clinical facility and has unique expertise in immunology of infectious diseases and immunoassay for vaccine related issues. The formation of this partnership has been designed with the goal to enhance the success in the development of a Hia conjugate vaccine.

Government funded surveillance and vaccine development work

Another unique aspect of developing the Hia vaccine is that it has been a government-based initiative. The NML of PHAC identified the potential need for an Hia vaccine through its laboratory surveillance program funded by the Government of Canada. The lead scientist at the NML on this file has knowledge on bacterial vaccines and professional relationships with scientists at the NRC, which opened up collaborative opportunities. A small investment from the Government of Canada allowed scientists at the NRC to purify the Hia capsular polysaccharide and develop the required conjugation reaction to produce a research batch of the Hia conjugate vaccine. Immunogenicity studies in laboratory animals have confirmed that the Hia conjugate vaccine can induce bactericidal antibodies, which is a recognized surrogate marker for protective immunity against *H. influenzae*. Hence, studies to date have provided the pre-clinical proof of concept that the Hia conjugate vaccine approach is likely to be as effective as the Hib conjugate vaccine.

Current epidemiological surveillance has revealed that the population most at risk of developing severe invasive Hia diseases are Indigenous children under the age of five and immunocompromised Indigenous adults living in North America and other regions. Much effort has gone into consulting the most affected communities. In Canada, two workshops (including the workshop with proceedings being published in this issue of CCDR) have been conducted that include participants from Indigenous communities and investigators at the Northern Ontario School of Medicine, who continue to engage the Indigenous communities in their research.

Conclusion

Using evidence to inform practice is a complex undertaking. In the case of vaccine development, evidence to demonstrate burden of illness, laboratory studies, consultations with public health stakeholders, those affected by the disease, regulatory experts and industry partners are the critical components in the process. Yet in the case of Hia vaccine, two unique and additional elements are also notable: the fact that government funding and research identified the problem; and that a government partnership led to a proof-of-concept for a vaccine which facilitated the engagement of others in further developing this solution. The evolving nature of infectious microbes is likely to continue to change the epidemiology of invasive *H. influenzae*

disease. Therefore, continued surveillance that includes strain characterization is essential to follow the potential spread of Hia in North America and around the world and, perhaps in the future, to document its decline in response to a new vaccine.

Authors' statement

All authors (LB, ADC, MU, MGB and RSWT) had input into the concept of this editorial. LB and RSWT prepared the first draft and all authors contributed to the final version with comments and suggestions.

Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the official positions of the Public Health Agency of Canada or the United States Centers for Disease Control and Prevention.

Conflict of interest

ADC, MGB, and RSWT have no conflicts of interest to declare.

MU holds an Investigator Initiated Research Grant from Pfizer for an unrelated study. LB is a Senior Scientific Advisor with Inventprise/InventVac, Redmond, Washington/Vancouver, British Columbia and a Strategic Advisor to NEOMED-LABS, Montreal, Quebec; and he has worked with the NRC Vaccine and Immune Therapeutics Group (HHT) from 2011 to 2015 and as a consultant for NRC in relation to Hia vaccine development. He worked with Sanofi Pasteur from 1988 to 2010 on Hib and combination vaccine development.

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Developing a vaccine for *Haemophilus influenzae* serotype a: Proceedings of a workshop

AD Cox[1]*, L Barreto[1], M Ulanova[2], MG Bruce[3], RSW Tsang[4] on behalf of the Conference contributors[5]

Abstract

Since the late 1990s there has been an emergence of *Haemophilus influenzae* serotype a (Hia) infections, especially in Indigenous communities in the northern regions of Canada and Alaska associated with significant morbidity and approximately a 10% mortality. A Hia vaccine could potentially prevent this disease and save the health care system millions of dollars in both acute and long-term care.

On March 23–24, 2016, the National Research Council (NRC), the Public Health Agency of Canada (PHAC) and the Canadian Institutes of Health Research (CIHR) co-organized a meeting on *H. influenzae* serotype a (Hia) to examine the current state of disease epidemiology and a potential vaccine solution path. The meeting included representatives from academia, federal and territorial public health units, hospital laboratories, federal departments involved in Aboriginal health, advocacy organizations for Indigenous peoples and industry.

Representatives from industry confirmed having the capacity and the interest to support preparation of clinical trial batches. Canadian regulatory authorities have expressed a willingness to help ensure appropriate measures are in place for licensure purposes. Furthermore, there is the capacity and interest in performing some clinical trials in Indigenous communities in both Canada and Alaska. Recommendations for next steps included: complete pre-clinical studies, improve epidemiological surveillance to better understand the extent of the disease in the rest of North America and globally, establish engagement mechanisms with national Indigenous organizations to ensure their peoples are fully involved in the process and explore funding opportunities to prepare clinical lots and undertake clinical trials.

Affiliations

[1] Human Health Therapeutics Portfolio, National Research Council, Ottawa, ON

[2] Northern Ontario School of Medicine, Lakehead University, Thunder Bay, ON

[3] Artic Investigation Program, Division of Preparedness and Emerging Infections, US Centers for Disease Control and Prevention (CDC), Anchorage, AK

[4] National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB

[5] All conference contributors are noted at the end of the paper

***Correspondence:** andrew.cox@nrc-cnrc.gc.ca

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Introduction

Haemophilus influenzae is a Gram-negative bacterium that can cause a range of infections from otitis media to sepsis. *H. influenzae* strains include those that have on their surfaces polysaccharide capsules which divide the strains antigenically into six different capsular serotypes (a to f) and those without capsules (termed non-typeable). In the past, *H. influenzae* serotype b (Hib) was the most common cause of meningitis in children until a glycoconjugate vaccine based upon the Hib polysaccharide capsule became part of the routine infant immunization schedule in Canada and the United States (US) in the early 1990s (1). Although the Hib vaccine has been very effective in decreasing Hib infections, since the late 1990s there has been a growing number of cases of *H. influenzae* serotype a (Hia), especially in Indigenous communities in the northern regions of Canada and Alaska (2). The infection with Hia can be severe. In a recent study among young children, 42% reported meningitis, 19% bacteremic pneumoniae, 25% bone, joint and soft tissue infection and 11% died (3). There is currently no vaccine.

On March 23–24, 2016, the National Research Council (NRC), the Public Health Agency of Canada (PHAC) and the Canadian Institutes of Health Research (CIHR) co-organized a meeting on Hia to examine the current state of disease epidemiology and potential vaccine solution path. It included representatives from academia, federal and territorial public health units, hospital laboratories, federal departments involved in Aboriginal health, advocacy organizations for Indigenous peoples and industry.

This article summarizes the information shared during this meeting by highlighting recent trends in the epidemiology of Hia in Canada and elsewhere, discusses how Indigenous peoples have and can be involved in Hia vaccine development, summarizes Hia immunology and pre-clinical Hia vaccine research, considers different options for vaccine development and identifies recommendations for moving forward.

Epidemiology of *Haemophilus influenzae* serotype a

Hia globally: An overview

Dr. Raymond Tsang

To investigate the global presence of Hia, an interrogation of the *H. influenzae* Multi-Locus Sequence Typing website (4) was performed on March 4, 2016. From this data set it was apparent that Hia has been observed in North and South America, Africa, Europe, Asia and Australia. The earliest documentation of Hia infection was in the Gambia, Papua New Guinea and the Dominican Republic in 1980, indicative of a global distribution of this pathogen. Similarly, the Multi-Locus Sequence Typing website also described a cluster of invasive Hia disease cases in New Mexico in 2009–2010 which was found to be caused by a strain of Hia with the same sequence type as a strain seen in Alaska (5).

There is some evidence that since the introduction of Hib vaccine, the incidence of Hia has been rising in certain regions. For example, in a population-based study in Utah in children under 18 years old from 1998 to 2008 (6), the incidence rate of Hia disease cases increased from 0.8/100,000 to 2.6/100,000. In a similar study, the incidence of invasive Hia disease in those over 65 years old was 2.7/100,000 (7). In Brazil, before the introduction of the Hib conjugate vaccine, 97.8% of all invasive *H. influenzae* disease was due to Hib, while Hia accounted for only 0.5% of the disease (8). Five years after the introduction of the Hib conjugate vaccine, the overall incidence of Hib meningitis in the general population had decreased from 2.39 to 0.06 per 100,000. However, transient serotype replacement by two clones of Hia was observed (9). The changing epidemiology of invasive *H. influenzae* disease globally requires further study.

Hia in Canada: A case series

Dr. David Scheifele

The Immunization Monitoring Program ACTive (IMPACT) is an active, hospital-based surveillance network based at 12 children's hospitals across Canada. IMPACT hospitals account for over 90% of tertiary care pediatric beds in Canada (10,11). Invasive *H. influenzae* disease (all serotypes) has been monitored since 2007. A case is defined by an isolate obtained from a normally sterile site and is confirmed as serotype Hia by the National Microbiology Laboratory (NML, PHAC, Winnipeg). The cases observed are a combination of provincial-origin cases and those referred from the territories.

A total of 102 Hia cases have been observed since 2007, an average of 12.5 cases per year, with territorial referrals representing one-third of the cases. Most cases were observed in Winnipeg, Edmonton and Montréal, which serve as referral centers for the territories. For the provincial-origin cases it was possible to determine from the postal-code information linked to each case that there was considerable geographic spread, but a key observation was that this disease was not just a far northern risk. Based upon the pediatric cases observed, it was clear that greater than half were in infants less than one year old, some just a few weeks old. Approximately two-thirds of the cases occurred before two years of age. The illness was often severe, requiring intensive care; nine percent died as a result of the infection. Almost all cases were of Indigenous origin. In terms of severity, half of those infected developed meningitis, while pneumonia, otitis media and septic arthritis were also prominent. Over half of those with meningitis experienced seizures, reflecting advanced infection at diagnosis.

Hia in Quebec

Dr. Andrée-Anne Boisvert

Invasive Hia infections are a significant health problem for Indigenous children living in Northern Quebec, specifically Nunavik and James Bay Cree where 40 of the 62 cases from 2006-2015 have been observed (2). The majority of cases are seen in the young with 66% being less than five years of age. This corresponds to a peak of approximately 100 cases per 100,000 people for all age groups, 225 per 100,000 in those less than five years of age and 350 per 100,000 in those less than one year. In the James Bay Cree territory, these numbers are higher than was observed for Hib disease in the pre-vaccine era. The mortality rate is 15% and all deaths were in the Inuit population. The cases almost routinely involve helicopter evacuation (Medi-Vac) to an urban centre.

Hia in Nunavut

Dr. Kim Barker

The population of Nunavut is 32,000, of which 90% are Inuit. Nunavut has a publicly funded vaccine for Hib. The majority of all invasive *H. influenzae* cases reported from 2007 onwards have been due to Hia (over 60%) and within the Hia cases over 90% were less than two years old. There was a slight preponderance of male cases becoming ill (3). Rates of Hia are generally similar among the regions of Nunavut, except for certain years in which Kitikmeot showed a spike in incidence. These spikes correspond to rates of 140–160 cases per 100,000.

The severity of the disease progression is rapid. Due to the remoteness of some regions and the rapidity with which the disease progresses, there is a total reliance upon helicopter evacuation (MediVac) for every child that contracts invasive Hia disease. At an average of six cases per year, and a cost of $55 K for each evacuation, transportation costs alone for Hia in Nunavut is approximately $0.33M each year.

Hia in Alaska

Dr. Michael Bruce

Since 2000, there have been over 50 cases of invasive Hia disease in Alaska (5) *(and MGB's unpublished data*). This corresponds to 60% of all *H. influenzae* disease occurring in Alaska. Of those cases, 85% were concentrated in the western region of the state. The disease is mostly observed in the very young with 33% being less than seven months old, 67% being less than one year old and 83% less than 2 years old. Eight months is the mean age of invasive Hia cases; 67% are male, with 92% of Indigenous background. These correspond to annual incidence rates of 13 per 100,000 for those less than two years old and 44 per 100,000 for Alaskan Natives less than two years

of age. Over 90% of invasive Hia cases were age-appropriately vaccinated for Hib and over 80% of those taken ill required hospitalization with an eight percent case fatality rate. Due to the remote location, air transport was needed for 80% of cases. There has been little variation in the three sequence types (ST 576, ST 23 and ST 56) observed over the past decade, with ST56 dominating recently (5). The choice of carrier protein was also critical to the success of the Hib vaccine in Alaska as a switch to the outer membrane protein complex (OMPC) of *Neisseria meningitidis* from diphtheria toxoid as the carrier protein was necessary to generate protective titers (12) and a subsequent shift from OMPC to a genetic variant of diphtheria toxoid (CRM) as the carrier facilitated a breakthrough of Hib disease that was only corrected by a return to OMPC as the carrier protein (13,14).

Engaging Indigenous people in Hia vaccine development

Early engagement with Indigenous peoples is absolutely vital in order to ensure that the communities who are currently at the greatest risk of this emerging pathogen are involved and aware of the threat and possible solution.

CIHR and "two-eyed seeing" in First Nations, Inuit and Métis research

Dr. Simon Brascoupé

The priorities of the CIHR include enhanced patient experiences and outcomes through health innovation, health and wellness for Aboriginal peoples, a healthier future through preventive action and improved quality of life for persons living with chronic conditions. These priorities are to be considered in parallel with the strategic direction of the Institute of Aboriginal Peoples' Health which is: First Peoples and communities driving First Nations, Inuit and Métis (FNIM) health research and knowledge translation, in order to transform First Peoples' health through Indigenous ways of knowing and wellness, strength and resilience for First Peoples.

It is clear that these priorities resonate strongly with the development of a Hia glycoconjugate vaccine. However, it is necessary to ensure that this development is done with the Indigenous populations and considering the Indigenous perception of health and wellness. This will require a move from research on FNIM to research with and by FNIM. It is vital to deploy "two-eyed seeing", i.e., a western viewpoint and an Indigenous perspective, to create a new norm of excellence in FNIM research, enhancing relevance of community research priorities and FNIM knowledges, values and cultures.

Assembly of First Nations engagement principles

Dr. Marlene Larocque

The Assembly of First Nations (AFN) is a policy body which supports First Nations' Health. It will generate information with partners into better outcomes for First Nations. The engagement principles for partnerships with AFN include the following: policies/programs with First Nations involvement work better, the earlier the engagement, the better, the CIHR guidelines on Aboriginal health are a good resource, there is a need to have a holistic approach to protect Indigenous knowledge and consider Indigenous practices to keep children safe. It is also critical to recognize that the burden of disease may be influenced by the physical environment such as overcrowding and lack of access to safe, running water.

Health Canada First Nations and Inuit Health Branch

Kathleen Lydon-Hassan

Health Canada First Nations and Inuit Health Branch (FNIHB) works with its partners to improve health outcomes, provide access to quality health services and support greater control of the health system by First Nations and Inuit. The overall goal is for the federal, provincial, territorial governments and the First Nations and Inuit peoples to work together on a shared path to improved health. FNIHB supports immunization programming to on-reserve peoples by either directly delivering or financially supporting First Nations on-reserve communities and/or organizations in the delivery of immunization.

Hia immunity and pre-clinical Hia vaccine research

Naturally acquired immunity to Hia

Dr. Marina Ulanova

Researchers at the Northern Ontario School of Medicine have been working diligently to establish relationships with the First Nations population in the community and work closely with the Sioux Lookout Meno Ya Win Health Centre to examine the specificity of naturally acquired immunity to Hia. Northern Ontario is a region where invasive disease has a high incidence. Between 2002–2016, incidence rates of Hia infections in children less than five years old ranged from 7.7 to 23.2 per 100,000 (15,16).

Intriguingly, the activity of naturally acquired bactericidal antibodies against Hia is higher in Indigenous compared to non-Indigenous adults, with geometric mean titers being 351 compared to 183 respectively and immunoglobulin M (IgM) being more prevalent than immunoglobulin G (IgG) in the Hia capsular polysaccharide specific antibody repertoire (17). Significantly however, this study clearly revealed that both Indigenous and non-Indigenous healthy adults have high titers of bactericidal antibodies to Hia, illustrating that Hia is present in the whole community and not just in the Indigenous members of the community (17).

Critically, it was clearly demonstrated that naturally acquired serum bactericidal activity against Hia is nearly 100% due to antibodies to the capsular polysaccharide. Bactericidal activity was readily removed via absorbance with purified capsular polysaccharide of Hia. Absorbance of sera with an antigenically cross-reactive polysaccharide of *Streptococcus pneumoniae* serotype 6B had no effect on the bactericidal titers against Hia, emphasizing the necessary specificity to achieve protection and

providing clear support for the glycoconjugate vaccine based upon the capsular polysaccharide of Hia approach.

Hia vaccine development research

Dr. Andrew Cox

Pre-clinical research and development studies have been carried out in the NRC laboratories. Significant achievements have been made including the following:

- The growth of several Hia strains with non-bovine approved media in 30L fermenters and two PHAC established seed lot cell bank strains.
- A 400 mg/L yield of Hia capsular polysaccharide.
- Purity of capsular polysaccharide isolation has been confirmed by nuclear magnetic resonance spectroscopy.
- Sizing of capsular polysaccharide in readiness for conjugation has been optimized via sonication methodologies.
- Oxidation of the sized capsular polysaccharide has been achieved and degree of oxidation established by nuclear magnetic resonance spectroscopy.
- Conjugation has been optimized via direct reductive amination with several carrier proteins including human serum albumin, CRM and protein D.
- Immunogenicity of conjugates has been established by enzyme-linked immunosorbent assay (ELISA) following mice and rabbit immunizations.
- Functional activity of derived antisera has been illustrated with best titers observed with CRM as carrier protein in serum bactericidal assays, a recognized correlate of protection for Hib disease.

In addition to these achievements, no cross reactivity in terms of recognition or functionality was observed between Hia sera and Hib strains and vice-versa, illustrating specificity of the response and the need for a Hia specific vaccine. Proof of concept has been established as all Hia strains examined were killed by conjugate vaccine derived sera.

Further studies will focus on establishment of functional sera with acceptable adjuvants (e.g. alum) and the examination of levels of immunogenicity provoked by alternate carrier proteins.

Considerations in vaccine development

There are many key considerations to contemplate when moving a vaccine from the pre-clinical stage to the next stages of the development pathway. These include the ability to produce clinical material of good manufacturing practice (GMP) grade, ensuring that all regulatory considerations (be it quality assurance or clinical trial sizes) are in place and to have the necessary infrastructure to run the clinical trials.

Clinical trial capabilities in Canada

Dr. Scott Halperin

The Canadian vaccine research environment is supported and monitored by IMPACT (10,11), the Canadian Association for Immunization Research and Evaluation (CAIRE) (18) and the Canadian Immunization Research Network (19). IMPACT's role is to establish the burden of a given disease, test vaccine effectiveness and safeguard vaccine safety monitoring. CAIRE's role is to encourage and enhance applied vaccinology research so that Canadians have timely access to new and improved vaccines. The Canadian Immunization Research Network is a multi-disciplinary network with a hundred researchers across Canada at more than 35 sites, supported by PHAC and CIHR. It has a focus on the late stage of the vaccine lifecycle from safety to programming. It provides a formal infrastructure for research and collaboration and its prime objectives are to test vaccine safety and effectiveness and maintain a rapid response capacity.

The Canadian Immunization Research Network operates a clinical trials network via a core network of clinical trial sites across Canada. It has the ability to conduct rapid trials in large and specialized groups, including pediatric and at-risk populations' capabilities and has done trials with the First Nations and Métis population (20).

The Canadian Immunization Research Network could provide the following contributions to Hia vaccine development: Burden of disease studies, Phase 1/Phase 2 clinical trials, modelling and cost effectiveness studies (MODERN), knowledge, attitudes, beliefs and behaviours studies and program evaluation.

Regulatory considerations

Dr. Richard Siggers

Beginning with the pre-clinical research and development stage and continuing through the post-market authorization period, awareness of regulatory considerations will facilitate product development efficiencies and bolster confidence in the safety and quality of marketed products. It is recommended that direct consultation with national regulatory authorities be considered at each stage of product development. For example, a meaningful approach to product characterization is critical to the success of manufacturing biologics. Product characterization is meant to identify key quality attributes of products shown to have an appropriate safety profile and to be efficacious in clinical studies. These key quality attributes will be used throughout the post-licensure stage as measures of product consistency and ensures that commercially manufactured product is representative of product tested successfully in clinical studies. Investing resources in product characterization early in the development stage will ensure that product quality and safety is not negatively impacted as the manufacturing process evolves from pilot scale to commercial scale.

The manufacturing of biologics (i.e. vaccines) is complex due to the inherent variability and diversity of starting materials, the complexity of the biological systems utilized in the manufacturing processes, the possibility of adventitious agent contamination and the numerous manufacturing processes which all have the potential of impacting product quality. Consequently, there is a need to apply quality control throughout the various stages of the manufacturing process to ensure the risk is not deferred to the final lot release tests which may not always be able to detect all biologically relevant changes in product quality. In addition, monitoring the manufacturing process mitigates the risk batch failures and market supply shortages. Setting appropriate specifications is critical to ensure product characteristics are maintained throughout the product's lifecycle. It is also important to note that similar products developed independently may have different quality specifications, as long as these specifications are

supported by the quality attributes of the clinical lots shown to be safe and efficacious. In conclusion, knowledge of regulatory considerations and discussions with national regulatory authorities throughout the product development stages will help to avoid unnecessary delays and potentially expensive setbacks for manufacturers.

Production of glycoconjugate vaccines by industry

Dr. Richard Kensinger, Dr. Don Gerson and Pradip Ghate

Industrial representatives from Inventprise, PnuVax and Sanofi detailed that their facilities all have current GMP manufacturing capacity at a scale at least consistent with the requirements needed for the Hia vaccine and significant experience in the production of glycoconjugate vaccines.

In addition to the GMP requirements, the speakers highlighted the following key considerations that are often overlooked but critical to glycoconjugate vaccine production requirements including:

- Defining critical quality attributes at the start, before transfer to manufacturing.
- Thorough characterization of the seed lot.
- Ongoing monitoring of impurities as free polysaccharide is not the product.
- Assessing process scalability through physicochemical characterization to demonstrate product comparability.
- Ensuring adequate amounts of glycoconjugate vaccine. Estimated needs are: Phase I, 3-5g PS; Phase II, 10g PS; Phase III, 10-100g PS depending upon dose requirements.

Each industrial representative confirmed that they had the capacity and/or the interest in contributing to the clinical lot production of this glycoconjugate vaccine.

Public-private partnerships in vaccine development

Drs. Mark Kane and Jason Crawford

Vaccine development globally has transitioned from a pseudo "cottage industry" where countries' public health institutes or local companies produced vaccines to one where it is perceived that "only Big Pharma can make a new vaccine". Organizations such as the Global Alliance for Vaccine and Immunization have made some progress in challenging the dogma that the developing world only gets a vaccine if it is profitable in the industrialized world, but much more needs to be done in this regard. Hia vaccine could follow the precedent set by the MenAfriVac vaccine for a new development model. The challenge, however, is that the Gates Foundation or the Vaccine Alliance are probably not interested in supporting a vaccine for potentially small populations in rich countries (US and Canada). Thus, the solution will be to identify federal government funding opportunities. It is also possible that Hia disease could expand in much the same way that the Hib disease did.

It was apparent that generating an advanced market commitment is a good strategy for this kind of product. It is important to start with the end in mind and try to establish who the recipients would be. It is probable that this product will warrant orphan vaccine status which would have implications for clinical trial monitoring and likely increase the need for increased post-market scrutiny. The vaccine could be ready for clinical market within two years and the opportunity to build upon the Hib vaccine experience will be tremendously helpful. It is imperative that this Hia vaccine is presented to national Indigenous organizations in order to partner and develop strategies with them to confirm the need and illustrate the potential of this product. It would be very useful to develop a working group structure to formalize efforts. This would include the development of a business plan to show that there would be a "benefit" to having the product available. This does not necessarily translate to profitability for the manufacturer, but has to illustrate what the benefit would be to the "investor" and, of course, the recipients. A modelling study on the cost-effectiveness and impact of such a vaccine would be crucial to help illustrate the value. There is a clear need to better define the burden of the disease.

Thus the key points to consider in terms of epidemiology, economics and vaccine development are:

- Do we have enough epidemiological data on burden in Indigenous and Alaskan native peoples?
- Do we have enough data from the US, Canada and the rest of the world? How can we encourage collaboration to get more global data?
- Do we have preliminary cost-effectiveness data? Who will carry out this modelling analysis?
- Do we have a strategy for consideration of what carrier protein to use? Would we consider two glycoconjugate vaccines with different carrier proteins, one for Canada and one for Alaska?

Recommendations and next steps

The workshop concluded with an all-participant roundtable to discuss all the matters raised during the presentations and to consider the key components to focus upon in order to effectively move this potential vaccine solution further along the development pathway.

The following is a list of the recommendations identified during the workshop:

1. Complete pre-clinical studies:
    - The choice of protein carrier should be carefully evaluated as the Alaskan experience points to the importance of the carrier in order to induce protective immunity in infants less than six months old.
    - The ability of adjuvants approved for human use (e.g. alum) to elicit protective titers needs to be established.
    - There is a need to establish and obtain regulatory approval for bactericidal assay with human sera to illustrate laboratory correlate of protection with clinical trial studies.

2. Improve epidemiological surveillance to better understand the extent of the disease in the rest of North America and Globally:
    - Work with partners nationally and internationally (e.g. Pan American Health Organization) to better define global epidemiology.
3. Establish engagement mechanisms with national Indigenous organizations:
    - Explore mechanisms to appropriately engage with AFN, Inuit Tapiriit Kanatami and other advocacy groups to ensure that Indigenous groups are involved in the process to set direction and make decisions.
4. Explore funding opportunities to prepare clinical lots and undertake clinical trials:
    - Prepare a business plan/policy paper to demonstrate value of a Hia vaccine.
    - Demonstrate economic burden of disease and develop modelling simulations to illustrate cost-effectiveness of a Hia vaccine solution.
    - Formalize a working group to co-ordinate activities.

Conclusion

Following the introduction of the Hib vaccine in the mid-1980s, there has been a remarkable decrease in the number of reported cases of Hib disease. Since the late 1990s there has been a concomitant increase in Hia infections in Indigenous communities in Alaska and the northern regions of Canada. Young infants and children from our North American arctic communities continue to suffer and die from an infection that appears to be preventable. All the elements are now present to develop the Hia vaccine.

Conflict of interest

ADC, MGB, and RSWT have no conflicts of interest to declare.

MU holds an Investigator Initiated Research Grant from Pfizer for an unrelated study. LB is a Senior Scientific Advisor with Inventprise/InventVac, Redmond, Washington/Vancouver, British Columbia and a Strategic Advisor to NEOMED-LABS, Montreal, Quebec; and he has worked with the NRC Vaccine and Immune Therapeutics Group (HHT) from 2011—2015 and as a consultant for NRC in relation to Hia vaccine development. He worked with Sanofi Pasteur from 1988 to 2010 on Hib and combination vaccine development.

Contributors

Kim Barker, Department of Health, Government of Nunavut, Iqaluit, NU

Luis Barreto, National Research Council, Ottawa, ON

Andrée-Anne Boisvert, Montreal Children's Hospital, Montréal, QC

Simon Brascoupé, Carleton University, Ottawa, ON

Michael Bruce, US Centers for Disease Control and Prevention (CDC), Arctic Investigations Program, Anchorage, AK, US

Cindi Corbett, Public Health Agency of Canada, Winnipeg, MB

Andrew Cox, National Research Council, Ottawa, ON

Jason Crawford, Centre for Drug Research and Development, Vancouver, BC

Don Gerson, PnuVax, Montréal, QC

Pradip Ghate, Inventprise, Seattle, WA, US

Scott Halperin, Dalhousie University, Halifax, NS

Mark Kane, Inventprise, Seattle, WA, US

Richard Kensinger, Sanofi, Swiftwater, PA, US

Marlene Larocque, Assembly of First Nations, Ottawa, ON

Isabelle Letourneau, Canadian Institutes for Health Research, Montréal, QC

Kathleen Lydon-Hassen, Health Canada, Ottawa, ON

David Scheifele, University of British Columbia, Vancouver, BC

Richard Siggers, Health Canada, Ottawa, ON

Raymond Tsang, Public Health Agency of Canada, Winnipeg, MB

Marina Ulanova, Northern Ontario School of Medicine, Thunder Bay, ON

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Summary of the NACI Statement on Seasonal Influenza Vaccine for 2017–2018

W Vaudry[1], R Stirling[2] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Influenza is a respiratory infection caused primarily by influenza A and B viruses. Vaccination is the most effective way to prevent influenza and its complications. The National Advisory Committee on Immunization (NACI) provides recommendations regarding seasonal influenza vaccines annually to the Public Health Agency of Canada (PHAC).

Objective: To summarize the NACI recommendations regarding the use of seasonal influenza vaccines for the 2017–2018 influenza season.

Methods: Annual influenza vaccine recommendations are developed by NACI's Influenza Working Group for consideration and approval by NACI, based on NACI's evidence-based process for developing recommendations. The recommendations include a consideration of the burden of influenza illness and the target populations for vaccination; efficacy and effectiveness, immunogenicity and safety of influenza vaccines; vaccine schedules; and other aspects of influenza immunization. These recommendations are published annually on the Agency's website in the NACI Advisory Committee Statement: *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine* (the Statement).

Results: The annual statement has been updated for the 2017–2018 influenza season to incorporate recommendations for the use of live attenuated influenza vaccine (LAIV) that were contained in two addenda published after the 2016–2017 statement. These recommendations were 1) that egg-allergic individuals may be vaccinated against influenza using the low ovalbumin-containing LAIV licensed for use in Canada and 2) to continue to recommend the use of LAIV in children and adolescents 2–17 years of age, but to remove the preferential recommendation for its use.

Conclusion: NACI continues to recommend annual influenza vaccination for all individuals aged six months and older, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk, and others as indicated.

Affiliations

[1] NACI Influenza Working Group Chair, University of Alberta, Edmonton, AB

[2] Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada, Ottawa, ON

***Correspondence:** naci-ccni@phac-aspc.gc.ca

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Introduction

Influenza and pneumonia is ranked among the top 10 leading causes of death in Canada (1). Although the burden of influenza can vary from year to year, it is estimated that in a given year, there are an average of 12,200 hospitalizations related to influenza (2) and approximately 3,500 deaths attributable to influenza (3). The National Advisory Committee on Immunization (NACI) provides recommendations regarding seasonal influenza vaccines annually to the Public Health Agency of Canada (PHAC). The objective of this article is to summarize the NACI recommendations for the use of seasonal influenza vaccine for the 2017–2018 influenza season. Complete details can be found in the *Statement on Seasonal Influenza Vaccine for 2017–2018* (4).

Methods

In the preparation of the 2017–2018 seasonal influenza vaccine recommendations, NACI's Influenza Working Group (IWG) identified and reviewed evidence regarding the administration of live attenuated influenza vaccine (LAIV) in egg-allergic individuals and vaccine effectiveness of LAIV and inactivated influenza vaccine (IIV) in children and adolescents 2–17 years of age. Following the review and analysis of this information, the IWG proposed updated recommendations for vaccine use to NACI, based on NACI's evidence-based process for developing recommendations (5). NACI critically appraised the available evidence and approved the specific recommendations brought forward. Complete details of the literature review, rationale and relevant considerations for the updated recommendations can be found in the *Addendum – LAIV Use in Egg Allergic Individuals* (6), the *Addendum – LAIV Use in Children and Adolescents* (7),

and the *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018* (4).

For the review of LAIV use in egg-allergic individuals, data were obtained from three prospective cohort studies in the United Kingdom (UK) and Canada (8-10). Post-licensure safety data from the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) was analyzed to seek reports of adverse events in influenza vaccine recipients who describe a history of allergy to eggs.

Data on LAIV vaccine effectiveness in children and adolescents were obtained primarily from American studies using the test-negative design: the United States Influenza Vaccine Effectiveness Network (US Flu VE Network) (2010–2016) (11-14), the Influenza Clinical Investigation for Children (ICICLE) study (2013–2014 through 2015–2016 influenza seasons) (15-17) and the US Department of Defense (DoD) (2013–2014 and 2015–2016 influenza seasons) (13,18). The American Household Influenza Vaccine Effectiveness (HIVE) study derived vaccine effectiveness data using an alternative household cohort design (2012–2013 and 2013–2014 seasons) (19,20). Data on LAIV vaccine effectiveness from outside of the United States of America came from the Canadian Sentinel Practitioner Surveillance Network (SPSN) (2013–2014 and 2015–2016 seasons) (21,22), Germany (2012–2013 season) (23), the UK sentinel surveillance network (2013–2014 through 2015–2016 seasons) (24-26), and Finland (2015–2016 season) (27). These studies used the test-negative design (21-26), with one prospective cohort study (27) and two cluster randomized trials (28,29).

This article also presents information not provided in the published addenda or statement: figures summarizing the LAIV vaccine effectiveness data from the cited studies, by influenza season and influenza strain, as well as LAIV vaccine effectiveness data used to inform NACI's decision that were not publicly available when the Addendum was finalized, but have subsequently been published (30,31).

Results

New for the 2017–2018 influenza season

There were two changes in NACI recommendations for the use of seasonal influenza vaccine for the 2017–2018 influenza season. Both changes related to updated recommendations on the use of LAIV.

LAIV is safe for egg-allergic individuals

All influenza vaccine products authorized for use in Canada are manufactured from influenza virus grown in chicken eggs, which may result in the vaccines containing trace amounts of residual egg protein. The formulation of LAIV licensed for use in Canada contains a low amount of residual ovalbumin (less than 0.24 µg/dose) (*written communication from AstraZeneca*), which is comparable to the amounts in IIVs available in Canada.

At the time of publication of the *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016–2017* (32), NACI did not recommend LAIV use in egg-allergic individuals due to a lack of data available to support this practice.

However, the safety of LAIV in egg-allergic individuals has now been studied in more than 1,100 children and adolescents (2–18 years of age) in the UK and Canada (8-10). After careful review of recently published studies, NACI concludes that egg-allergic individuals may be vaccinated against influenza using the low ovalbumin-containing LAIV licensed for use in Canada. The full dose of LAIV may be used without prior vaccine skin test and in any settings where vaccines are routinely administered. LAIV also appears to be well tolerated in individuals with a history of stable asthma or recurrent wheeze; however, it remains contraindicated for individuals with severe asthma (defined as currently on oral or high-dose inhaled glucocorticosteroids or active wheezing) or for those with medically attended wheezing in the seven days prior to immunization. The use of LAIV in egg-allergic individuals is a change from previous NACI statements.

Complete details of the literature review, rationale and relevant considerations for the updated recommendations can be found in the *Addendum – LAIV Use in Egg Allergic Individuals* (6) and the *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018* (4).

Current evidence supports the continued use of LAIV in children and adolescents 2–17 years of age but does not support its preferential use

At the time of publication of the *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016–2017* (32), NACI recommended the preferential use of LAIV in children and adolescents 2–17 years of age who did not have contraindications to the vaccine. This recommendation was based upon randomized placebo controlled studies and post-marketing safety data that showed LAIV to be safe, efficacious and immunogenic in children and to provide better protection against influenza than trivalent IIV, especially in young children (less than six years of age), with weaker evidence of superior efficacy in older children (33).

The adjusted vaccine effectiveness estimates for LAIV and IIV against any influenza in children and adolescents (2–17 years of age) are summarized by study for the 2010–2011 through 2014–2015 (**Appendix Figure 1**) and 2015–2016 (**Appendix Figure 2**) influenza seasons. Summaries of adjusted vaccine effectiveness estimates by study and vaccine type are also provided for influenza A(H1N1)pdm09 (**Appendix Figure 3**), influenza A(H3N2) (**Appendix Figure 4**) and influenza B (**Appendix Figure 5**) for these same influenza seasons (Note: In some influenza seasons, sample sizes were too small to derive vaccine effectiveness estimates for all influenza strains).

Based upon the US Flu VE Network data showing that LAIV provided no protective benefit during the influenza A(H1N1) dominant 2015–2016 influenza season and no evidence of effectiveness against the dominant circulating strains in the two prior influenza seasons (2013–2014 and 2014–2015), the American Advisory Committee on Immunization Practices (ACIP) recommended during its June 2016 meeting that LAIV should not be used during the 2016–2017 influenza season (34). LAIV continued to be recommended for use in children in the UK and Finland for the 2016–2017 season (35). Studies conducted in both of these countries and in Canada found a statistically significant overall protective effect of LAIV in children for 2015–2016, although sample sizes limited the precision of those estimates (22,24,27). The United States Food and Drug Administration (US FDA) has also determined that specific regulatory action for LAIV was not necessary at the time, following a review of manufacturing and clinical data supporting licensure and the totality of evidence presented at the June

2016 ACIP meeting, and continues to find that the benefits of quadrivalent LAIV outweigh any potential risks (36). Quadrivalent LAIV remains licensed for use in the US. The FDA's determination was made taking into account the limitations of observational studies in estimating vaccine effectiveness and the seasonal variability of influenza vaccine effectiveness.

After careful review of available studies from the last several influenza seasons, NACI concludes that the current evidence is consistent with LAIVs providing comparable protection against influenza to that afforded by IIV in various jurisdictions and has revised its recommendations on the use of influenza vaccine in children and adolescents 2–17 years of age:

1. In children and adolescents without contraindications to the vaccine, any of the following vaccines can be used: quadrivalent LAIV, quadrivalent inactivated influenza vaccine (QIV) or trivalent inactivated influenza vaccine (TIV).
2. The current evidence does not support a recommendation for the preferential use of LAIV in children and adolescents 2–17 years of age.

Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used in children and adolescents 2–17 years of age. If a quadrivalent vaccine is not available, TIV should be used.

The observational study data reviewed highlight the challenge in interpreting the vaccine effectiveness of LAIV and IIV when point estimates by influenza subtype are derived based on small sample sizes associated with wide confidence intervals. Therefore, in making its recommendations, NACI recognizes the need to continue to closely monitor the data on the vaccine effectiveness of LAIV by influenza subtype and the relative effectiveness of LAIV compared to IIV. NACI has also identified the need for further research to address current knowledge gaps:

3. NACI strongly encourages further multidisciplinary (e.g. epidemiology, immunology, virology) research to investigate the reasons for the discordant 2015–2016 vaccine effectiveness estimates between studies and explanations for poor LAIV effectiveness against A(H1N1)pdm09 reported in some studies.
4. NACI strongly recommends that sufficient resources be provided to enhance influenza-related research and sentinel surveillance systems in Canada to improve the evaluation of influenza vaccine efficacy and effectiveness to provide the best possible evidence for Canadian influenza vaccination programs and recommendations.

Complete details of the literature review, rationale and relevant considerations for the updated recommendations can be found in the *Addendum – LAIV Use in Children and Adolescents* (7) and the *Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2017–2018* (4).

Summary of NACI recommendations for the use of influenza vaccines for the 2017–2018 influenza season

NACI continues to recommend influenza vaccination for all individuals aged six months and older who do not have contraindications to the vaccine, with particular focus on people at high risk of influenza-related complications or hospitalization, people capable of transmitting influenza to those at high risk of complications, and others as indicated in **Table 1**.

Table 1: Groups for whom influenza vaccination is particularly recommended

People at high risk of influenza-related complications or hospitalization

- All pregnant women[1].
- Adults and children with the following chronic health conditions:
  - cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma);
  - diabetes mellitus and other metabolic diseases;
  - cancer, immune compromising conditions (due to underlying disease, therapy or both);
  - renal disease;
  - anemia or hemoglobinopathy;
  - neurologic or neurodevelopment conditions[2];
  - morbid obesity (body mass index [BMI] of 40 years and over);
  - children and adolescents (age 6 months to 18 years) undergoing treatment for long periods with acetylsalicylic acid, because of the potential increase of Reye's syndrome associated with influenza.
- People of any age who are residents of nursing homes and other chronic care facilities.
- People 65 years of age and older.
- All children 6 to 59 months of age.
- Indigenous peoples.

People capable of transmitting influenza to those at high risk

- Health care and other care providers in facilities and community settings who, through their activities, are capable of transmitting influenza to those at high risk of influenza complications.
- Household contacts (adults and children) of individuals at high risk of influenza-related complications (whether or not the individual at high risk has been immunized):
  - household contacts of individuals at high risk, as listed in the section above;
  - household contacts of infants under six months of age as these infants are at high risk of complications from influenza but cannot receive influenza vaccine;
  - members of a household expecting a newborn during the influenza season.
- Those providing regular child care to children 59 months of age and under, whether in or out of the home.
- Those who provide services within closed or relatively closed settings to persons at high risk (e.g. crew on a ship).

Others

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

[1] The risk of influenza-related hospitalization increases with length of gestation (i.e. it is higher in the third than in the second trimester)

[2] These include seizure disorders, febrile seizures and isolated developmental delay in children and neuromuscular, neurovascular, neurodegenerative, neurodevelopmental conditions and seizure disorders in adults, but exclude migraines and neuropsychiatric conditions without neurological conditions

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

Table 2: Choice of influenza vaccine for selected age and risk groups (for persons without a contraindication to the vaccine)[1]

Recipient by age group	Vaccine types available for use	Comments
Children 6–23 months of age	• TIV • QIV • ATIV	TIV, QIV and ATIV are authorized for this age group NACI recommends that, given the burden of influenza B disease, QIV should be used. If QIV is not available, either unadjuvanted or adjuvanted TIV should be used
Children 2–17 years of age	• TIV • QIV • Quadrivalent LAIV	**In children without contraindications to the vaccine, any of the following vaccines can be used: LAIV, QIV or TIV** **The current evidence does not support a recommendation for the preferential use of LAIV in children and adolescents 2–17 years of age** Given the burden of influenza B disease in children and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent formulation of influenza vaccine be used in children and adolescents 2–17 years of age. If a quadrivalent vaccine is not available, TIV should be used. LAIV is not recommended for children with immune compromising conditions LAIV, TIV or QIV can be used in children with chronic health conditions and without contraindications (see full statement for more details) (4)
Adults 18–59 years of age	• TIV • QIV • Quadrivalent LAIV	TIV and QIV are the recommended products for adults with chronic health conditions TIV and QIV, instead of LAIV, are recommended for health care workers LAIV is not recommended for adults with immune compromising conditions
Adults 60–64 years of age	• TIV • QIV	TIV and QIV are authorized for use in this age group
Adults 65 years of age and older	• TIV • QIV • ATIV • High-dose TIV	Given the burden of Influenza A(H3N2) disease and evidence of better efficacy in this age group, it is expected that high-dose TIV should provide superior protection compared with the standard-dose intramuscular vaccine for older adults.
Pregnant women	• TIV • QIV	LAIV is not recommended because of the theoretical risk to the fetus from administering a live virus vaccine

Abbreviations: ATIV, adjuvanted trivalent inactivated influenza vaccine; LAIV, live attenuated influenza vaccine (quadrivalent formulation); QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine
[1] Updated recommendations noted in bold

Conclusion

NACI continues to recommend annual influenza vaccination for all individuals aged six months and older (noting product-specific age indications and contraindications), with particular focus on people at high risk of influenza-related complications or hospitalization, including all pregnant women; people capable of transmitting influenza to those at high risk; and others as indicated. For the 2017–2018 influenza season, NACI has also updated LAIV use recommendations: 1) egg-allergic individuals may be vaccinated against influenza using the low ovalbumin-containing LAIV licensed for use in Canada, and 2) LAIV continues to be recommended for use in children and adolescents 2–17 years of age, but is no longer recommended preferentially.

Table 3: Recommended influenza vaccine dosage and route, by age, for the 2017–2018 influenza season

Age group	TIV without adjuvant[1] Intramuscular	QIV without adjuvant[2] Intramuscular	TIV without adjuvant, high-dose (Fluzone® High-Dose) Intramuscular	MF59-adjuvanted TIV (Fluad Pediatric® or Fluad®) Intramuscular	LAIV (FluMist® Quadrivalent) Intranasal	Number of doses required
6–23 months	0.5 mL[3]	0.5 mL[3]	N/A	0.25 mL	N/A	1 or 2[4]
2–8 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1 or 2[4]
9–17 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1
18–59 years	0.5 mL	0.5 mL	N/A	N/A	0.2 mL (0.1 mL per nostril)	1
60–64 years	0.5 mL	0.5 mL	N/A	N/A	N/A	1
65 years and older	0.5 mL	0.5 mL	0.5 mL	0.5 mL	N/A	1

Abbreviations: LAIV, live attenuated influenza vaccine (quadrivalent formulation); N/A, not applicable; QIV, quadrivalent inactivated influenza vaccine; TIV, trivalent inactivated influenza vaccine
[1] Influvac® 18 years and older, Fluviral® 6 months and older, Agriflu® 6 months and older, Vaxigrip® 6 months and older, Fluzone® 6 months and older
[2] Flulaval® Tetra 6 months and older, and Fluzone® Quadrivalent 6 months and older
[3] This information differs from the product monograph. Published and unpublished evidence suggest moderate improvement in antibody response in infants, without an increase in reactogenicity, with the use of full vaccine doses (0.5 mL) for unadjuvanted inactivated influenza vaccines (37,38). This moderate improvement in antibody response without an increase in reactogenicity is the basis for the full dose recommendation for unadjuvanted inactivated vaccine for all ages. For more information, refer to *Statement on Seasonal Influenza Vaccine for 2011–2012* (39)
[4] Children 6 months to less than 9 years of age who have never received the seasonal influenza vaccine require two doses of influenza vaccine, with a minimum interval of four weeks between doses. Eligible children less than 9 years of age who have properly received one or more doses of seasonal influenza vaccine in the past should receive one dose per influenza vaccination season thereafter

Authors' statement

This statement was prepared by the Influenza Working Group: Vaudry W (Chair), Grohskopf L, Henry E, Kumar D, Langley J, Lavoie M, McElhaney J, McGeer A, Moore D, Vinh D, Warshawsky B, Xiong J

Conflict of Interest

None.

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Ex-officio representatives: Barnes K (National Defence and the Canadian Armed Forces), Charos G (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC]), Coleman G (Biologics and Genetic Therapies Directorate, Health Canada [HC]), Gallivan J (Marketed Health Products Directorate, HC), Pennock J (CIRID, PHAC), Pless R (CIRID, PHAC), Wong T (First Nations and Inuit Health Branch, HC)

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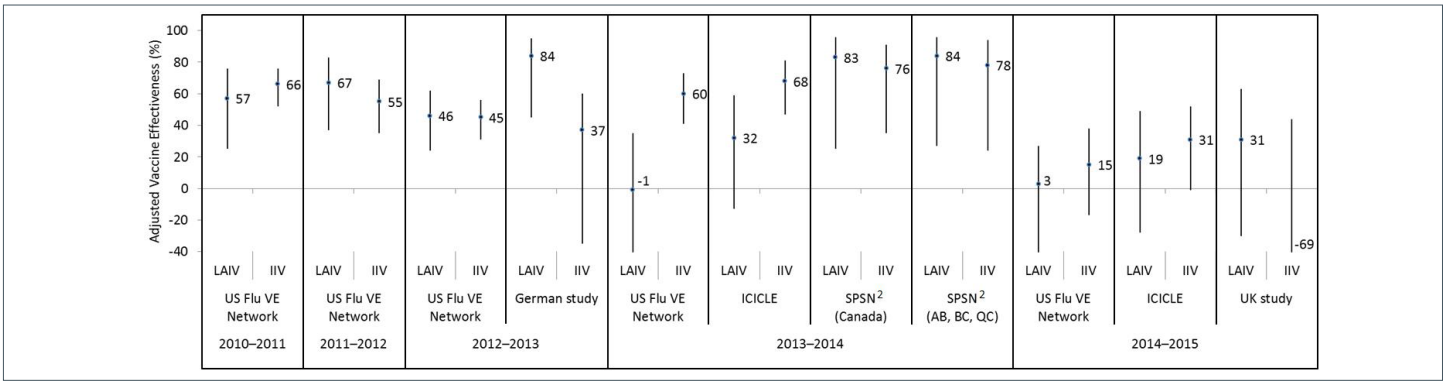
Appendix

Figure 1: Adjusted vaccine effectiveness estimates against any influenza by study and vaccine type for the 2010–2011 through 2014–2015 influenza seasons in children and adolescents 2–17 years of age[1]

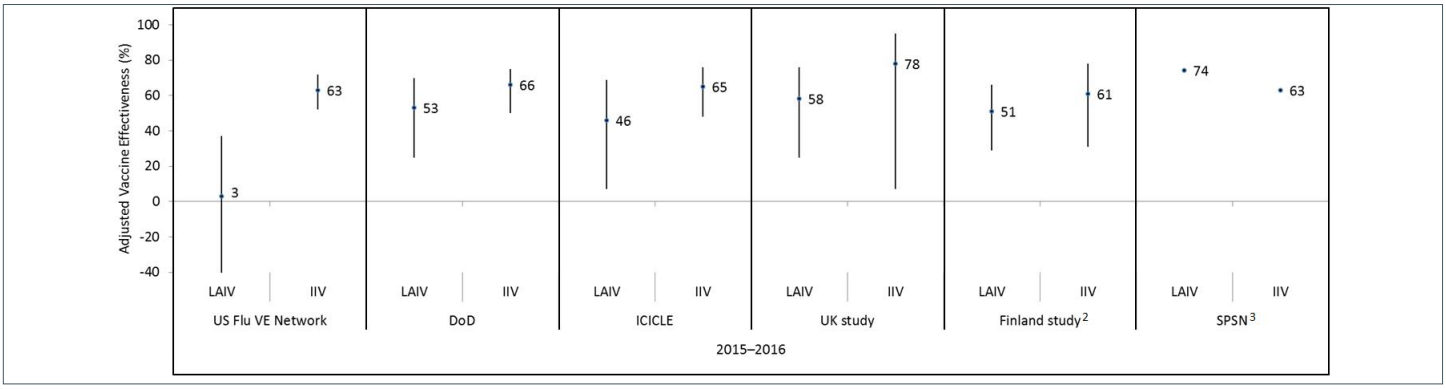


Abbreviations: ICICLE, Influenza Clinical Investigation for Children study; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; SPSN, Canadian Sentinel Practitioner Surveillance Network; US FLU VE Network, United States Influenza Vaccine Effectiveness Network; %, percentage

[1] For each study in the forest plot, the black circle represents the vaccine effectiveness point estimate and the vertical bar represents the corresponding 95% confidence interval. The 95% confidence interval lower limits are truncated at -40%

[2] The Canadian SPSN reported unadjusted vaccine effectiveness estimates for children and adolescents 2–19 years of age. SPSN is comprised of sentinel practitioners in the provinces of Alberta (AB), British Columbia (BC), Manitoba (MB), Ontario (ON) and Quebec (QC). LAIV was publicly funded in AB, BC and QC for the 2013–2014 influenza season

Figure 2: Adjusted vaccine effectiveness estimates against any influenza by study and vaccine type for the 2015–2016 influenza season in children and adolescents 2–17 years of age[1]



Abbreviations: DoD, United States Department of Defense; ICICLE, Influenza Clinical Investigation for Children study; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; SPSN, Canadian Sentinel Practitioner Surveillance Network; UK Study, United Kingdom Study; US FLU VE Network, United States Influenza Vaccine Effectiveness Network; %, percentage

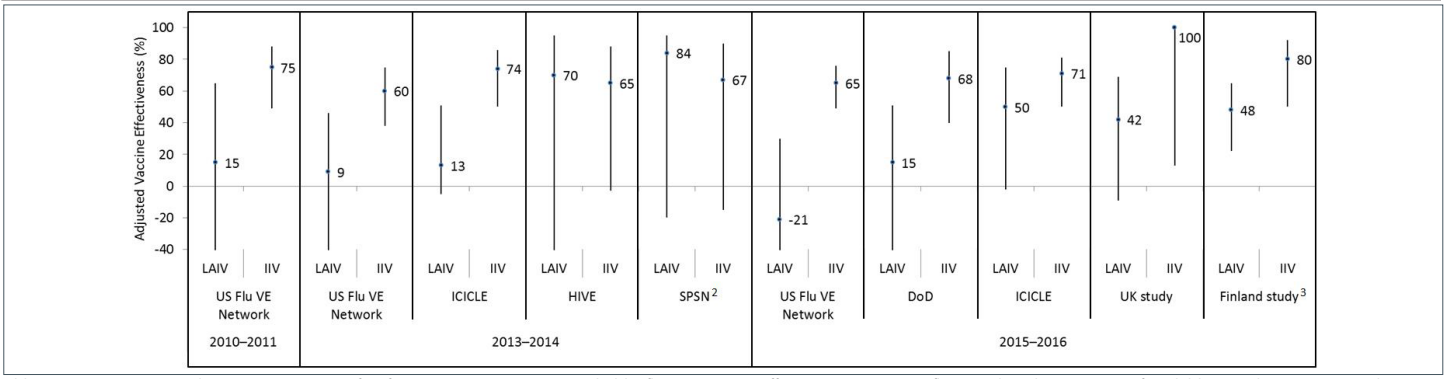
[1] For each study in the forest plot, the black circle represents the vaccine effectiveness point estimate and the vertical bar represents the corresponding 95% confidence interval. The 95% confidence interval lower limits are truncated at -40%

[2] The Finland national cohort study reported vaccine effectiveness in children two years of age

[3] The Canadian SPSN reported wide and overlapping 95% confidence intervals (exact values not publicly available at time of writing)

Appendix continued

Figure 3: Adjusted vaccine effectiveness estimates against influenza A(H1N1)pdm09 by influenza season, study and vaccine type in children and adolescents 2–17 years of age for A(H1N1)pdm09-dominant seasons since 2009[1]



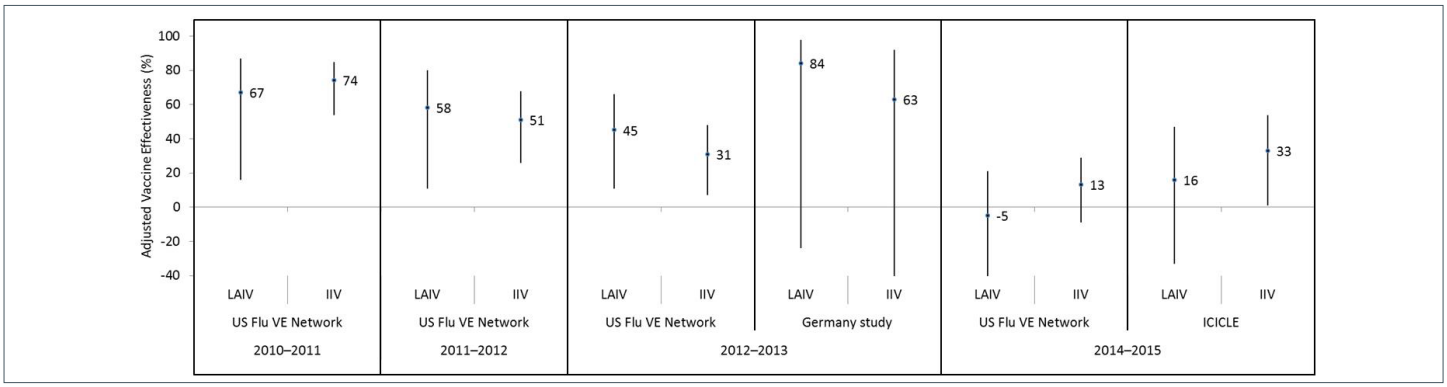
Abbreviations: DoD, United States Department of Defense; HIVE, American Household Influenza Vaccine Effectiveness; ICICLE, Influenza Clinical Investigation for Children study; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; SPSN, Canadian Sentinel Practitioner Surveillance Network; UK Study, United Kingdom Study; US FLU VE Network, United States Influenza Vaccine Effectiveness Network; %, percentage

[1] For each study in the forest plot, the black circle represents the vaccine effectiveness point estimate and the vertical bar represents the corresponding 95% confidence interval. The 95% confidence interval lower limits are truncated at -40%

[2] The Canadian SPSN reported unadjusted vaccine effectiveness estimates

[3] The Finland national cohort study reported vaccine effectiveness against influenza A in children two years of age

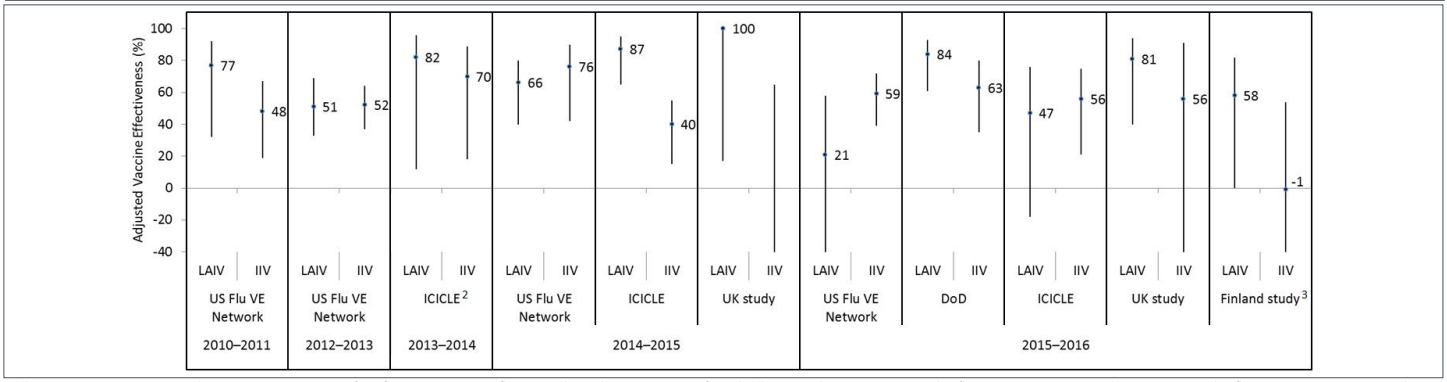
Figure 4: Adjusted vaccine effectiveness estimates against influenza A(H3N2) by influenza season, study and vaccine type in children and adolescents 2–17 years of age for A(H3N2)-dominant seasons since 2009[1]



Abbreviations: ICICLE, Influenza Clinical Investigation for Children study; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; US FLU VE Network, United States Influenza Vaccine Effectiveness Network; %, percentage

[1] For each study in the forest plot, the black circle represents the vaccine effectiveness point estimate and the vertical bar represents the corresponding 95% confidence interval. The 95% confidence interval lower limits are truncated at -40%

Figure 5: Adjusted vaccine effectiveness estimates against influenza B since 2009 by influenza season, study and vaccine type in children and adolescents 2–17 years of age[1]



Abbreviations: DoD, United States Department of Defense; ICICLE, Influenza Clinical Investigation for Children study; IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine; UK Study, United Kingdom Study; US FLU VE Network, United States Influenza Vaccine Effectiveness Network; %, percentage

[1] For each study in the forest plot, the black circle represents the vaccine effectiveness point estimate and the vertical bar represents the corresponding 95% confidence interval. The 95% confidence interval lower limits are truncated at -40%

[2] The ICICLE study reported vaccine effectiveness against influenza B/Yamagata for the 2013–2014 influenza season

[3] The Finland national cohort study reported vaccine effectiveness in children two years of age

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Summary of the NACI Update on the Recommended Use of Hepatitis B Vaccine

B Henry[1], O Baclic[2] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Infant and adolescent hepatitis B (HB) immunization programs have been successfully implemented in all Canadian provinces and territories since the 1990s. Following the introduction of universal immunization programs, the incidence of HB has decreased in all age groups. However, the duration of protection against chronic infection, as measured by preserved T- and B-cell memory, remains unknown.

Objectives: To review the evidence on long-term protection against HB in adolescents who received routine immunization in infancy, determine the level of risk of HB infection in Canadians with diabetes and assess the timing of re-vaccination of individuals with immunocompromising conditions.

Methods: The National Advisory Committee on Immunization (NACI) Hepatitis Working Group reviewed key questions and performed an evidence review and synthesis. In consideration of the burden of illness to be prevented, the target population and issues related to safety, immunogenicity, efficacy and effectiveness of the vaccine, the group proposed recommendations for vaccine use to NACI. All evidence was rated and summarized in tables. NACI approved specific evidence-based recommendations and elucidated the rationale and relevant considerations in the Statement update.

Results: In addition to the epidemiological data assessment, NACI reviewed evidence from efficacy and effectiveness studies with up to 30 years of follow-up data as well as data from 39 publications on immune response following the administration of a HB booster dose in individuals who were immunized as infants. Based on the conducted review, NACI did not find evidence that would support a change to its current recommendation that there is no need for routine booster immunization of individuals immunized in infancy and that there is no evidence to support preferential immunization schedules or routine immunization of individuals with diabetes.

Conclusion: NACI now recommends that following immunization of immunocompromised individuals, initial annual monitoring of HB antibody levels may be considered.

Affiliations

[1] NACI Hepatitis Working Group Chair, Victoria, BC

[2] Centre for Immunization and Respiratory Infectious Diseases (CIRID), Public Health Agency of Canada, Ottawa, ON

***Correspondence:** naci-ccni@phac-aspc.gc.ca

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Introduction

In unvaccinated individuals, the risk of chronic hepatitis B (HB) infection varies with age. Up to 95% of infants, 50% of children less than five years of age and 10% of adolescents and adults will develop a chronic infection (1). Although protection following a completed primary schedule is believed to be long lasting, the exact duration is not known. Presence of T- and B-cell memory is required for long-term protection (2-7). Following the introduction of universal immunization programs in all Canadian provinces and territories in the 1990s, the incidence of HB has decreased in all age groups (8). A summary of the current recommendations for HB vaccine is available in the *Canadian Immunization Guide* (9).

National Advisory Committee on Immunization (NACI) is a committee of immunization experts from across Canada that provides ongoing medical, scientific and public health advice to the Public Health Agency of Canada (PHAC) on vaccines authorized for sale in Canada. The NACI Hepatitis Working Group consists of NACI members, liaison members and other vaccine experts who systematically review and synthesize available scientific and other technical information (e.g. disease burden, vaccine characteristics, unpublished study data) pertaining to specific questions or issues concerning hepatitis A and hepatitis B vaccines (10).

Methods

The Hepatitis Working Group reviewed key questions and performed a review and synthesis of evidence on long-term

protection against HB in adolescents who received routine immunization in infancy and the timing for re-vaccination of people with immunocompromising conditions. The group also reviewed epidemiological data and research evidence to determine the level of risk of HB infection in Canadians with diabetes. In consideration of the burden of illness to be prevented, the target population, safety, immunogenicity, efficacy and effectiveness of the vaccine, the Hepatitis Working Group proposed recommendations for vaccine use to NACI. All evidence was rated and summarized in evidence tables. NACI approved specific evidence-based recommendations and elucidated the rationale and relevant considerations in the Statement Update.

Results

In 2013, there were 0.5 cases of acute HB infection per 100,000 population and 12 cases of chronic HB infection per 100,000 population reported through the Canadian Notifiable Disease Surveillance System (CNDSS) (10). According to Canadian Health Measures Survey (CHMS) data, the prevalence of present HB infection in individuals 14 to 79 years of age is estimated to be 0.4%, with the highest infection rate reported in non-white (1.8%) and the foreign-born (1.6%) populations (11).

Based on a review of studies with up to 30 years of data, NACI did not find evidence that would suggest reduced long-term vaccine effectiveness in individuals who were immunized as infants. In addition, NACI also reviewed 39 publications which reported data on immune memory following the administration of a HB challenge dose and did not find evidence that would support the need for a routine HB vaccine booster dose in routine immunization programs.

Based on the reviewed evidence, NACI issued four recommendations for the use of HB vaccines in Canada (see **Text box**).

National Advisory Committee on Immunization (NACI) recommendations for the use of Hepatitis B vaccines in Canada

Recommendation 1: NACI does not recommend routine booster doses of HB vaccine for immunocompetent individuals following the completion of a recommended HB immunization schedule given in infancy. (NACI Evidence Grade B Recommendation)

NACI concludes that there is fair evidence to make this recommendation, based on the limited information available through epidemiological and literature reviews summarized in this statement. Continuous, long-term assessment of enhanced epidemiological data for the appearance of acute disease or the HBsAg carrier state in immunized populations (general population and groups-at-risk) is required before revising current recommendations. National enhanced surveillance systems should, as a minimum, include information on: age, sex, comorbidities, vaccination and immigration status.

Recommendation 2: NACI recommends that adults with diabetes not be considered as a separate high risk group for immunization with HB vaccine. (NACI Evidence Grade I Recommendation)

NACI recommends HB vaccine for all individuals without contraindications who wish to decrease their risk of HB, including individuals with Type 1 and Type 2 diabetes. American data suggest a higher prevalence of previous or current HB infection among adults with diabetes compared to adults without diabetes, but similar Canadian epidemiological data are lacking. As there are notable differences between health care systems in the USA and Canada, and there is no current indication of higher risk of infection for individuals with diabetes in the general Canadian population, NACI does not have sufficient evidence to consider these individuals a separate high risk group for immunization with HB-containing vaccine. NACI will continue to monitor the evidence as it evolves.

Recommendation 3: For immunocompromised individuals, initial annual monitoring of HB antibody levels following HB immunization may be considered. (NACI Evidence Grade B Recommendation)

Optimal timing and frequency of further serological testing should be based on the severity of the immunocompromised state and whether the risk of HB is still present. In immunocompromised persons who initially responded to HB vaccine, booster immunization is required if anti-HBs titres fall below 10 IU/L. This recommendation is in line with similar recommendations made by the US Advisory Committee on Immunization Practices (ACIP), World Health Organization (WHO) and Australia's national immunisation technical advisory group. For individuals with chronic kidney disease and on dialysis who are known to respond sub-optimally to HB vaccination and in whom anti-HBs concentrations decline rapidly, NACI has previously recommended annual evaluation of HB antibody levels.

Recommendation 4: Immunization with HB-containing vaccine should be provided according to determined provincial and territorial (P/T) schedules. (NACI Evidence Grade I Recommendation)

There are several authorized schedules for HB vaccines in Canada. Over the last 2 decades, all P/Ts have effectively implemented prenatal HB screening and at-risk infant immunization programs. With marked reductions in HB incidence that have been observed across Canada and no data demonstrating an obvious advantage of any of the used schedules, optimal timing of primary HB vaccination remains to be contingent on existing P/T epidemiology and specific programmatic considerations. Epidemiological information demonstrating failure of universal prenatal screening and routine immunization programs (i.e. detection of HBV infection in infants and children awaiting immunization) should be collected and analysed on an ongoing basis, so that appropriate changes can be made to existing HB immunization programs as needed.

A complete review of evidence and full NACI recommendations on the use of HB vaccine are published in the NACI Statement Update (10) and the hepatitis B vaccine chapter of the *Canadian Immunization Guide* (9).

Conclusion

NACI now recommends that, following immunization of immunocompromised individuals, initial annual monitoring of HB antibody levels may be considered.

Authors' statement

This statement was prepared by the Hepatitis Working Group: Henry B (Working Group Chair), Baclic O, Brophy J, Choudhri Y, Coleman G, Gilca V, Ismail S, Marchant-Short S, Pham-Huy A, Salvadori M, Warrington R

Conflict of interest

None.

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NACI members: Gemmill I (Chair), Quach C (Vice-Chair), Dayneka N, Deeks S, Henry B, Marchant-Short S, Salvadori M, Sicard N, Vaudry W, Vinh D, Warrington R

Liaison representatives: Blake J (Society of Obstetricians and Gynaecologists of Canada), Brophy J (Canadian Association for Immunization Research and Evaluation), Cohn A (Centers for Disease Control and Prevention, United States), Cole T (Canadian Immunization Committee), Emili J (College of Family Physicians of Canada), Lavoie M (Council of Chief Medical Officers of Health), Mah C (Canadian Public Health Association), Moore D (Canadian Paediatric Society), Pham-Huy A (Association of Medical Microbiology and Infectious Disease Canada)

Ex-officio representatives: Barnes K (National Defence and the Canadian Armed Forces), Charos G (Centre for Immunization and Respiratory Infectious Diseases [CIRID], Public Health Agency of Canada [PHAC]), Coleman G (Biologics and Genetic Therapies Directorate [BGTD], Health Canada [HC]), Gallivan J (Marketed Health Products Directorate [MHPD], HC), Pennock J (CIRID, PHAC), Wong T (First Nations and Inuit Health Branch [FNIHB], HC)

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OVERVIEW

Mycobacterium chimaera infections in post–operative patients exposed to heater–cooler devices: An overview

T Ogunremi[1]*, G Taylor[2], L Johnston[3], K Amaratunga[1,4], M Muller[5], A Coady[1], K Defalco[1], K Dunn[1], J Johnstone[6], S Smith[2], J Embree[7], B Henry[8], J Stafford[9] on behalf of the Infection Prevention and Control Expert Working Group[10]

Abstract

A multi-country outbreak of *Mycobacterium chimaera* infection associated with contaminated heater–cooler devices (HCDs) has been reported, with more than 70 cases in Europe and the United States and two cases in Canada to date. The epidemiological and microbiological characteristics of this outbreak provide evidence for common-source transmission of *M. chimaera* from the exhaust air of intrinsically contaminated HCDs to patients during cardiac surgery. To date, all reported cases have been associated with Stöckert 3T HCDs manufactured at one plant by LivaNova prior to September 2014. Implantation of prosthetic material increases the risk of infection. Infections usually present as prosthetic valve endocarditis, vascular graft infection or disseminated infection. Reported mortality rates have varied, but were often over 40%.

Several measures are recommended to facilitate case-finding and mitigate risk of exposure. The feasibility of some risk mitigation measures and their effectiveness in reducing the risk of exposure are yet to be determined. Until HCDs are redesigned in a manner that prevents water contamination and aerosolization, separating the HCD exhaust air from the operating room air during surgery may be the most effective risk mitigation strategy. However, possible unintended consequences of this approach should be considered. This overview summarizes findings from peer-reviewed and other relevant national documents on key features of the outbreak, including the source, identified risk factors for infection, signs and symptoms of infection, burden of disease, risk mitigation measures, management challenges and knowledge gaps.

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Affiliations

[1] Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada, Ottawa, ON

[2] Department of Medicine, University of Alberta, Edmonton, AB

[3] Queen Elizabeth II Health Science Centre and Dalhousie University, Halifax, NS

[4] Department of Medicine, University of Ottawa, Ottawa, ON

[5] St. Michael's Hospital, Toronto, ON

[6] Public Health Ontario, Toronto, ON

[7] University of Manitoba, Winnipeg, MB

[8] Office of the Provincial Health Officer, Ministry of Health, Victoria, BC

[9] Department of Health, Government of New Brunswick, Fredericton, NB

[10] All working group contributors are noted at the end of the paper

***Correspondence:** toju.ogunremi@phac-aspc.gc.ca

Introduction

Health care–associated infections related to medical device contamination and biofilm formation have been documented in the literature (1). Recently, heater–cooler devices (HCDs) used during cardiopulmonary bypass (CPB) for cardiac surgeries and during extracorporeal membrane oxygenation (ECMO) have come under scrutiny due to infections linked to contaminated devices (2,3).

Heater-cooler devices have water tanks that pump temperature-controlled water through closed circuits to external heat exchangers that regulate patient body temperature by convection (4). The device is equipped with a radiator and fan to facilitate constant dissipation of excess heat through grid openings and the stirring of water in the tank results in aerosolization via the exhaust air (4,5). HCDs are subject to biofilm formation. A biofilm is an aggregate of microorganisms embedded within an extracellular matrix that adhere to each other and to internal surfaces, such as the interior of HCDs.

Several types of microorganisms have been isolated from contaminated HCDs, including nontuberculous mycobacteria (NTM), which are ubiquitous in soil and water and have been linked to health care–associated infections (6-9). Investigations of NTM infection clusters following cardiac surgery detected *Mycobacterium chimaera* as the causative microorganism. *M. chimaera* is a slow-growing NTM included in the *Mycobacterium avium* complex (3,9-12). It is less susceptible to disinfection procedures due to its cell wall constituents and its ability to form biofilms. Isolation and identification of *M. chimaera* from clinical specimens requires specialized microbiological techniques

(3). Transmission was associated with a single model of HCD manufactured by Sorin (now LivaNova) (3,13). Cultures from HCD water tanks, water circuits and air samples taken while HCDs were in use have grown *M. chimaera* (5,8,9,11).

Although *M. chimaera* contamination of ECMO devices has been reported, contamination did not spread to the air in the room while the devices were running and no ECMO-associated *M. chimaera* infections were reported (2,14). Nonetheless, the need to assess potential patient exposure from ECMO has been recognized since patients treated with ECMO, who are often critically ill and highly immunocompromised, may be exposed to the device for an extended period of time (2). National guidance documents and safety communications describing risk mitigation measures and testing recommendations in Canada, United Kingdom (UK), United States (US) and Australia have been published (13,15-20).

The objective of this overview is to summarize relevant literature on the current multi-country outbreak of *M. chimaera* infection. The source of exposure, risk factors for infection, signs and symptoms of infection, disease burden, risk mitigation measures, challenges and gaps are summarized. This overview may be a helpful resource for Canadian health care facilities and providers who use HCDs. It may also support informed decision-making by authorities responsible for implementing infection prevention and control measures.

Scope

A worldwide literature search was undertaken by the Health Library (Health Canada) using Ovid MEDLINE, EMBASE and Global Health databases for studies published from January 1, 2007 to March 8, 2017. The search strategy was developed using database-specific thesauri for "*Mycobacterium chimaera*", "heater-cooler devices", and "cardiac surgery". The search was limited to studies in English and French with no filters applied to limit retrieval by study design. A grey literature search was also conducted by the Health Library to identify relevant national guidance documents and safety communications. The reference lists of relevant guidance documents were hand searched for additional relevant studies.

Full texts of all relevant studies were screened to identify those reporting on HCD-associated *M. chimaera* infection in postoperative cardiac surgery patients and any risk mitigation measures described. A narrative synthesis of the relevant peer-reviewed publications, national guidance documents and/or safety communications was done.

Findings

A total of 95 articles were retrieved from peer-reviewed and grey literature searches, including a reference list search of identified documents. Information from 38 relevant documents was included in this overview. Fifty-seven articles were excluded for one of several reasons including studies that reported on case(s) already described in detail elsewhere; studies that focused on NTM in general (not specifically *M. chimaera*); studies that did not discuss patient exposure or transmission; and national guidance documents or safety communications that did not provide additional information to that obtained from similar documents from Canada, the US, Australia and Europe.

Source of exposure

To date, all cases of *M. chimaera* infection reported internationally have been associated with Stöckert 3T HCDs manufactured in Germany by LivaNova before September 2014 (3,9,13,15,21-23). Phylogenetic analysis by whole genome sequencing and other means showed that isolates from infected patients and from water and exhaust air of used and new Stöckert 3T HCDs were closely related, suggesting global distribution of contaminated HCDs and a hospital-independent, common source for the current outbreak (5,9,12,22,24-26). LivaNova implemented changes to their disinfection processes in an attempt to reduce the risk of *M. chimaera* contamination of 3T HCDs manufactured after September 2014 (13,15,27,28). Tests conducted on HCDs manufactured by a different company detected *M. chimaera* in the water but not in air samples, and the isolate obtained was genetically distinct from isolates obtained from Stöckert 3T HCDs (12,25,29).

During surgeries, the HCD is often positioned adjacent to the cardiopulmonary bypass machine and the patient. Recently, one of the considerations related to minimizing patient exposure to exhaust air from the HCD has to do with the feasibility of positioning the HCD immediately beside the floor-level exhaust in the operating room.

Risk factors for infection

Cases of *M. chimaera* infection following exposure to HCDs during cardiopulmonary bypass have been reported in patients who had undergone surgery in Europe (UK, France, Switzerland, Netherlands, Germany, Ireland and Spain) as well as in the US, Australia, Canada and Hong Kong Special Administrative Region (18). Patients undergoing cardiac surgery involving cardiopulmonary bypass where body temperature is regulated by HCDs are at risk of exposure and infection (8). Patients undergoing cardiopulmonary bypass for over two hours had higher odds of NTM infection (odds ratio: 16.5; 95% CI: 3.2–84) (8). In hospitals where at least one HCD-associated *M. chimaera* infection was identified, the risk of a patient getting an infection was approximately 0.1–1% (11,30,31). Of 115,664 surgical procedures in England involving repair or replacement of cardiac valves (between 2007 and 2014), the risk of NTM infections increased from less than 0.2/10,000 person-years before 2010 to 1.65/10,000 person-years in 2013 (29).

Implantation of prosthetic material (e.g., heart valve, vascular graft, left ventricular assist device) increased the risk of infection (3,11,13,29). Limited data suggest that heart transplants may also increase the risk of infection (3,32).

No case has occurred in operating room personnel exposed to aerosolization from HCDs.

Signs and symptoms of infection

Signs and/or symptoms of invasive *M. chimaera* infection following exposure to aerosols from an HCD may not occur for months or years after exposure, with a mean time between exposure and diagnosis of 1.6 years (range: 0.1–6.3 years) (3,10,14,23,32). The infection usually presents as prosthetic valve endocarditis, vascular graft infection or disseminated infection although a variety of extracardiac sites may also be infected (**Table 1**) (9-11,13,18,29,33). Clinical manifestations of infection are diverse and symptoms may be nonspecific (12,23). In some cases, extracardiac manifestations preceded cardiovascular disease (11). A description of a compatible syndrome for NTM infection published by the Canadian Public Health Laboratory Network (CPHLN) is shown in Table 1 (16).

Table 1: Clinical symptoms of patients with *Mycobacterium chimaera* infection

Type of symptoms	Clinical symptoms
Constitutional	Recurrent or prolonged fever, fatigue, shortness of breath, weight loss, night sweats
Cardiac	Prosthetic valve endocarditis and/or prosthetic vascular graft infection
Extracardiac	Bone infection, sternotomy surgical wound infection, mediastinitis, hepatitis, bloodstream infection, ocular infection (panuveitis, multifocal choroiditis, chorioretinitis)
Immunologic/ embolic	Splenomegaly, cytopenia
Infants	Febrile episodes and failure to thrive

Reproduced with permission from the Canadian Public Health Laboratory Network (16)

Disease burden

M. chimaera infection requires aggressive medical treatment with combination antimycobacterial therapy and sometimes repeat surgical intervention. The infection generally results in substantial morbidity with prolonged hospitalization, adverse effects of medical and surgical treatment, and/or treatment failure (3,11,18,29). In Europe, at least 52 cases have been reported as of January 2017 (12,18). Three cases have been identified in Australia, 24 in the US and two in Canada (20,23,32,34). Individual patient information was not always reported. From the data available, most cases were in older adults although patient age ranged from one to 81 years old, including two pediatric patients. Approximately 83% of the patients were male. Most studies reported a mortality rate over 40% (see **Table 2**) (3,11,12,29,32) and mortality was high when significant delays in diagnosis occurred and patients were severely ill when appropriate antimycobacterial treatment was implemented. It remains unclear whether increased awareness and earlier diagnosis will reduce the mortality associated with *M. chimaera infection*.

Table 2: Reported mortality from *Mycobacterium chimaera* infection associated with heater–cooler devices

Reference (country / region)	Number of patients diagnosed	Number of deaths (mortality) %
Kohler et al., 2015 (Europe) (11)	10[1]	4 (40%)[2]
Chand et al., 2016 (Europe) (29)	18[3]	9 (50%)
Appenheimer et al., 2016 (US) (32)	24	NR (46%)[4]
European Centre for Disease Prevention and Control, 2016 (Europe) (18)	52[5]	10 (<19%)[6]
Haller et al., 2016 (Germany) (9)	5	1 (20%)[7]
Tan et al., 2016 (US) (33)	3	2 (67%)[6,7]
Public Health England, 2017 (Europe) (12)	26	15 (58%)
Australian Commission on Safety and Quality in Health Care, 2017 (Australia) (20)	3	0 (0%)

Table 2 Abbreviations: NR, not reported; US, United States; %, percentage
[1] Nine cases were confirmed and one was probable
[2] An additional death was not linked to M. chimaera infection
[3] All cases were probable
[4] Number of deaths were not reported
[5] Some of these cases have been reported in other publications
[6] Cause of death not described or not all deaths attributed to the infection
[7] Percent mortality not reported in the study, was calculated for inclusion in this table

Risk mitigation measures

Key measures identified to facilitate case-finding and mitigate future exposure to *M. chimaera* are summarized in **Table 3**.

Table 3: Recommended measures to facilitate case-finding and mitigate future risk of *Mycobacterium chimaera* exposure

Risk mitigation measure	Additional context and/or limitation
Health care provider notification and education (11,12,28,32)	• Cases have been detected via provider notification. • Earliest implicated surgery was performed in 2007. • Maintain high clinical suspicion for *M. chimaera* or other NTM infection in patients (who underwent surgery involving CPB with use of HCDs from 2007 to implementation of risk mitigation measures).
Patient notification (8,12,28,32)	• To date, no cases have been identified via patient notification. • Testing is not recommended for asymptomatic exposed individuals. • Until effective risk mitigation measures are implemented, information regarding potential exposure should be provided to patients prior to surgery.
Enhanced prospective NTM surveillance (9,21)	• The ECDC has published a protocol for case detection.
Ensure traceability of HCDs in use (12)	• Individual units used in each surgery should be recorded in the event of a later infection.
Remove potentially contaminated HCDs from service (12,15,27)	• Where possible, all Stöckert 3T HCDs manufactured by LivaNova prior to September 2014 should be removed from service. • In some settings, risk of deferring surgery exceeds risk of surgery with use of proven or suspect contaminated HCD.
Replace contaminated HCDs, plus accessories, tubing and connectors, to prevent recontamination (13,15,27,35)	• LivaNova implemented a program to, in some circumstances, provide users with a loaner device to continue surgical procedures while their devices are undergoing deep disinfection. International demands for replacement of HCDs may result in a backlog in supply.
Use manufacturer's operation protocol including updated cleaning and disinfection procedures (3,9,12,15,27,28,35)	• Maintain log of cleaning and disinfection of HCDs. • Regularly check manufacturer's website for relevant updates. • Current decontamination protocols are yet to be validated. Studies have challenged the effectiveness of these protocols, suggesting a systematic decontamination failure. Biofilm removal is essential for effective decontamination of HCDs.
Routine microbiological testing of HCDs in use (12,15,17,25,27,36)	• This is not widely adopted because of the high rate of false negative results and the lack of standardized and validated methods for sample collection, processing and detection of *M. chimaera*. • The Canadian Public Health Laboratory Network and the US FDA advise against obtaining routine environmental cultures from HCDs for *M. chimaera*.
Apply engineering solutions to enable reliable separation of HCD exhaust air from operating room air (4,5,12,13,15,18,25,26,37)	Options include: • Place the HCD outside the operating room with tubing connected through an opening

Table 3: Recommended measures to facilitate case-finding and mitigate future risk of *Mycobacterium chimaera* exposure (continued)

Risk mitigation measure	Additional context and/or limitation
Apply engineering solutions to enable reliable separation of HCD exhaust air from operating room air (4,5,12,13,15,18,25,26,37) (Continued)	in the wall (ensuring operating room positive air pressure is maintained). Although this is the most reliable solution, the unintended consequences of this solution (e.g., possibly altered airflow in operating rooms and a longer distance between the HCD and surgical field) are unknown. • Encase the HCD in custom-made housing with separate ventilation (e.g., connected to the operating room exhaust conduit). Attachments to the HCD may need to be approved by the manufacturer. The unintended consequences of this solution (e.g., effects of custom-made housing on how well the device functions) are unknown. • If unable to reliably separate HCD exhaust air from operating room air, move the HCD as far as possible (preferably more than five metres) from the surgical field with the vent exhaust directed away from both the patient and the exposed instruments, and if possible, place the HCD close to the room air exhaust. Smoke dispersal experiments demonstrated that exhaust air from HCDs was propelled to merge with ultraclean airflow near the ceiling of the operating room. As a result, it is unclear whether this approach is useful in separating HCD exhaust air from operating room air (4).

Abbreviations: CPB, cardiopulmonary bypass; ECDC, European Centre for Disease Prevention and Control; HCD, heater–cooler device; NTM, nontuberculous mycobacteria; US FDA, United States Food and Drug Administration

Challenges and gaps

Table 4 summarizes the challenges and gaps in evidence informing the clinical management of *M. chimaera* infection.

Table 4: Challenges and gaps in evidence informing the management of *Mycobacterium chimaera* infection

Challenge / gap	Additional context
The magnitude of the risk of *M. chimaera* infection and the extent of the outbreak is unknown (12,14,29)	• High prevalence of *M. chimaera* in HCDs has been reported (up to 80% in Denmark). • The risk of patient infection currently appears to be low; however, if infection occurs, the impact on the patient could be severe. • The risk of infection and clinical presentation among the pediatric patient population is unknown.
Delay in symptom onset and diagnosis of infection (3,10,14,23,32)	• Documented time from exposure to diagnosis was between 0.1–6.3 years (mean of 1.6 years). • Few laboratories are equipped to culture and identify *M. chimaera*, which could contribute to delay in diagnosis. • Slow growth of *M. chimaera* culture contributes to delayed diagnosis. • Early collection of dedicated mycobacterial culture can result in diagnosis within a shorter timeframe than is commonly reported.
Effectiveness and adverse effects of therapy (3,11,29,32)	• *M. chimaera* infection can be very difficult to treat due to the microorganism's intrinsic resistance to many antimicrobial agents; its propensity for biofilm formation on implanted devices; and deep-seated infection sites that are challenging for antimicrobial penetration (e.g., endocarditis, graft infection and bone). • Therapy is prolonged and requires a combination of antimicrobial agents. • Disseminated infection has often required repeat surgical interventions with high mortality rates reported.

Table 4: Challenges and gaps in evidence informing the management of *Mycobacterium chimaera* infection (continued)

Challenge / gap	Additional context
Development of new HCD designs is pending (5,15)	• Construction of custom-built containers with HEPA filters to house HCDs that cannot be placed outside the operating room is underway, but their effectiveness is currently unknown. • HCD manufacturers are modifying HCD designs to limit aerosolization and prevent transmission.
Extent of HCD-associated infections caused by other microorganisms such as Legionella species is unknown (12,29)	• National surveillance in the UK (2007–2016) did not identify any cases of Legionnaire's disease in health care workers with potential occupational exposure to HCDs. • Postoperative cardiac surgery endocarditis due to Legionella species has not been reported during this outbreak.

Abbreviations: HCD, heater–cooler device; HEPA, high-efficiency particulate air; UK, United Kingdom

Discussion

Findings from this overview indicate a low but increased risk of *M. chimaera* infection with use of common source–contaminated HCDs during CPB (29). Given the long latency period, additional cases are expected. The true magnitude of risk following exposure is uncertain; current estimates are based on very limited data. Nonetheless, the risk of delaying cardiac surgery is generally considered far greater than the risk posed by this infection, even when the infection risk has not been entirely mitigated (28).

Future patient exposure may be prevented by implementing risk mitigation measures, including the use of uncontaminated HCDs or replacement of contaminated HCDs as soon as possible. Case finding may be expedited by the development of polymerase chain reaction (PCR)-based assays for rapid and reliable detection of *M. chimaera* in clinical or environmental samples.

Improved HCD designs that facilitate reliable decontamination and prevent aerosols from reaching the operative field are urgently needed (5,11). These developments may require collaborative discussions between medical device manufacturers, engineers and infection prevention and control experts.

This overview is limited by insufficient data to estimate the true magnitude of risk of infection and absence of data on efficacy and feasibility of risk mitigation measures.

Conclusion

The epidemiological and microbiological characteristics of this outbreak provide evidence for transmission of *M. chimaera* from the exhaust air of contaminated Stöckert 3T HCDs to patients during CPB, resulting in endocarditis, surgical site infections and/or disseminated infections. The true magnitude of risk following exposure is uncertain; it is currently estimated based on very limited data.

Strategies that separate the HCD exhaust air from the operating room air during surgery may be the most effective risk mitigation measures. The feasibility of implementing currently recommended risk mitigation measures is yet to be determined and studies are needed to determine if there are any unintended

consequences from implementation of these measures. Development of HCDs with new designs that are airtight and/or not susceptible to biofilm formation may help address this problem.

Authors' statement

TO – project administration, conceptualization, methodology, research, data abstracting and writing (original draft, review and editing); GT, LJ, MM – clinical expertise, intellectual content, review, editing and writing; KA - clinical expertise, intellectual content, review and editing; AC, K Defalco – review of abstracted data, research, review and editing; K Dunn – conceptualization, supervision, review and editing; JJ, SS, JE, BH, JS – clinical expertise, intellectual content, review and editing.

Conflict of interest

None.

Contributors

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Gwen Cerkowniak, Saskatoon Health Region, Saskatoon, SK

Maureen Cividino, Public Health Ontario, Toronto, ON

Della Gregoraschuk, Alberta Health Services, Edmonton, AB

Patsy Rawding, Nova Scotia Health Authority, Wolfville, NS

Sandra Savery, Centre de santé et services sociaux des Sommets, Sainte-Agathe-des-Monts, QC

Heidi Pitfield, Simcoe Muskoka District Health Unit, Barrie, ON

Patrice Savard, Centre hospitalier de l'Université de Montréal, Montréal, QC

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Evaluation of latent tuberculosis infection surveillance in Peel region, Ontario, 2010–2014

JA Majerovich[1,2], L Fernandes[2], M Varia[2]*

Abstract

Background: In Canada, identification and treatment of individuals with latent tuberculosis infection (LTBI) is a key component in preventing the progression of LTBI to active tuberculosis (TB). In Peel region, a large municipality in Ontario where half of the population is foreign-born, LTBI surveillance data are also critical to understanding the local epidemiology of TB.

Objective: To evaluate LTBI surveillance data collected through the integrated Public Health Information System (iPHIS) from 2010 to 2014 by assessing data quality and usefulness and to provide recommendations to improve surveillance for Peel region.

Methods: Using the European Centre for Disease Prevention and Control framework for surveillance evaluation, data quality was assessed based on completeness and validity of key variables in the iPHIS database. Usefulness of surveillance data in informing program decisions was assessed through interviews with stakeholders from Peel Public Health.

Results: Of 6,576 iPHIS records evaluated, data for gender and date of birth were greater than 99% complete, while more than half of the risk factor fields were blank or 'unknown'. A comparison of 192 paper charts to the corresponding iPHIS record identified coding errors in over 40% of iPHIS risk factor fields. Treatment completion documented in iPHIS (20%) was lower than data obtained from a follow-up telephone survey of cases (50%). Stakeholders found surveillance data to be useful (100%), however, recommendations were made for improvement of data collection and analysis.

Conclusion: Evaluating LTBI surveillance to improve data quality and usefulness for program planning is essential in an era of TB elimination. This evaluation resulted in standardization of data entry processes and continuation of direct follow-up with LTBI clients to confirm treatment completion. Work to understand barriers to treatment initiation and completion is currently underway.

Affiliations

[1] Field Service Training and Response Division, Public Health Agency of Canada, Ottawa, ON

[2] Peel Public Health, Mississauga, ON

***Correspondence:** monali.varia@peelregion.ca

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Introduction

Infection with *Mycobacterium tuberculosis* can result in latent tuberculosis infection (LTBI) or active tuberculosis (TB) (1). The progression of LTBI to active TB can be reduced by up to 90% with nine months of preventive treatment (1,2). The World Health Organization has identified that better identification and treatment of those with LTBI who are at higher risk of progressing to active TB is integral to the new TB elimination goals (3). Although Canada has a low incidence of TB overall, rates are higher among sub-populations such as immigrants from countries with high incidence of TB, travellers to these countries and Indigenous Canadians. The Region of Peel is a large municipality in Ontario with a population of 1.4 million. Half (50.5%) of Peel's population is foreign-born, many from TB-endemic countries. This is higher than the percentage of foreign-born individuals in Ontario (28.5%) (4). In 2014, the age-standardized active TB incidence rate in Peel was 9.1 per 100,000, compared to 4.0 per 100,000 for Ontario (5).

Approximately 1,200 LTBI cases are reported each year to the local health department, Peel Public Health (PPH) (6).

Identification and treatment of individuals with LTBI at increased risk of progressing to active TB is a pillar of the strategy to prevent the progression of LTBI to active TB. *Canadian Tuberculosis Standards* target at least 80% of those LTBI cases that start treatment will complete the required number of doses (1). Peel LTBI surveillance data are used to monitor treatment completion, identify population groups at higher risk of active disease and evaluate the effectiveness of program interventions.

Despite the importance of surveillance to evaluate the effectiveness of TB prevention and control efforts, there is limited published evidence evaluating LTBI surveillance (7-9). The objectives of this study were to evaluate LTBI surveillance data collected through Ontario's integrated Public Health Information System (iPHIS) by assessing two surveillance attributes—data

quality (data completeness and validity) and usefulness, and provide recommendations to improve LTBI surveillance in Peel region.

In Ontario, iPHIS is the database used by all public health departments to report information on cases of reportable diseases (including LTBI) to the Ministry of Health and Long-Term Care, as mandated under Ontario's *Health Protection and Promotion Act*, R.S.O. 1990 (10,11). Data on LTBI cases are passively reported to PPH by local reporting sources such as community clinicians and hospitals. When a case of LTBI is reported to PPH, public health nurses document case information in a paper-based client chart, which is then entered into iPHIS. Surveillance data are routinely analyzed by PPH epidemiologists for programming implications.

Methods

The evaluation of the LTBI surveillance system was based on the European Centre for Disease Prevention and Control (ECDC) framework (12). This framework was chosen because of its focus on data quality, which was a primary objective of the surveillance evaluation. The surveillance attributes that were assessed are summarized in **Table 1**. Internal completeness, and internal and external validity were selected because program decisions are based on the information available in iPHIS. Usefulness was chosen to identify surveillance strengths and opportunities for improving the use of data for public health action.

Table 1: Latent tuberculosis infection evaluation surveillance attributes

Attribute	Definition
Internal completeness	Proportion of complete data fields within the database
Internal validity	Extent of errors within the surveillance system, e.g. coding errors in translating from one level of the system to the next
External validity	Whether information recorded about cases is correct when compared to an external database or 'gold standard'
Usefulness	Whether surveillance results are used for public health action

Internal completeness: Internal completeness was measured by calculating the proportion of missing (i.e., blank and 'unknown') responses for selected variables. These include: client demographics (date of birth, gender, origin), risk factors (behavioural social factors, exposure settings, medical risk factors) and treatment variables (treatment start date and treatment end date as specified by the client or their physician). Relevant data fields from all Peel LTBI cases reported from 2010 to 2014 were extracted from the iPHIS database using Cognos ReportNet and analyzed using Stata 14.

Internal validity: Using PPH's paper-based charts for LTBI cases as the standard, internal validity was assessed by comparing data in iPHIS with the paper chart for selected variables. Due to the large number of LTBI cases, a sample size of 203 LTBI cases from 2014 was calculated based on a 95% confidence level, a population size of 1,157, a hypothesized 20% frequency of the outcome factor in the population and a design effect of 1.0 for a random sample (www.openepi.com/SampleSize/SSPropor.htm). Every fifth chart from 2014 was sampled and 192 charts were assessed because some of the charts could not be immediately located.

External validity: External validity was assessed by comparing LTBI treatment completion data from 2010 to 2014 in iPHIS to treatment completion data obtained from active telephone follow-up of LTBI cases. The telephone survey of LTBI cases was conducted by PPH staff from July 2015 to April 2016 with cases known to have started treatment. Given the length of treatment for LTBI is typically nine months for the first-line regimen (1), the 208 clients contacted were likely diagnosed with LTBI in 2014 and 2015.

Usefulness: Eight semi-structured interviews were conducted in person with internal stakeholders from PPH to assess the usefulness of LTBI surveillance for informing public health action. Stakeholders were chosen to represent a range of viewpoints, from frontline public health nurses who are directly involved in the system's operation to public health decision-makers, including the medical officer of health. Stakeholders were asked about actions taken as a result of surveillance data, surveillance challenges and opportunities. Responses were recorded in text format and data analysis was performed by three PPH epidemiologists (JAM, MV and the TB epidemiologist) who first assessed themes individually and then came to consensus regarding common themes using a facilitated small group method.

Results

Internal completeness: Of 6,576 LTBI cases, data for gender and date of birth were almost 100% complete (**Table 2**). Of LTBI cases who had missing or 'unknown' origin (n=1,716), 0.1% had birth province documented and 1.9% had immigration birth country documented. Completeness was suboptimal for the data fields for treatment end date (64.6% incomplete), treatment start date (52.3% incomplete) and risk factor (54.7% incomplete).

Table 2: Internal completeness of latent tuberculosis infection data fields

Variable	Total number of records	Number (%) of records with missing data field	Number (%) of records with 'unknown' data field	Number (%) of records with complete data
Date of birth	6,576	0 (0)	0 (0)	6,576 (100)
Gender	6,576	0 (0)	46 (0.7)	6,530 (99.3)
Origin	6,576	7 (0.1)	1,709 (26.0)	4,860 (73.9)
Risk factor	6,576	270 (4.1)	3,326 (50.6)	2,980 (45.3)
Treatment start date	6,576	3,436 (52.3)	0 (0)	3,140 (47.7)
Treatment end date[1]	3,140	2,030 (64.6)	0 (0)	1,110 (35.4)

Abbreviation: %, percentage
[1] Calculated using the total number of clients that started LTBI treatment as the denominator

Internal validity: Except for risk factor data, all variables assessed had high internal validity (>94%) (**Table 3**). Fifty-seven percent of responses for risk factor in iPHIS did not match the paper-based chart. Of those records that did not match on medical risk factor, 46.3% had 'unknown' medical risk factor entered in iPHIS, whereas in the chart, the client's physician had specifically documented that there were no medical risk factors. In addition, 10.9% of the charts reviewed had a medical risk factor documented in the paper chart that was not entered in iPHIS.

Table 3: Internal validity of latent tuberculosis infection data fields (N=192[1])

Variable	Number (%) of records with valid data
Gender	191 (99.5)
Date of birth	190 (99.0)
Treatment outcome status	190 (99.0)
Reason treatment ended	189 (98.4)
Immigration birth country	188 (97.9)
Treatment end date	185 (96.4)
Treatment start date	181 (94.3)
Risk factor	110 (57.3)

Abbreviation: %, percentage
[1] Total number of paper-based charts reviewed

External validity: Active follow-up by telephone with 208 LTBI cases that had no recorded treatment end date in iPHIS identified a treatment completion rate of 50%. This is compared to treatment completion documented in iPHIS which was approximately 20% from 2010 to 2013 (**Table 4**). In 2014, treatment completion for LTBI in iPHIS was 28%, however, this includes clients that were part of the telephone survey where the treatment end date was subsequently entered into iPHIS. No new intervention was instituted that could account for the increase.

Table 4: External validity of latent tuberculosis infection treatment completion rates

Year	Total number of cases that started treatment	Number (%) of cases with treatment completion in iPHIS
2010	723	141 (19.5)
2011	698	149 (21.3)
2012	589	118 (20.0)
2013	602	115 (19.1)
2014	528	149 (28.2)

Abbreviations: %, percentage; iPHIS, integrated Public Health Information System

Usefulness: The response rate for the key stakeholder interviews was 100%. Overall, surveillance data were found to be useful for program planning and implementation (100%). However, three themes emerged with some recommendations to improve usefulness of LTBI surveillance data:

1. Passive surveillance which relies on clinicians to submit completed forms is a barrier to completeness of information on risk factors and treatment completion. One interviewee stated that "data is as good (complete) as what we get from doctors…we see data gaps in risk factors and treatment completion". Electronic medical record alerts were suggested as one strategy to improve reporting among community clinicians. Another respondent elaborated on the consequences of incomplete data in terms of the ability to develop effective interventions for prevention and control. "(There are) gaps in physician reporting requirements and completion of the surveillance forms…we don't know who to target and monitor more closely."
2. Surveillance data are used by PPH staff for public health action. One interviewee stated, "A surveillance report showed high rates of active TB and a low rate of reported LTBI in one municipality of Peel…so the TB nurses did physician outreach on who to screen to improve LTBI diagnosis" (in an effort to detect and treat LTBI cases to prevent progression to active TB).
3. Usefulness of LTBI surveillance data for program action can be refined with improved data analysis and collection of data specific to the local context. One interviewee asked, "How effective are our data in telling the LTBI story in Peel? Do Peel's active TB cases arise from known LTBI cases (where there was an opportunity to intervene)?" Another respondent stated that current policies for screening immigrants are resource intensive for "not a lot of transmission risk (in Peel); we need to tailor TB interventions to the local context."

Discussion

The evaluation of LTBI surveillance in Peel identified high data completeness (>99%) for demographic variables, high data validity (>99%) for most fields in iPHIS and LTBI treatment completion that is higher than what was documented in iPHIS. However, less than half of risk factor data in iPHIS is complete and just over half is valid, highlighting some of the limitations of the iPHIS system and the need to modify data entry and case management processes. Nonetheless, LTBI surveillance in Peel has proved useful for informing public health action, such as physician outreach interventions.

Several opportunities were identified to improve data quality. With 54.7% of LTBI risk factor data missing or 'unknown', next steps include standardizing processes for data entry. Because there is no field to capture 'no medical risk factors', this information was recorded in iPHIS as 'unknown' explaining in part the reason for this discordance. However, 10.9% of LTBI cases also had a documented medical risk factor in the paper chart that was not entered in iPHIS. The accuracy of risk factor data in iPHIS is particularly relevant from a cost-benefit perspective as resources could be mobilized to follow-up LTBI cases that are at increased risk of progressing to active TB (e.g. because of a medical risk factor). Valid and complete risk factor data are required to identify population groups at increased risk and in need of targeted measures.

The high percentage (64.6%) of missing or 'unknown' treatment end date data is being addressed. The current passive physician reporting system contributes to the low percentage of recorded LTBI treatment completion. Active telephone follow-up of LTBI clients by public health staff better captures treatment

completion data; however, with over 1,200 LTBI cases reported to Peel annually, this may not be sustainable. In the longer term, technology solutions that facilitate clinician reporting of risk factors and treatment completion to public health are being explored. Engaging community clinicians in an external stakeholder consultation would also be worthwhile to determine how to best address the challenges they face in reporting LTBI data.

One strength of this evaluation is that it provides direction to improve the usefulness of surveillance data, such as specific analyses to better understand the Peel LTBI population. For example, internal stakeholders discussed the public health role for management of LTBI detected during TB screening of new immigrants to Canada. The emergence of this theme from the interview data led Peel to re-analyze TB data from 2015, which identified that 23% of foreign-born TB cases are diagnosed within one to five years of immigrating to Canada, compared to 40% diagnosed with active TB after living in Canada for more than 15 years (unpublished). While this may be due to several reasons (e.g. development of chronic conditions which increase the risk of reactivation, or travel back to country of birth resulting in re-exposure to TB), the greatest risk for TB among Peel cases may not be at the time individuals immigrate to Canada when public health currently intervenes. Additional analyses to examine the differences between LTBI clients that complete treatment and those who do not is also underway.

Two limitations influence the evaluation results. Ideally, the assessment of external validity requires that surveillance data would be measured against a 'gold standard'. The authors of this article did not have access to LTBI patient records kept by community clinicians, therefore a telephone survey of LTBI cases to determine whether treatment was completed was used as the 'gold standard' comparison. While PPH telephone follow-up with a sample of LTBI cases indicated that treatment completion was under-reported in iPHIS, the extent of under-reporting could not be quantified. However, there is also a risk that LTBI cases may not be aware that they did not complete the full nine months of treatment, so self-reporting on treatment completion may have been an overestimate. The second limitation was the inability to assess external completeness (or sensitivity), i.e., the extent to which Peel LTBI cases are captured by the current surveillance system. A study that evaluated LTBI surveillance in Massachusetts observed that substantial under-ascertainment of LTBI was likely and that mandatory reporting does not appear sufficient for LTBI detection (7). The authors suggest that enhanced targeted testing, active LTBI surveillance or laboratory-based surveillance may be needed to eliminate TB in the United States. These strategies may have applicability in Peel region as well.

LTBI surveillance data that are of high quality and useful for informing public health action are essential to TB prevention and control. Canadian TB standards target at least 80% treatment completion in LTBI cases that start treatment. In this evaluation telephone follow-up of Peel LTBI cases identified a treatment completion rate of 50%, but this rate remains below the national target. While PPH continues active surveillance to ascertain true LTBI treatment completion rates, work to understand barriers to treatment initiation and completion in Peel region is also underway. It is anticipated that this surveillance evaluation will have relevance for other jurisdictions in Canada and other developed countries, particularly with sub-populations that have higher rates of active TB. Evaluating and improving LTBI surveillance is fundamental to advancing TB elimination efforts in Canada.

Authors' statement

JAM – conceptualization, methodology, formal analysis, investigation, writing-original draft, review and editing
LF – conceptualization, writing-review and editing
MV – conceptualization, methodology, writing-review and editing, supervision

Conflict of interest

None.

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LINKS

Bacteremia in children following introduction of conjugated pneumococcal vaccines

Source: Greenhow TL, Hung YY, Herz A. Bacteremia in children three to 36 months old after introduction of conjugated pneumococcal vaccines. Pediatrics. 2017 Mar 10. pii:e20162098. doi:10.1542/peds. 2016-2098 (Epub ahead of print). Available from: https://www.ncbi.nlm.nih.gov/pubmed/28283611.

Background and objectives: In June 2010, Kaiser Permanente Northern California replaced all 7-valent pneumococcal conjugate vaccine (PCV7) vaccines with the 13-valent pneumococcal conjugate vaccine (PCV13). Our objectives were to compare the incidence of bacteremia in children three to 36 months old by three time periods: pre-PCV7, post-PCV7/pre-PCV13, and post-PCV13.

Methods: We designed a retrospective review of the electronic medical records of all blood cultures collected on children three to 36 months old at Kaiser Permanente Northern California from September 1, 1998 to August 31, 2014 in outpatient clinics, in emergency departments and in the first 24 hours of hospitalization.

Results: During the study period, 57,733 blood cultures were collected in the population of children three to 36 months old. Implementation of routine immunization with the pneumococcal conjugate vaccine resulted in a 95.3% reduction of *Streptococcus pneumoniae* bacteremia, decreasing from 74.5 to 10 to 3.5 per 100 000 children per year by the post-PCV13 period. As pneumococcal rates decreased, *Escherichia coli*, *Salmonella* spp. and *Staphylococcus aureus* caused 77% of bacteremia. Seventy-six percent of all bacteremia in the post-PCV13 period occurred with a source.

Conclusions: In the United States, routine immunizations have made bacteremia in the previously healthy toddler a rare event. As the incidence of pneumococcal bacteremia has decreased, *E coli*, *Salmonella* spp. and *S aureus* have increased in relative importance. New guidelines are needed to approach the previously healthy febrile toddler in the outpatient setting.

Risk assessment for *Mycobacterium chimaera*

Source: Government of Canada. Summary assessment of public health risk associated with Mycobacterium chimaera infections in patients exposed to heater-cooler devices in Canada**.** Public Health Agency of Canada. April 28 2017. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/risk-assessment-non-tuberculous-mycobacteria-contamination-heater-cooler.html.

The public health risk of infections with *Mycobacterium chimaera* (*M. chimaera),* one type of non-tuberculous mycobacterium (NTM), in Canadian patients exposed to heater-cooler devices (HCD) used during cardiopulmonary bypass is currently not defined, but believed to be low to medium. The number of confirmed cases internationally is small compared to the number of patients exposed to heater-cooler devices while undergoing cardiopulmonary bypass surgery. However, given the long latency period, additional cases should be expected. To date, only the Stöckert 3T heater-cooler devices manufactured by LivaNova PLC (formerly Sorin Group Deutschland GmbH) before September 2014 have been associated with *M. chimaera* infections.

While the magnitude of risk of exposure to *M. chimaera* is uncertain, the risk of delaying cardiac surgery is generally considered far greater than the risk posed by this infection, even when the infection risk has not been entirely mitigated. Transmission of NTM, such as *M. chimaera*, between persons is extremely rare and public health case management is not required. This assessment is based on limited available evidence and is subject to review and change as new information becomes available.

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