

Inside this issue: Emerging and re-emerging infections

Be assured that the risk of MERS-CoV is low in Canada and preparedness plans are in place. In this issue, read about the ever-changing influenza virus and how it evolved during the 2012-2013 flu season as well as a systematic review and that reveals tetanus can still (though rarely) happen post-tetanus vaccine. We also provide commentaries on a new vaccine initiative and some well-deserved accolades for the group that has been providing Canadian clinical and public health care providers vaccine recommendations for 50 years: the National Advisory Committee on Immunization (NACI).

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Useful links

National Collaborating Centre for Infectious Disease (NCCID): [Effectiveness of School Closure for the Control of Influenza A Review of Recent Evidence](#)

National Collaborating Centre for Infectious Disease (NCCID): [Influenza and influenza-like illness](#)

MERS-CoV– Low risk to Canadians

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Abstract

Middle East respiratory syndrome – Coronavirus (MERS-CoV) -- is a novel coronavirus that has caused a number of community-acquired cases and health care associated outbreaks in Saudi Arabia and the United Arab Emirates (UAE) as well as sporadic cases in other countries, especially in the Middle East. The evidence to date links MERS-CoV cases with exposure to camels, including camel products or to probable or confirmed human cases of MERS-CoV. It typically presents as an acute respiratory illness and is associated with a 35% mortality rate. Based on available information at this time, the current risk to Canadians for acquiring MERS-CoV infections is considered low. However, the International Health Regulations Committee concerning MERS-CoV has cautioned that the upsurge of cases seen this past spring (2014) may be predictive of an increase in cases related to the Hajj – an annual pilgrimage to Mecca in Saudi Arabia that took place in early October 2014. Although the overall risk is low, the Public Health Agency of Canada and its National Microbiology Laboratory (NML) in close collaboration with provincial and territorial partners, the Canadian Public Health Laboratory Network (CPHLN) and infection prevention and control experts have developed a number of preparedness guidance documents and protocols to address the risk of an imported case of MERS-CoV in Canada.

Introduction

The novel coronavirus was first identified in April 2012 and later became known as Middle East respiratory syndrome – Coronavirus (MERS-CoV) when it first appeared in the Arabian Peninsula. The virus continues to circulate widely in this geographic region. Although the source is not fully understood, there appears to be a close link with the virus found in camels and the persons affected. Coronaviruses are a large family of viruses that can cause a range of infectious diseases from a mild cold to Severe Acute Respiratory Syndrome (SARS) (1) which was responsible for the serious 2003 outbreak in Toronto, Ontario and a number of other countries. MERS-CoV is genetically distinct from the SARS virus and unlike SARS, MERS-CoV does not appear to transmit easily from person to person (2, 3).

The main symptoms of MERS-CoV include breathing difficulties, fever, cough, muscle aches, chest pain, vomiting and diarrhea. In severe cases, illness can progress to multi-system organ failure leading to death (1,4). There have been reports (mostly of secondary cases) that have tested positive for the virus in the absence of clinical symptoms (1). Currently, there is no specific antiviral treatment or vaccine available for MERS-CoV. Treatment is supportive and primarily focused on vital organ functions (1). Approximately one-third of cases result in death (5).

As the outbreak has unfolded, it has become clear that Health Care Workers (HCWs) in the affected countries are particularly at risk from MERS-CoV when sub-optimal infection prevention and control measures exist (1).

Ongoing monitoring of MERS-CoV continues to be a public health priority, both in Canada and internationally, as concerns persist that over time, MERS-CoV may become capable of sustained human-to-human transmission.

Last year was the tenth anniversary of the SARS event and most Canadians are still very much aware of the impact it had on Canada. With MERS-CoV now well into its second year, Canadians continue to need and seek information about its level of risk. Since the spring of 2013, the Public Health Agency of Canada (the Agency) has been meeting this need for information by conducting regular risk assessments on MERS-CoV and posting both detailed and summary level data that includes evolving epidemiological information and any new scientific findings.

The purpose of this risk assessment summary is to describe the methodology, the assessment of the risk, the risk mitigation and leading to the current risk-level of MERS-CoV to Canadians residing in the country.

Methodology

The information included in this risk assessment summary is based on currently available evidence on MERS-CoV as of date of publication and applies to persons living in Canada only. Evidence or best information available considered in this risk assessment has been derived from published literature, Agency developed information and a number of international public health organizations, including:

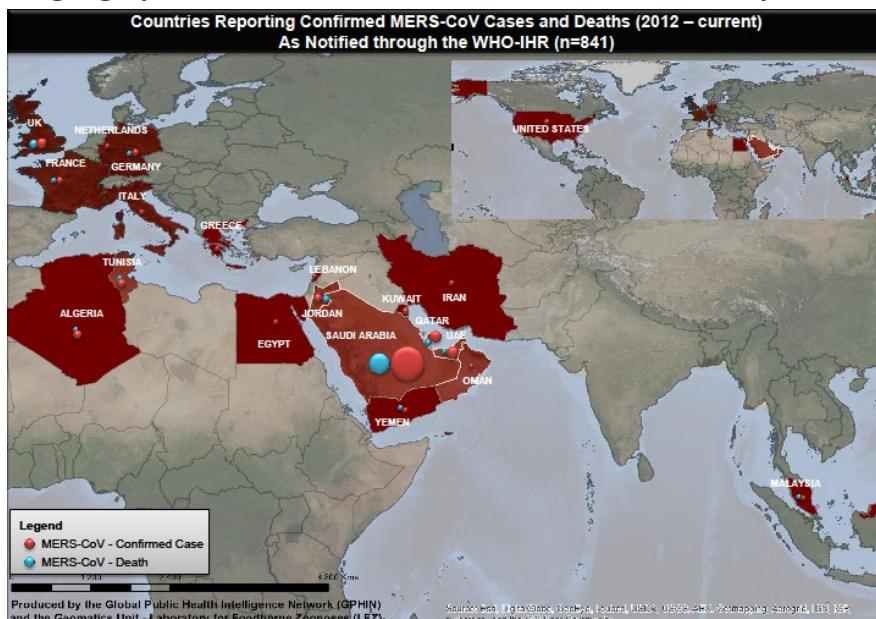
- The World Health Organization's (WHO) risk assessment, summary updates and interim recommendations for at-risk groups (6).
- International Health Regulation (IHR) notifications of confirmed cases and deaths from reporting countries.
- European Centre for Disease Prevention and Control (ECDC) risk assessments (7).
- The biosafety advisories (8) and interim guidance for the infection prevention and control of MERS-CoV in acute-care settings (9) from the Public Health Agency of Canada.

Summary of the risk event

Event summary

Cases of MERS-CoV have been detected primarily in the Middle East, specifically in the Kingdom of Saudi Arabia (KSA) and also in Jordan, Qatar, the UAE, Kuwait, Yemen, Oman, Lebanon and Iran. Travel-related cases have also been reported by eleven countries: Europe (the United Kingdom, France, Italy, Greece, Germany and the Netherlands), North Africa (Tunisia, Egypt and Algeria), Southeast Asia (Malaysia) and North America (the United States of America) (5). Limited secondary transmission has been reported in only two of the previously mentioned countries (10). There have been no cases identified in Canada (**Figure 1**).

Figure 1: Worldwide geographical distribution of MERS-CoV cases, as of September 23, 2014



Source: Public Health Agency of Canada

As of September 23, 2014, the WHO has reported 846 confirmed human cases, including 298 deaths (**Table 1**). In 2013 and 2014, increased numbers of cases and deaths have been reported in the spring months. However, in April and May 2014, a sharp upsurge in cases was reported from KSA accounting for 48% of all cases and 38% of all deaths reported to date (5). A total of 113 retrospective cases between May 2013 to May 2014 were reported in late June 2014 and partly account for the surge in cases reported in the spring of 2014 (11).

Table 1: Confirmed cases of MERS-CoV by country reporting as September 23, 2014*

Country reporting	cases	deaths
Algeria	2	1
Egypt	1	0
France	2	1
Germany	2	1
Greece	1	1
Iran	5	2
Italy	1	0
Jordan	11	6
Kuwait	3	1
Lebanon	1	0
Malaysia	1	1
Netherlands	2	0
Oman	2	2
Qatar	7	4
Saudi Arabia	726	264
Tunisia	3	1
United Arab Emirates	69	9
United Kingdom	4	3
United States of America	2	0
Yemen	1	1
Total	846	298

*Source: Personal communication - WHO IHR Regional Contact Point, Pan American Health Organization, and Canada-IHR National Focal Point September 2014.

Based on available case-level data from the WHO (5), the majority of cases have been adult males (median age in the mid- to late-40s) with comorbidities and who exhibit a tendency to experience more severe illness and poorer outcomes than those without. Individuals with diabetes, renal failure and chronic lung disease as well as immunocompromised persons are at higher risk of severe disease from MERS-CoV infection. Secondary cases generally present with milder disease or no symptoms; however severe illness, including death, has been observed in secondary cases including healthcare workers (HCWs). The case fatality proportion is 35%.

Evidence from camel serology studies and genetic sequencing of the virus suggests that camels are likely a primary source for MERS-CoV infections in humans. Other animal studies have not detected MERS-CoV antibodies, including those involving sheep, cows, goats, water buffalo, swine and wild birds (12). Persons having had contact with camels or camel products (e.g. raw milk or meat, secretions or excretions (including urine)) are at increased risk of infection with MERS-CoV. Transmission patterns of secondary cases in healthcare settings and households have also been shown to be at increased risk of infection (5). On June 13, 2014 the WHO reported evidence supporting the role of camels as a primary reservoir responsible for the ongoing introduction of

the virus to the human population that does not result in sustained transmission (12). Only a few instances of transmission within households have been reported and no large family clusters have been identified (5).

According to Breben et al (2013), the virus' reproductive number (R_0) was found to be less than one ($R_0 = 0.60$) and was also inferior to the reproductive number of SARS ($R_0 = 0.80$) (13). However, the authors cautioned that MERS-CoV's R_0 may increase with population density and may also be affected by community age and contact structure. Cauchemez et al (2013) obtained similar R_0 estimates for MERS-CoV epidemic potential, but found that R_0 values increased when infection control measures were not in place (14). In addition, transmissibility may increase in populations with comorbidities and R_0 's may be underestimated if cases received an intervention soon after onset. The authors concluded that while MERS-CoV is a slowly growing epidemic, intensive public health measures around cases paired with improved diagnostic techniques would be sufficient to contain the spread of the disease and mitigate morbidity and mortality.

Assessment of risk

Based on the best available information, the current risk to Canadians for acquiring MERS-CoV infections is considered low. This assessment is based on the following observations and facts:

- No sustained human-to-human transmission has been observed. The primary route of transmission is still believed to be direct or indirect contact with camels or camel products. Intensive screening of MERS-CoV contacts revealed very few instances of household transmission and there has been no increase in the size or number of observed household clusters. The recent increase in cases reported during summer 2014 were primarily due to breaches in, or lack of, appropriate infection prevention and control measures in health facilities in Saudi Arabia and the UAE.
- There has been no change in the clinical presentation of MERS-CoV.
- There has been no indication that international spread has occurred and recently exported cases have not resulted in sustained onward transmission. The last exported case to a country outside the Middle East was in late May 2014 to Algeria. This did not result in any symptomatic or asymptomatic secondary spread (15).
- The pandemic potential of MERS-CoV has not been reached and is expected to remain low with infection Prevention and Control measures in place.
- The Agency, in collaboration with IPC experts, has developed evidence-based IPC guidelines for use in Canadian healthcare settings.
- Canada has strong public health surveillance and health care infrastructure in addition to established communication protocols.
- The IHR Emergency Committee concerning MERS-CoV at its sixth meeting on June 16, 2014 achieved consensus that the conditions for a public health emergency of international concern (PHEIC) had not yet been met (16). The next Committee is scheduled for September 25, 2014.

Risk mitigation

In the event of an importation of MERS-CoV to Canada, the Agency and the National Microbiology Laboratory (NML) in close collaboration with provincial and territorial partners (PT), the Canadian Public Health Laboratory Network (CPHLN) and infection prevention and control experts have developed a number of preparedness guidance documents and protocols (**Table 2**). Since 2009, Canada and its PT partners have established robust surveillance and communications systems designed to detect and report emerging pathogens such as MERS-CoV utilizing the Severe Acute Respiratory Infection (SARI) surveillance system. In addition, the PHAC-CIHR

Influenza Research (PCIRN) Serious Outcome Surveillance (SOS) Network consisting of 45 participating adult hospitals across Canada is designed to detect SARI hospital ICU admissions.

Table 2: Relevant MERS-CoV documents from the Public Health Agency of Canada

Relevant MERS-CoV documents from the Agency	
1. <u>Summary of Assessment of Public Health Risk to Canada Associated with MERS-CoV</u> (10)	This risk assessment summary is updated frequently and provides the most current risk assessment for Canadians.
2. <u>Travel Health Notice for MERS-CoV</u> (17)	This document provides travellers with recommendations for travel to affected countries for MERS-CoV. Although there have not been any reports of a direct link between acquiring MERS-CoV infection from attendance at mass gathering events such as a Hajj and the performance of Umrah, travellers are still advised to take precautions when travelling to Saudi Arabia or other countries in the Middle East affected by MERS-CoV.
3. <u>Biosafety Advisory on MERS-CoV</u> (8)	The information provided in this advisory assists laboratories in implementing proper biosafety procedures when handling samples containing MERS-CoV.
4. <u>Interim guidance for the infection prevention and control of MERS-CoV in acute care settings</u> (9)	This document provides infection prevention and control (IPC) guidance to healthcare organizations and healthcare workers for the management of patients presenting to healthcare facilities in Canada with suspected or confirmed MERS-CoV infection.
5. <u>Interim National Surveillance Guidelines for Human infection with MERS-CoV</u> (18)	This document provides surveillance guidelines for the early detection and containment of MERS-CoV in Canada.

Discussion

Recent investigative findings on MERS-CoV support the theory that camels play a significant role in the ongoing transmission of the virus. However, there are several instances where an exposure to camels could not be found. Therefore, the human animal interface in this event requires further study to better understand risk factors and the underlying mechanisms associated with transmission and also to identify effective measures in the prevention of further zoonotic spread (1). Outbreak investigations will need to focus on contact tracing to identify mild or asymptomatic cases and to increase knowledge of potential risk of further transmission (5). This information is required to accurately determine the best use of public health resources should an importation occur in Canada.

Concerns continue around the possible transmission of MERS-CoV during mass-gathering events such as the Hajj and the performance of Umrah in Saudi Arabia. However, a seroprevalence study conducted in 2013 in adult pilgrims during that year's Hajj did not detect MERS-CoV in any of the 5,235 samples tested (19). Further, there have been no reported confirmed cases of MERS-CoV associated with the 2012 and 2013 Hajj pilgrimages. The upsurge of cases seen this past spring suggesting increased community circulation may be predictive of a proportionate increase in cases related to the upcoming Hajj event between October 1st and October 6th, 2014 (16).

Conclusions

The public health risk posed by MERS-CoV to Canada continues to be low based on available information at this time. The Agency, through ongoing event monitoring, conducts regular and timely risk assessments posed by MERS-CoV to Canadians and will provide this information in a timely manner.

Acknowledgements

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Conflict of interest

There are no conflicts of interest to declare.

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Influenza in Canada, 2012-2013 season

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Abstract

Objective: This report summarizes influenza activity in Canada during the 2012-13 influenza season (August 26, 2012-August 24, 2013) from data obtained through the FluWatch surveillance program.

Methods: FluWatch collected information from six primary indicators of influenza activity that describe the epidemiologic and virologic behaviour of influenza in Canada: sentinel laboratory-based influenza detections; strain characterization and antiviral resistance for circulating influenza viruses; primary care consultation rates of influenza-like illness; regional influenza activity levels; influenza-associated severe outcomes; and pharmacy surveillance.

Results: The influenza season peaked nationally between late December 2012 and early January 2013 with influenza A(H3N2) identified as the predominant circulating influenza strain until early March, when influenza B became the predominant circulating strain. The cumulative reported hospitalization rates for all age groups were 25.0 per 100,000. Influenza A most greatly affected adults ≥ 65 years of age and influenza B most greatly affected children ≤ 19 years of age.

Conclusion: The influenza season was moderately severe. When compared to the previous two seasons, which were considered relatively mild, there was a significant increase in laboratory detections for influenza, as well as hospitalizations associated with influenza in 2012-13.

Introduction

Influenza is a respiratory infection usually caused by influenza A or B viruses. In Canada, it generally occurs each year during the late fall and winter months. Influenza infection causes primary illness and can also lead to severe secondary medical complications, including viral pneumonia, secondary bacterial pneumonia and worsening of underlying medical conditions. It is estimated that in Canada, an average of 12,200 hospitalizations are related to influenza (1-3) and approximately 3,500 deaths are attributable to influenza annually (4).

National influenza surveillance is coordinated through the FluWatch program of the Centre for Immunization and Respiratory Infectious Diseases (CIRID) at the Public Health Agency of Canada. The primary objectives of this program are early detection and timely reporting of influenza activity in Canada and abroad as well as monitoring circulating strains of influenza virus such as antigenic characterization, identification of new subtypes and changes in antiviral resistance.

FluWatch collected data and information on influenza activity from a variety of sources and disseminated it weekly during the active influenza season (September to mid-May) and biweekly during the low season (mid-May to August). Information was available to health professionals and the public through e-mail and the FluWatch website www.phac-aspc.gc.ca/fluwatch/.

This report provides an epidemiologic and virologic summary of influenza activity in Canada during the 2012 - 2013 season.

Methods

This report is based on the six primary indicators of influenza activity reported by the FluWatch program on a weekly basis across Canada and between August 26, 2012 (week 35) and August 24, 2013 (week 34): (I) sentinel laboratory-based influenza and other respiratory virus detections; (II) strain characterization and antiviral resistance for circulating influenza viruses; (III) primary care consultation rates of influenza-like illness (ILI) by sentinel practitioners; (IV) regional influenza activity levels; (V) influenza-associated hospitalizations and deaths; and (VI) pharmacy surveillance.

These data sets come from ongoing public health surveillance and are exempt from research ethics board approval.

Surveillance dataset

(I) Sentinel laboratory-based influenza detections

Influenza detections were reported through the sentinel laboratory-based Respiratory Virus Detections Surveillance System (RVDSS) in aggregate and with case details. Participating laboratories reported the total number of tests performed for influenza and the total number of positive tests. Samples from the territories are tested by reference laboratories in nearby provinces and aggregated into provincial results. Samples with case-level data were attributable to a territory and reported independently from the province testing the sample.

(II) Strain characterization and antiviral resistance for circulating influenza viruses

The NML conducted national surveillance on human influenza virus strains in collaboration with provincial laboratories and other Canadian hospital- and university-based laboratories. A subset of weekly influenza detections across Canada were referred to the NML for further testing to provide strain characterization and evaluation of antigenic changes, as well as antiviral resistance in the circulating influenza virus strains.

(III) Primary care consultation rates of ILI by sentinel practitioners

CIRID recruited and managed the participation of sentinel physicians in seven provinces and three territories. In the remaining three provinces (British Columbia, Alberta and Saskatchewan), sentinel recruitment and reporting was managed by independent provincial programs. For one clinic day each week, sentinels reported the total number of patients seen for any reason (denominator) and the total number of patients meeting a standard national case definition for ILI (numerator).

(IV) Regional influenza activity levels and outbreaks

Provinces and territories were subdivided into surveillance regions. Provincial and territorial epidemiologists assessed the weekly influenza activity level in their respective jurisdictions based on laboratory reports of influenza detections, presence of ILI and reports of outbreaks of influenza or ILI. There were four standard categories of activity: no activity, sporadic activity, localized activity and widespread activity. Outbreaks in hospitals and long-term care facilities (LTCF) were reported weekly, where an outbreak was defined as two or more cases of ILI within a seven-day period and included at least one laboratory-confirmed case of influenza.

(V) Influenza-associated hospitalizations and deaths

Hospitalizations and deaths associated with laboratory-confirmed influenza virus infections were reported by participating provinces and territories and two hospital surveillance networks. In 2012 - 13, eight provinces and territories (AB, MB, SK, ON, PE, NL, NT, YK) reported influenza-associated hospitalizations and deaths in their jurisdictions. The Canadian Immunization Monitoring Program ACTive (IMPACT) is a network of paediatric tertiary

care hospitals with 12 centres in eight provinces representing approximately 90% of all tertiary care paediatric beds in the country. The PHAC-CIHR Influenza Research Network-Severe Outcomes Surveillance (PCIRN-SOS) network comprises of 40 adult hospitals in six provinces, representing more than 17,000 adult acute-care beds in Canada. Hospitalizations and deaths reported from IMPACT or PCIRN also may be included in provincial/territorial reporting.

(VI) Pharmacy surveillance – prescription sales

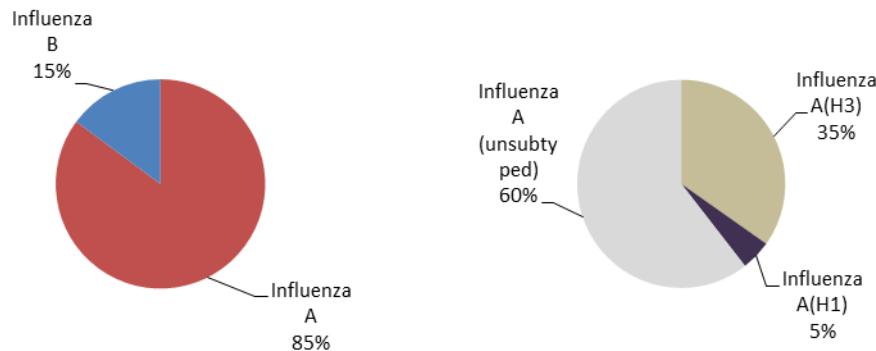
The pharmacy surveillance system is coordinated by the Centre for Foodborne, Environmental and Zoonotic Infectious Diseases (CFEZID) using data provided by participating pharmacies to RxCanada. In 2012 - 13, approximately 2,500 stores from 15 major pharmacy chains contributed over-the-counter and prescription data. Participating pharmacies were present in all provinces and territories except Nunavut and 85% of health regions in Canada. Data was collected on new and refill prescription medications purchased, which are categorized as “antiviral” (including oseltamivir, zanamivir and amantadine) and “other” (all other prescriptions).

Results

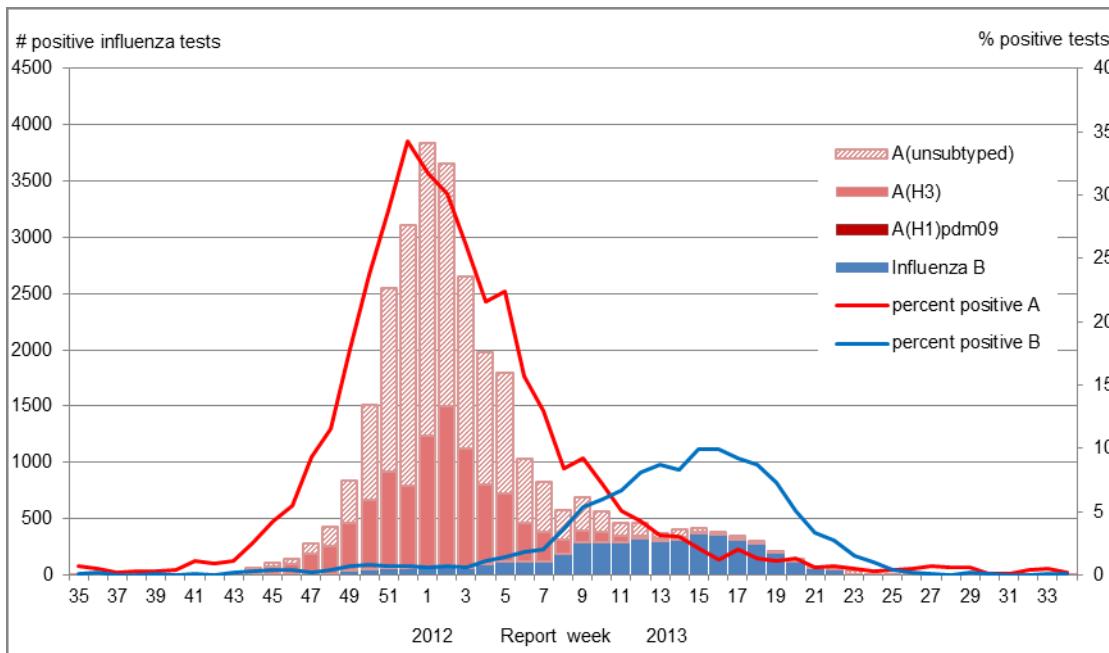
Sentinel laboratory-based influenza and other respiratory virus detections

During the 2012 - 13 season, sentinel laboratories tested 190,376 specimens for influenza and 31,737 (16.7%) were positive. Of the positive specimens, 27,020 (85.1%) were influenza A and 4,717 (14.9%) were influenza B. Among the seasonal influenza A viruses, 10,669 (39.5%) were subtyped and 9,395 (88.1%) were influenza A (H3N2) and 1,274 (11.9%) were influenza A (H1N1) (**Figure 1**).

Figure 1: Percentage of laboratory detections of influenza in Canada, by type and subtype, 2012-13



Based on laboratory reporting, the season peaked nationally between week 52 and week 1 (December 23, 2012 to January 5, 2013) with 35.0% of respiratory specimens testing positive for influenza. Influenza A(H3N2) was the predominant influenza strain during the 2012-13 season. Influenza A(H3N2) was predominant until between week 10 and 11 (March 3 to 16, 2013), when influenza B became the predominant circulating strain (**Figure 2**).

Figure 2: Sentinel laboratory detections of influenza in Canada, by week and type/subtype, 2012-13

The relative proportion of each type and subtype circulating and the time that influenza activity peaked varied by geographic region. The percentage of positive specimens was highest in week 52 for parts of western and central Canada (British Columbia, Alberta, Ontario, Quebec) and Newfoundland. The proportion of positive tests was highest in Saskatchewan in week 2, Manitoba in week 3 and in the remaining Atlantic provinces in week 5 for New Brunswick and week 6 for PEI and Nova Scotia. Influenza A was the predominant strain in all the provinces for the season, with the proportion of laboratory tests positive for Influenza A ranging from 72.2% in Saskatchewan to 99.2% in PEI. From case-based data, for which laboratory data for the territories can be identified, influenza activity appears to have peaked in Nunavut in week 5 (January 27–February 2, 2013) and in Northwest Territories in week 17 (April 21 - 27, 2013). No data is available for Yukon Territory.

Among the 26,546 cases for which information on age and type/subtype was received this season, adults ≥ 65 years of age comprised 41.1% of the influenza cases (Table 1). Approximately 45% of the influenza A cases occurred in adults ≥ 65 years of age and 45.9% of the influenza B cases occurred in children ≤ 19 years of age.

Table 1: Cumulative case-based laboratory detections in Canada, by age, type/subtype, August 26, 2012 to August 24, 2013

Age groups (years)	Cumulative (August 26, 2012 to August 24, 2013)						
	Influenza A				B	Influenza A and B	
	A Total	A(H1) pdm09	A(H3)	A (UnS)	Total	#	%
<5	3040	224	847	1969	853	3893	14.7%
5-19	1672	72	633	967	1081	2753	10.4%
20-44	3568	359	1236	1973	731	4299	16.2%
45-64	3766	331	1239	2196	703	4469	16.8%
65+	10068	138	3767	6163	842	10910	41.1%

Unknown	219	30	183	6	3	222	0.8%
Total	22333	1154	7905	13274	4213	26546	100.0%
Percentage²	84.1%	5.2%	35.4%	59.4%	15.9%		

Antigenic characterization and antiviral resistance

The NML antigenically characterized 1,514 influenza viruses during the 2012 - 13 influenza season. The 662 influenza A (H3N2) viruses were antigenically similar to the vaccine strain A/Victoria/361/2011 and the 250 A(H1N1)pdm09 viruses were antigenically similar to the vaccine strain A/California/07/09. Among the influenza B viruses, 464 were antigenically similar to the vaccine strain B/Wisconsin/01/2010 (Yamagata lineage) and 138 were similar to B/Brisbane/60/2008 (Victoria lineage; component of the 2011 - 2012 seasonal influenza vaccine).

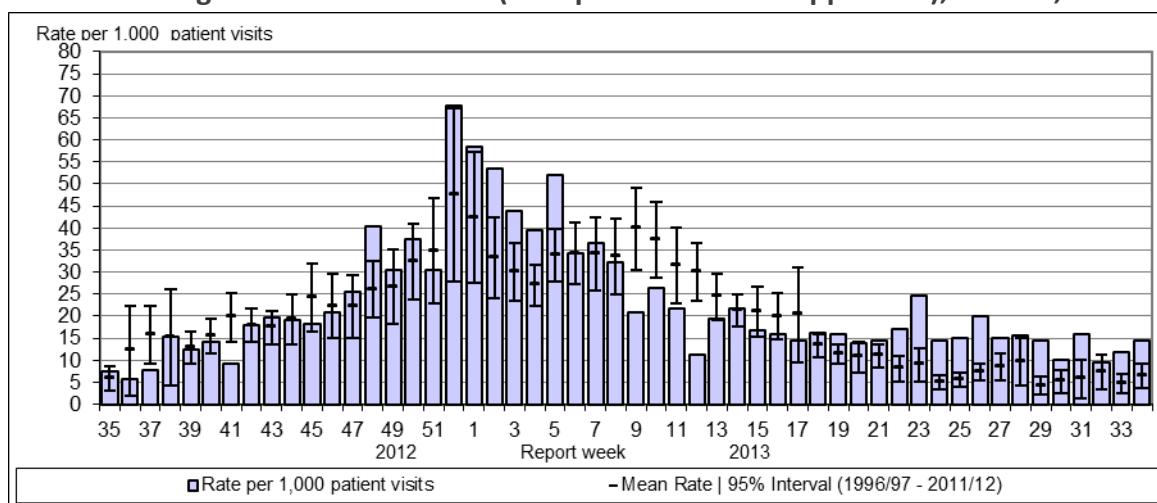
The NML tested 1,508 influenza viruses for resistance to oseltamivir, 1,505 viruses for resistance to zanamivir and 1,344 influenza A viruses for resistance to amantadine. Of 653 A (H3N2) viruses tested, 1 (0.2%) was resistant to oseltamivir and zanamivir. Of 254 A (H1N1) viruses tested, one(0.4%) were resistant to oseltamivir and all were susceptible to zanamivir. Of 601 B viruses tested, three (0.5%) were resistant to oseltamivir and zanamivir. All but one A (H3N2) virus was resistant to amantadine.

Primary care consultation rates of influenza-like illness (ILI)

Of the 450 sentinels submitting at least one ILI report during the season, 97% reported during the active influenza season (October to May / weeks 40 to 20), with 46% reporting for at least 15 of the 33 weeks during the active period.

The peak ILI consultation rate was 67.7 per 1,000 patient visits and occurred during the week ending December 29, 2012 (week 52), similar to the peak percentage of laboratory tests positive for influenza (**Figure 3**). The weekly ILI consultation rates exceeded the expected range, based on mean observations rates for the previous seasons since 1996 - 97 (excluding rates from the pandemic period), in week 48 and between weeks 52 (2012) and week 5 (2013). Weekly ILI consultations rates remained within or below the expected range for the rest of the season.

Figure 3: Influenza-like illness (ILI) consultation rates by report week, compared to the 1996-97 through to 2012-13 seasons (with pandemic data suppressed), Canada, 2012-2013



The highest ILI consultation rates were reported in children with an average of 44.3 visits for ILI per 1,000 patient visits in those 0 to 4 years of age and 46.2 per 1,000 patient visits in those 5 to 19 years of age during the active influenza period (week 40 - week 20) in the 2012 - 13 season.

Regional influenza activity levels and outbreaks

Provincial and territorial epidemiologists report the geographic distribution of influenza in their jurisdiction. The geographic distribution of influenza was most extensive during the week ending January 12, 2013 (week 2) with 14 regions reporting widespread activity and 26 regions reporting localized activity. The week ending June 15, 2013 (week 24) was the first week none of the regions reported widespread or localized influenza activity following the active influenza season. There were 53 hospital outbreaks and 676 LTCF outbreaks reported during the season, with the number of outbreaks peaking during the week ending January 12, 2013 (week 2).

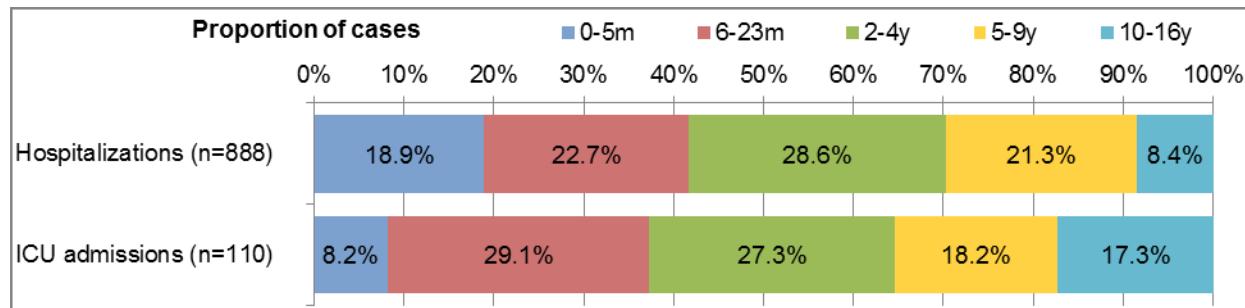
Influenza-associated severe outcomes (hospitalizations and deaths)

During the 2012 - 13 influenza season 5,110 influenza-associated hospitalizations were reported from eight provinces and territories. Cumulative reported rates (per 100,000 population) for hospitalizations by age groups were calculated based on the population of participating provinces and territories. The cumulative hospitalization rate for all age groups was 25.0 per 100,000. By age group, the hospitalization rates were 66.4 (0-4 years), 8.6 (5-19 years), 6.5 (20-44 years), 15.4 (45-64 years) and 94.1 (\geq 65 years). The cumulative death rate was 1.7 per 100,000.

In addition to provincial/territorial reports, Cases were also reported by two hospital surveillance networks. IMPACT reported 889 paediatric hospitalizations and PCIRN-SOS reported 1,812 adult hospitalizations. ICU admission was required for 13% of the paediatric hospitalizations and 12% of the adult hospitalizations (Figure 4). Influenza A was the predominant strain identified in hospitalized cases.

Figure 4. Percentage of hospitalizations, ICU admissions and deaths with influenza reported by age group, Canada, 2012-13

a) Paediatric hospitalizations (\leq 16 years of age, IMPACT)



b) Adult hospitalizations (\geq 16 year of age, PCIRN-SOS)



Of the 889 children hospitalized, 70% (n=624) were younger than five years of age and 47% (n=419) were healthy prior to infection. A total of 329 hospitalized children had underlying health conditions for which influenza

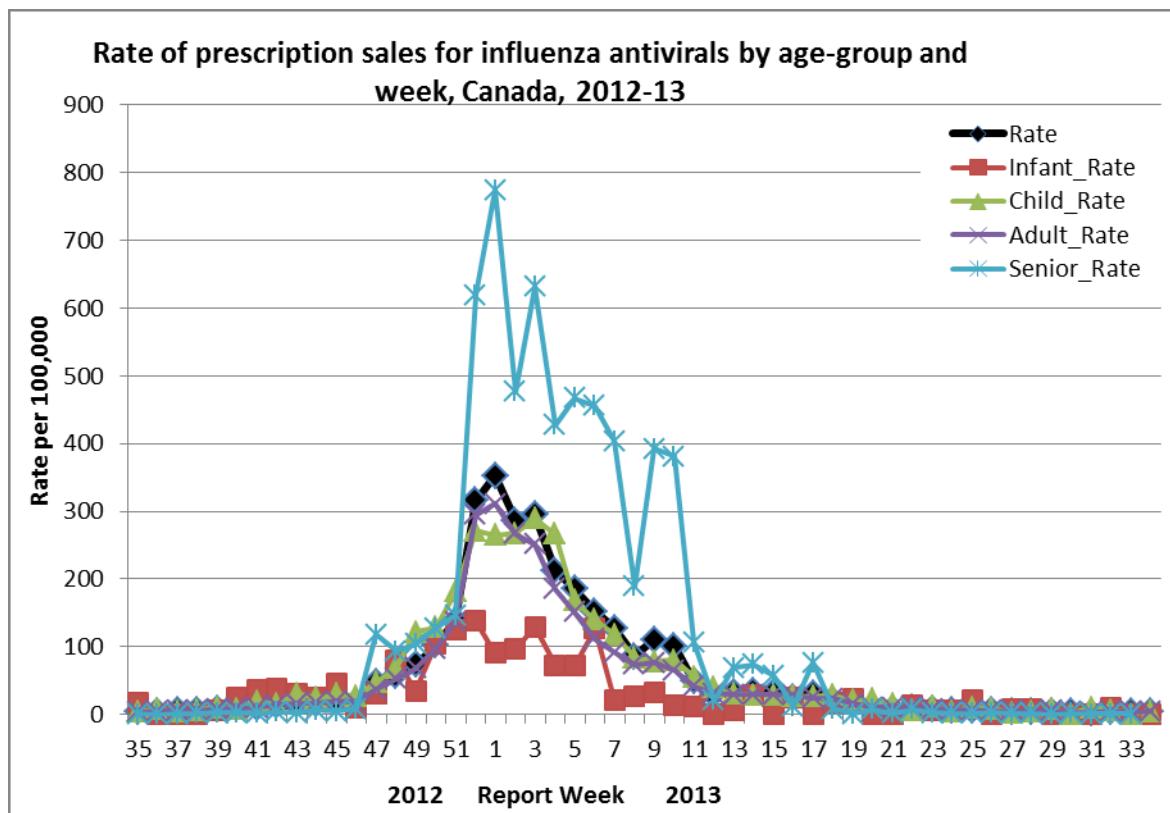
immunization is recommended by the National Advisory Committee on Immunization (5). Only one paediatric death was reported.

Of the 1,812 adults hospitalized, 68% (n=1,230) were ≥ 65 years of age and 107 resulted in death. Of the 286 individuals who were admitted to ICU or died, 122 had underlying medical conditions, two had no underlying medical conditions and medical history was unknown for the remaining individuals.

Antiviral drugs - pharmacy surveillance

The overall Canadian antiviral prescription rate peaked in week 1 at 349 antiviral prescriptions per 100,000 new prescriptions dispensed. The antiviral prescription rate was highest in those ≥ 65 years of age and peaked at 750 prescriptions per 100,000 prescriptions dispensed and was lowest in infants (0-2 years of age) and peaked at 138 prescriptions per 100,000 prescriptions dispensed (**Figure 5**).

Figure 5: Rate of prescription sales for influenza antivirals by age group and week, Canada, 2012-2013



Discussion

The various indicators of influenza surveillance during the 2012 - 13 season peaked in late December 2012 to early January 2013, which is in keeping with the expected pattern of the seasonal influenza epidemic. Influenza A (H3N2) was the predominant circulating influenza strain for the season and constituted the majority of influenza illness until early March 2013 when influenza B became the predominant circulating strain.

The 2012 - 13 season was moderately severe compared to the previous two seasons (9, 10). An increase in the impact of influenza was seen in the number of positive laboratory tests for influenza reported, with almost twice as many positive detections compared to 2010 - 11 and almost three times the detections in 2011 - 12. The same

trend was seen in the cumulative rate of hospitalizations and deaths reported by participating provinces and territories. The cumulative hospitalization and death rate per 100,000 was 14.6 and 1.1 respectively in 2010 - 11 and 8.5 and 0.5 for 2011 - 12 (data not published). The number of outbreaks reported this season in hospitals and LTCFs was the highest since 2004 - 05.

Characterization and antiviral resistance testing from the NML suggests that the circulating influenza viruses demonstrated little antigenic drift and remained closely related to the WHO-recommended strains for the 2012 - 13 trivalent influenza vaccine. Despite this antigenic concordance, some studies reported low to moderate vaccine effectiveness during the 2012 - 13 season (6-8). All but a small percentage of viruses tested remained sensitive to neuraminidase inhibitors.

There are a number of limitations that need to be considered when interpreting results from the FluWatch surveillance program. Laboratory testing, surveillance and reporting protocols have varied prior to, during and post-pandemic and vary between provinces and territories. Therefore comparisons of laboratory findings (e.g. percentage of positive tests and number of positive laboratory-confirmed cases) over time as well as differences between jurisdictions need to be interpreted in light of these differences. Several factors affect the number of isolates sent to the NML such as limitations to culture isolates in provincial laboratories and samples of clinical interest. A greater proportion of the early isolates may also be analyzed to get a better understanding of the circulating strains for the coming season. Because only a subset of influenza viruses is characterized by the NML, the distribution of strain information is not representative of influenza detections reported by all laboratories contributing to RVDSS. Age-specific data for ILI consultation rates as well as laboratory testing for influenza may be affected by biases in health care utilization and physician testing behaviour. ILI consultation rates across time and between jurisdictions may vary with sentinel participation, differences in coverage rates as well as the co-circulation of other respiratory viruses. The true number of individuals affected by influenza in the population is not reflected in the data as FluWatch relies on sentinel data sources.

Duplicate reporting of hospitalizations and deaths is possible where a reporting jurisdiction has one or more hospitals participating in IMPACT or PCIRN-SOS. The reason for hospitalization or cause of death reported by provinces and territories does not have to be attributable to influenza for reporting purposes. Not all provinces/territories report aggregate hospitalizations or deaths, which makes these data incomplete at the national level.

There are a number of limitations associated with the data sources used in the FluWatch program, however, these data sources collectively inform influenza epidemiology in Canada over the season and allow for comparison between seasons. The FluWatch program continues to strengthen influenza surveillance in Canada in collaboration with national and international surveillance partners.

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Conflict of interest

There are no conflicts of interests to declare.

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A systematic review of tetanus in individuals with previous tetanus toxoid immunization

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Abstract

Objectives: To assess the characteristics of tetanus in previously immunized individuals.

Methods: A systematic literature search was undertaken using Ovid MEDLINE(R) and EMBASE databases for articles published between 1946 and September 3, 2013. The search strategy was developed using MESH terms for “tetanus”, “immunization” and “vaccination”. Inclusion criteria were articles in English or French that described at least one case of tetanus, immunization history and/or the results of anti-tetanus antibodies. Articles were reviewed for relevant references.

Results: 51 unique articles published from 1946-2013 were included in the review. The articles described 359 cases of clinical tetanus in individuals with prior receipt of one or more doses of tetanus toxoid vaccine and/or levels of tetanus antibody titres generally considered protective. Of the 210 cases that reported patient status at discharge, 180 (85.7%) survived with only three cases reporting residual deficits.

Conclusion: Tetanus spores are ubiquitous and this report clearly documents that tetanus cases can occur in individuals previously immunized with tetanus toxoid vaccine. Clinicians should not rule out tetanus when clinical symptoms suggest it, regardless of the vaccination history. When treated, the prognosis for tetanus is good. Further research is needed to assess the incidence of tetanus in partially- and fully-immunized populations and determine whether this is due to waning immunity or vaccine failure.

Introduction

A previously healthy 22 year-old man presented to an emergency department in Ontario, Canada with symptoms of spasm and trismus consistent with tetanus. Twenty-seven days prior to presentation, he reported a minor injury to the left great toe that appeared to form an abscess. He lanced the abscess himself, but the wound worsened whereupon he sought medical treatment. Medical treatment consisted of antibiotics followed by systemic steroids for a suspected allergic reaction to the antibiotics. Past medical history revealed five documented and appropriately spaced doses of tetanus toxoid-containing vaccine: Diphtheria, tetanus, pertussis (DTP) at 2, 4 and 6 months, Diphtheria, tetanus, acellular pertussis, inactivated polio (DTaP-IPV) at 18 months and Tetanus, diphtheria (reduced), acellular pertussis (reduced) (Tdap) at 14 years of age, nine years previously. There was no documentation of a pre-school booster typically given at 4-6 years. No additional tetanus-containing vaccine was given when he initially sought medical treatment. At the hospital, the patient was treated with tetanus immune globulin, antibiotics and supportive care. During his course in hospital, the patient improved and was discharged 20 days after admission, with a full recovery reported 12 weeks following initial presentation.

Tetanus is the clinical manifestation of infection with *Clostridium tetani* (1). The exotoxin produced by tetanus bacilli acts on the spinal cord and causes painful muscular contractions, especially of the neck and masseter

muscles, thus the colloquial name “lockjaw” (2). More severe symptoms include respiratory problems, coma and death (2). Tetanus spores are ubiquitous in the environment and can infect any exposed wound (1). Prevention of tetanus is achieved through appropriate wound care and immunization (1).

Tetanus is rare in Canada with an average of four cases per year (range 1-10 per year) between 1990 and 2010 (3). Since the 1920s there has been a significant decrease in the number of deaths from tetanus due to the availability of vaccine and improvements in critical care (1, 2). The case fatality rate due to tetanus in unvaccinated persons varies significantly from 10% to over 80% with the very young and elderly being at greatest risk (1, 3, 4).

In Canada, the routine immunization schedule consists of four doses of tetanus toxoid-containing vaccine, given at 2, 4, 6 and 12 to 23 months of age (typically at 18 months of age), with a booster dose at age 4-6 years (3). After the completion of the first three doses of tetanus toxoid, more than 99% of individuals will have evidence of a protective antibody titre (3). Although traditionally a tetanus antibody titre of >0. 01 IU/mL by mouse neutralization assay has been considered protective; some studies have suggested a higher correlate of protection, such as 0.1 IU/mL. is required (5-7). Observational studies have demonstrated the efficacy of pre- and post-wound exposure immunization regimens (3). Subsequent booster doses are recommended at 10-year intervals, although the most recent edition of the *Canadian Immunization Guide* indicates that new evidence on the optimal timing of booster doses is currently under review (3). Depending on the nature of the wound and prior immunization history, post-exposure immunization (active and passive) may also be indicated (3).

Nevertheless, tetanus may still occur post immunization. Given the above case of tetanus with a history of a complete and documented primary series of tetanus toxoid, along with a “booster” nine years prior to presentation, a systematic review was conducted to assess the characteristics of tetanus in previously immunized individuals.

Methods

A systematic literature search was undertaken using Ovid MEDLINE(R) and EMBASE databases for articles published between 1946 and September 3, 2013. The search strategy was developed in MEDLINE using the following MESH terms: tetanus/, tetanus toxoid/, diagnosis/, diagnosis, differential/, immunization/, vaccination/. The controlled vocabulary was supplemented by the use of related keywords to increase the specificity of the search: “fully”, “preexisting”, “previous*”, “prior”, “presen*”, “protective”, “active”, “antibodies”, “immune*”, “vaccine*”. The search terms were combined using Boolean operators. No limits were applied to search in MEDLINE. The search in EMBASE, after the controlled vocabulary was translated to Emtree terms, was limited to non-MEDLINE content.

Abstracts were screened for the article being written in either English or French and a diagnosis of tetanus in one or more individuals. Abstracts meeting both screening criteria were obtained for full text review. Two authors (JPH, SEW) reviewed the articles for inclusion in the review.

In order to be included in the review, the article had to describe at least one case of tetanus, the immunization history of a fully or partially immunized case and/or present the results of anti-tetanus antibodies and be written in either English or French. The formal search was supplemented by PubMed snowball searches performed on articles meeting pre-specified inclusion criteria. In addition, a review of references from each relevant article was undertaken.

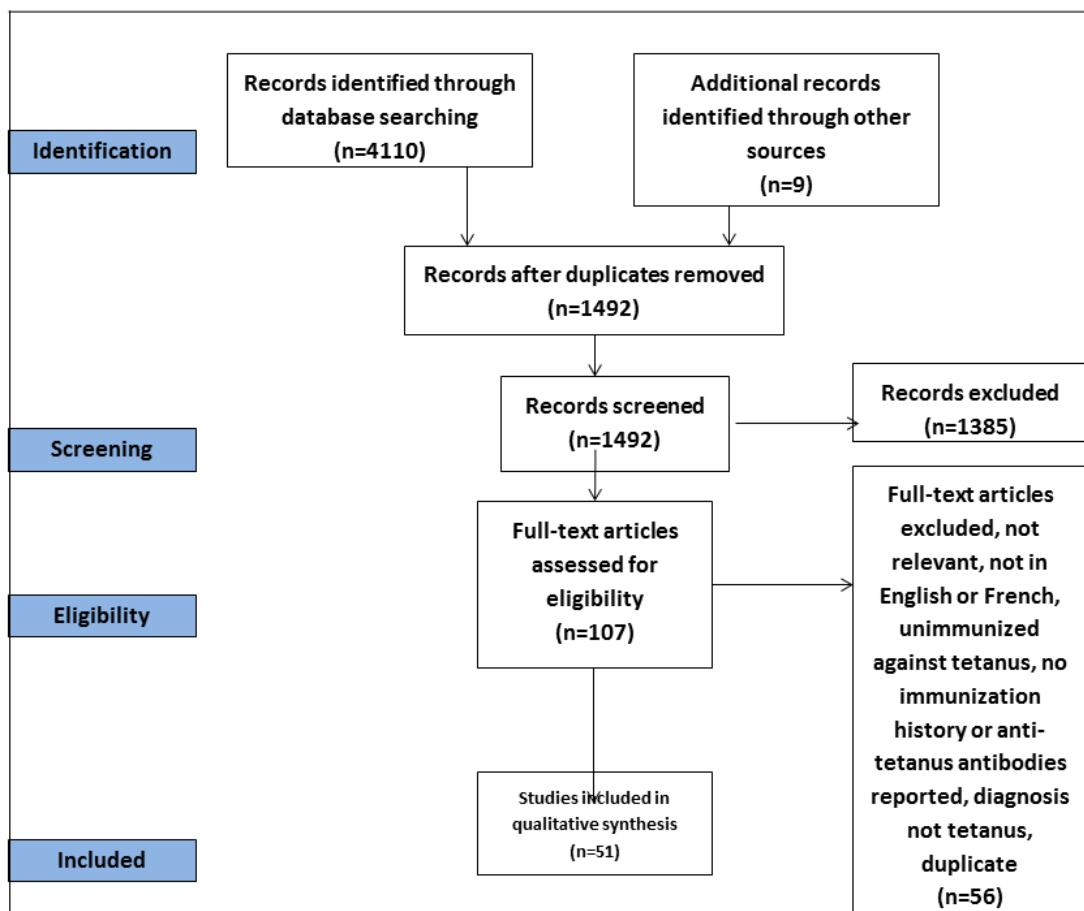
Relevant data, including number of tetanus cases, age, sex, antibody titre, clinical outcome, historic tetanus toxoid immunization, including number of doses and timing were abstracted and collated (Microsoft Excel 2010, Redmond, WA). One author (JPH) abstracted the data which was reviewed for accuracy by a second author (SEW). Discrepancies (which were rare) were resolved through consensus.

A formal quality assessment of individual articles was not undertaken. The retrieved articles included case reports, case series or surveillance reports. To the authors' knowledge, there is no validated tool for quality appraisal of these study designs. However, studies that were missing relevant data were excluded as per a priori inclusion and exclusion criteria. As this was a narrative synthesis of the literature, funnel plots and statistical assessments of heterogeneity were not appropriate measures of publication bias.

Results

Over 4000 articles were initially identified. Fifty-one unique articles were included in the review. **Figure 1** summarizes the literature search results.

Figure 1: Literature search results



In the 51 studies that were included there were 359 cases of clinical tetanus in individuals with prior receipt of one or more doses of tetanus toxoid vaccine and/or levels of tetanus antibody titres generally considered protective (8-9). The majority of studies (n=25) were based on data from the United States. Of 47 cases where age and sex were described, 26 (39.4%) were male with a median age of 26 years (range 1-79 years). Fourteen cases had tetanus antibody titres drawn prior to administration of antitoxin, while the remaining 345 cases had immunization confirmed on record review. All cases of tetanus were diagnosed based on clinically compatible symptoms and signs. The isolation of *Clostridium tetani* was not reported in any case.

Vaccination histories of cases were reviewed within the case reports. While inclusion criteria required all cases to have received one or more doses, only 175 (48.7%) reported the exact number of doses. Ninety-four cases

(26.2% of total cases) received three or more doses suggesting the primary series may have been completed, although it was not possible to assess the interval between doses. With respect to doses which occurred beyond early childhood and were described as “boosters” but which may or may not have been preceded by a complete primary vaccine series, 57 cases (15.9%) received a booster dose of tetanus toxoid within the last 10 years, 54 cases (15.0%) received a booster dose 10 or more years in the past and 248 cases (69.1%) last received a booster at an unknown interval (or no booster was given), or the case was not eligible for a booster (e.g. based on a historic policy or age) (data not shown). As more than half of the cases did not report the number of doses of tetanus toxoid received and there were a small number of deaths (n=30), it was not possible to analyze survival data by number of doses.

The high survival in published case reports suggest milder disease that is associated with better prognosis in individuals with a history of tetanus immunization (3, 4, 20-23). This is in keeping with an attenuation of clinical severity in immunized hosts that is recognized in other vaccine-preventable diseases (24-26).

Of the 180 of 210 (85.7%) cases that reported on clinical outcome survived to discharge and in cases that were followed beyond discharge, all except three (17,27,28) had complete resolution of symptoms. While survival generally appeared to improve over time, 42% of studies (n=149) did not report the clinical outcome so it was not possible to study survival trends as they related to other factors (e.g. systematic improvements in critical care over time and increased implementation of a 3-dose primary immunization series). The studies are summarized in **Tables 1 and 2**.

Table 1: Case reports of tetanus in individuals with complete data (detailed information on tetanus immunization history or tetanus antibody and clinical outcome)

Author / country	Study design/ number of cases (n)	Age (years) and sex ¹	Risk factors for tetanus ²	Vaccination history ³	Tetanus antibody titre at diagnosis ⁴	Patient outcome ⁵
Abrahamian(8) / United States	Case report/ n=1	45 M	IDU	?	++	-
Atabek(9)/Turkey	Case report/ n=1	7 F	Laceration	++	?	+
Aydin-Teke(29) / Turkey	Case report/ n=1	15 M	Injury	++	?	+
Bardenheier(22) / United States	Surveillance/ n=31	?	?	+ (15) ++ (16)	?	+ (30) -(1)
Berger(16)/ United States	Case report/ n=1	25 F	IDU	?	+	+
Boyd(30)/ Europe and Africa	Retrospective surveillance/ n=16	?	?	+/++	?	+ (11) -(5)
Boyer(31)/France	Case review/ n=10	?	?	+/++	?	+ (2) -(8)
Coniglione(32)/ United States	Case report/ n=1	29 M	Injury	++	++	+
Crone(17)/ United States	Case report/ n=3	29 M 42 F 57 F	?	++ + +	++(3)	+ - +(deficits)
de la Chapelle(33)/France	Case report/ n=1	52 M	Injury, IS	?	++	+
Dyce(27)/ United States	Case report/ n=1	24 F	Piercing	++	?	+(deficits)
Faust(34)/ United	Hospital	5 M	?	+	?	+

States	surveillance/ n=1					
Fiorillo(35) / Canada	Case report/ n=1	10 M	Injury	++	++	+
Hall(36) / United States	Case report/ n=2	?	?	+(2)	?(2)	+(1) -(1)
Hedrick(37) / United States	Case report/ n=2	10 M 45 M	Injury ?	++ +	?(2)	+(2)
Hopkins (this report) / Canada	Case report/ n=1	22 M	Injury, IS	++	?	+
König(10) / Germany	Case report/ n=1	14 M	Injury	++	?	+
Livorsi(11) / United States	Case report/ n=1	44 M	Injury	?	++	+
Lodha(38) / India	Case report/ n=2	3 F 4. 5 M	?(2)	? ++	?(2)	+(2)
Long(39) / United States	Surveillance/ n=6	?	Injury	++(6)	?	+(3) -(3)
Loscalzo(40) / United States	Case report/ n=1	23 F	Piercing	++	?	+
Luisto(12) / Finland	Retrospective case series/ n=5	5 M 10 F 12 M 13 F 15 F	Animal bite Infection Injury Injury Burn	++ ++ ++ ++ ?	?(5)	+(5)
Newton-John(23) / Australia	Case series/ n=19	?	?	++(13) +(6)	?	+(17) -(2)
Otero-Maldonado(28) / Puerto Rico	Case report and surveillance/ n=7	67 M ?(6)	Injury ?(6)	+ ?(6)	?(7)	+(deficits) +(5), -(1)
Pascual(21) / United States	Surveillance/ n=30	?	?	+(10) ++(20)	?(30)	+(10) +(19), -(1)
Passen(14) / United States	Case report/ n=1	35 M	Injury	++	++	+
Peterson(18) / Sweden	Case report/ n=1	12 M	Injury	++	++	+
Spittle(41) / New Zealand	Case report/ n=1	25 F	Injury	++	?	+
Tiwari(4) / United States	Surveillance/ n=55	?	?	+(26) ++(29)	?(55)	+(17), - (3), ?(6) +(24), - (1), ?(4)
Vieria(19) / Australia	Case report/ n=1	18 M	Injury	++	?	+

¹ M (male), F (female), ? (unknown/not reported)² ? (unknown/not reported)³ ++ (3 or more doses), + (1 or 2 doses), ? (exact number of doses not reported)⁴ ++ (>0. 1 IU/ml), + (0. 01-0. 09 IU/ml), ?=not measured⁵ + (alive at discharge), - (deceased), ? (unknown/not reported)

IDU = injection drug use

IS = immunosuppression

Table 2: Case reports of tetanus in individuals lacking complete data (detailed) information on tetanus immunization history and/or clinical outcome)

Author/ country	Study design/ number of cases (n)	Age (years) and sex ¹	Risk factors for tetanus ²	Vaccination history ³	Tetanus antibody titre at diagnosis ⁴	Patient outcome ⁵
Bankole(42) / Nigeria	Case series/ n=11	?	?	?	?	?
Beltran(43) / United States	Case report/ n=1	58 M	Animal bite	?	++	?
Bunch(44) / United States	Case series/ n=5	53 F 59 F 62 F 65 F 75 F	? Injury Infection Laceration Laceration	?(5)	?(5)	+(5)
Christensen(45) / United States	Case report/ n=1	10 M	Injury	+	?	?
Culbertson(46) / United States	Case report/ n=1	41 M	Burn, lacerations	?	?	+
deSouza(47) / India	Case control/ n=1	?	?	+	?	?
Earis(48) / United Kingdom	Case report/ n=1	66 F	Fungating tumour	?	?	+
Edsall(49) / multiple	Review of previously published cases ⁶ / n=4	?	?	?(4)	?	+ (3) -(1)
Ferris(50) / United Kingdom	Case report/ n=1	17 M	Trauma	?	?	+
Geeta(51) / India	Case series/ n=12	1 M ?(11)	?	++ +(11)	?	?
Hahn(52) / United States	Case report/ n=1	58 M	?	?	?	+
Henderson(53) / United States	Case series/ n=5	?	Various injuries; IDU	?	?	?
Iqbal(54) / Pakistan	Case series/ n=10	?	?	?	?	?
Lee(55) / Taiwan	Case series/ n=2	3 ? 5 ?	?(2)	?(2)	?(2)	?(2)
Masthi(56) / India	Case series/ n=2	?	?	?	?	?
O'Malley(13) / United States	Case report/ n=1	27 F	Piercing	?	++	?
Orwitz(57) / United States	Case report/ n=1	79 M	Infection	?	?	?
Percy(58) / United States	Case series/ n=1	?	?	+	?	?
Quackenbush(59) / United States	Case report/ n=1	44 F	Injury	?	?	+
Rushdy(20) / United	Surveillance	?	?	?	?	?

Kingdom	report/n=5						
Shimoni(15) / Israel	Case report/ n=1	34 M	?	?	?	?	+
Srigley(60) / Canada	Case report/ n=1	78 F	Injury	?	?	?	-

¹ M (male), F (female),? (unknown/not reported)

² ? (unknown/not reported)

³ ++ (3 or more doses), + (1 or 2 doses),? (exact number of doses not reported)

⁴ ++ (>0. 1 IU/ml), + (0. 01-0. 09 IU/ml),? =not measured

⁵ + (alive at discharge), - (deceased),? (unknown/not reported)

⁶ Studies described in table (p. 127). Original studies were obtained where possible (Long, Hall, Boyd, Boyer, Christensen). Remaining studies were not indexed in PubMed, MEDLINE or EMBASE. The Journal of the American Medical Association (JAMA) was contacted for the original reference list which was excluded from the published manuscript due to length, but no copy was archived. Cases summarized here are from Moss and Hedrick.

IDU = injection drug use

IS = immunosuppression

Discussion

To the authors' knowledge, this is the first systematic review which assesses the occurrence of tetanus in previously immunized individuals. Since 1946, at least 359 cases of tetanus have been described in previously immunized individuals and of those whose outcomes were reported, there was a survival rate of 85.7% with few cases reporting residual deficits at discharge. In cases that reported the number of doses of tetanus toxoid previously received by individuals, the clinical severity of disease appeared to be less compared to those who received fewer previous doses (although this could not be studied systematically due to the small number of deaths and cases symptomatic at discharge).

A previous review found a similar relationship between the number of doses and clinical severity. A review of 175 tetanus cases reported through routine surveillance between 1984 and 2000 in England and Wales found that clinical severity was greater in those with no previous history of immunization (although this did not reach statistical significance ($p=0. 068$) (20).

Potential explanations for the occurrence of clinical tetanus in the setting of past immunization could include: waning of vaccine-derived immunity; vaccine failure; the presence of an unrecognized immunodeficiency resulting in sub-optimal immune response to active vaccination; or compromised vaccine storage and handling resulting in reduced immunogenicity of the vaccine product. Alternatively, the burden of tetanus exotoxin may exceed an individual's immune response which may be additionally influenced by factors that cause immune suppression, such as chronic diseases or medications.

Limitations of this review include: the inability to assess how frequent this phenomenon is due to the lack of a denominator; potential publication bias; and incomplete data (e.g. survival). In addition, the inherent limitations of case studies and surveillance reports include: collection of source information (e.g. recall bias if self-reported, data quality and consistency if taken from databases; under-reporting or ability to capture all cases in a surveillance system); and a lack of a consistent clinical definition for tetanus in case reports created challenges in interpretation of the data.

Nonetheless, this study contributes significantly as it is possibly the first systematic review which summarizes the characteristics of tetanus in cases previously immunized with tetanus toxoid. Other strengths of this study include: the systematic methodology used to identify relevant studies; and the inclusion of articles from multiple countries, studies from 1946 through 2013 and studies in two languages.

Attenuation of disease severity in immunized hosts suggests the potential for under-reporting if the person does not present for medical care as well as the possibility of delayed diagnosis, although this was not consistently described in the included articles. This has important implications for the surveillance of vaccine-preventable diseases and clinical practice.

Future research directions might focus on understanding the incidence of tetanus in those with previous vaccination with tetanus toxoid and whether this is due to waning immunity or vaccine failure, the optimum timing of tetanus toxoid boosters and further research into the cut-off and role of anti-tetanus antibodies in determining immunity to tetanus.

Conclusions

Tetanus is a rare, but potentially lethal disease and *Clostridium tetani* are ubiquitous in the environment. A completed primary vaccine series and appropriate boosters clearly do not confer protective immunity in all recipients; however the survival rate is high in those with previously documented doses of tetanus toxoid. Clinicians should maintain a high index of clinical suspicion for tetanus when the clinical symptoms suggest it, regardless of vaccination history.

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Conflict of interest

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Collaboration on a public health-driven vaccine initiative

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Abstract

Disease surveillance can be used as an opportunity to determine priorities for research and the development of new therapeutics. This is evident in the work underway to develop a new vaccine to combat a serious invasive childhood disease: *Haemophilus influenzae* serotype a (Hia). Following the introduction of Hib vaccine into the routine childhood immunization schedule in Canada in the early 1990's, the Public Health Agency of Canada (PHAC) began to document the dropping rates of H influenzae serotype b (Hib) infection. However, invasive *H. influenzae* diseases due to non-Hib strains began to increase and in 2007, surveillance for invasive *H. influenzae* disease due to all serotypes as well as non-typeable strains was initiated. Current data suggests Hia is a cause of serious invasive disease, particularly in Aboriginal populations. Similar to Hib, Hia causes severe illnesses such as meningitis, sepsis and bacteremic pneumonia in young children under the age of five.

Given the emerging threat due to Hia in Aboriginal populations in Canada, PHAC formed a partnership with the National Research Council of Canada (NRC) to investigate the potential of creating a capsular polysaccharide vaccine against Hia. At the present time, candidate vaccine seed strains have been identified and PHAC and the NRC are working with the Northern Ontario School of Medicine, the US Centers for Disease Control and Prevention and others. The goal of this research is to identify and prepare a candidate vaccine against Hia while increasing the understanding of how such a vaccine would improve the health of a vulnerable population.

Introduction

One of the benefits of disease surveillance is that it can highlight the need or opportunity for new interventions. Surveillance provides an essential means of identifying diseases that create a significant burden within a population and helps to identify the need for vaccines, one of the most effective public health interventions to prevent disease. For example vaccines against smallpox have eradicated this disease (1) and polio has been eliminated from almost all countries of the world (2). As a result of surveillance data, vaccines have been created to prevent diseases such as *Streptococcus pneumoniae*, *Neisseria meningitidis* as well as influenza.

As part of its role to serve the public good, through surveillance, the public health sector can identify the need for and facilitate the development of new vaccines against diseases that cause significant morbidity and mortality in the population.

This article outlines a public health-driven collaboration that has emerged between the Public Health Agency of Canada (PHAC, or the Agency) and the National Research Council of Canada (NRC) to develop a vaccine that combats an emerging pathogen particularly prevalent within the Aboriginal population: *Haemophilus influenzae* serotype a (Hia).

The Public Health Agency of Canada

The Public Health Agency of Canada was created in 2004 to provide federal leadership to anticipate, respond and be accountable for public health issues and emergencies (3). The Agency was also envisioned as a means to improve collaboration between jurisdictions to protect and promote public health within the Canadian population.

Within the Agency, the Centre for Immunization and Infectious Respiratory Diseases (CIRD) (4) and the National Microbiology Laboratory (NML) (5) are primarily responsible for providing technical support for vaccine-preventable diseases. CIRD is responsible for epidemiological surveillance of many vaccine-preventable diseases, while NML provides laboratory surveillance, reference diagnostics and research. In cooperation, they provide data on emerging trends for a number of infectious diseases.

The National Research Council of Canada

The NRC began its work to develop vaccine technologies during the 1980's. Its area of expertise has developed over the years to include excellence in carbohydrate chemistry, immunochemistry and in developing partnerships to create new vaccines (6, 7, 8). The NRC has also developed expertise to improve current vaccines and technologies that enable ongoing vaccine innovation. Through the NRC, there are technical and advisory services, research facilities, licensing opportunities as well as program and partnership opportunities. This expertise has been applied to study carbohydrate antigens of encapsulated bacterial pathogens such as *Haemophilus influenzae* serotype b (9), *Neisseria meningitidis* (6, 7) and streptococci (10), which are important pathogens. Each of these pathogens has a polysaccharide capsule that enhances its virulence. In recent years, the NRC has focused on antigen selection, glycoconjugation technologies, adjuvant design and production of vaccine candidates all compatible with current Good Manufacturing Practices (cGMP). The NRC also has the capability to conduct pre-clinical in vivo trials to monitor efficacy and safety of products produced (11).

Invasive *Haemophilus influenzae* disease in Canada

Prior to the development of a *H. influenzae* serotype b (Hib) conjugate vaccine, Hib was a significant cause of meningitis, sepsis and bacteremic pneumonia in children under the age of five years. Based on national surveillance from 1986 – 87, approximately 700 cases of invasive Hib disease occurred per year. Hib vaccines were introduced into the routine childhood immunization schedule in Canada in the early 1990's. Since vaccine introduction, the incidence of Hib disease has dramatically declined. In the last five years where data is available at a national level (2008 - 2012), there has been an average of 26 cases of Hib disease reported across Canada per year (12). However, based on data from national surveillance programs, invasive *H. influenzae* diseases due to non-Hib strains have emerged in the last decade (13). Therefore, in 2007, a revised national case definition of invasive *H. influenzae* disease to include diseases due to all serotypes as well as non-typeable strains was endorsed (14).

Among the encapsulated serotypable *H. influenzae* strains, serotype b has been determined to be the most virulent followed by Hia and then others (15). Current data suggests *H. influenzae* serotype a (Hia) is a cause of serious invasive disease, particularly in the Aboriginal population (16). Similar to Hib, Hia causes severe illness such as meningitis, sepsis and bacteremic pneumonia in young children under the age of five. Since northern Canada has a relatively high indigenous population and Hia, being similar to Hib including its epidemiology, has replaced Hib as a cause of significant burden of invasive diseases in the post-Hib vaccine era (17). This trend has also been observed in Alaska, U.S.A. (18).

Public health-driven collaboration

Given the knowledge of an emerging threat due to Hia in Aboriginal populations in Canada and with the launch of a Vaccine Program within the NRC's Human Health Therapeutics portfolio, PHAC partnered with the NRC to investigate the potential to create a capsular polysaccharide vaccine against Hia for protection of Canadians. The initial meeting and consultation between PHAC and the NRC was held in 2011 to discuss the feasibility of developing a glycoconjugate vaccine against Hia. In October 2011, a workshop organized by PHAC, the NRC and the Northern Ontario School of Medicine (NOSM) was held at Lakehead University. This workshop included academic researchers from the NOSM and the Thunder Bay Regional Health Authority who discussed two neglected infectious diseases in Aboriginal communities (Hia and Helicobacter pylori) (19). Based on the groundwork from the initial meetings, a letter of intent on "Expanding Vaccine Development in Canada" was

signed between PHAC and the NRC in September 2012 and the joint Hia project was launched in March 2013. In December 2013, investigators from the Arctic Investigators Program of the US Centers for Disease Control and Prevention (CDC) joined the group as they had also observed a similar increase in Hia incidence within the Alaskan Aboriginal population.

At this point in time, candidate vaccine seed strains have been identified and are being characterized at the NML. Large-scale preparation of glycoconjugates based upon the capsular polysaccharide from Hia is now being carried out at the NRC. Serological assays including tests to measure protective immunity are being developed at the NOSM. Immunogenicity studies in animals that have received the glycoconjugates are being conducted at the NRC and sera derived from immunised animals are being evaluated against a range of clinical strains at NOSM.

The goal of this research is to identify and prepare a candidate vaccine against Hia while advancing understanding of how such a vaccine would improve health in a vulnerable population. Work to date has focused on how to provide a better understanding and characterization of the epidemiology of invasive Hia disease through improved surveillance activities. This is being done in collaboration with international partners such as the CDC and the Pan American Health Organization (PAHO). Additionally, on the laboratory side, this work will provide a proof of concept that capsular polysaccharide from Hia can be purified and conjugated to a carrier protein that will induce a protective immune response in experimental animals. Once a candidate vaccine has been shown to be safe and effective in pre-clinical trials, further production would require industry or other third party engagement.

Conclusion

This collaborative project is an excellent example of how government leadership can be effective in addressing a public health need. It also shows how identifying a Canadian research agenda can be expanded and applied internationally. Through surveillance, PHAC has the ability to identify opportunities for new vaccine strategies. The NRC has the technical expertise to develop and produce vaccine candidates. Together with additional partners such as academia and other governmental and non-governmental organizations, this model could lead to further vaccine innovation.

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Conflict of interest

There are no conflicts of interest to declare.

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The National Advisory Committee on Immunization (NACI): A celebration of fifty years of service

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Abstract

The National Advisory Committee on Immunization (NACI) celebrates its fiftieth anniversary in October 2014. This paper outlines the history of NACI and its activities over the past 50 years. After its formation in 1964, NACI undertook the development of guidance for the few vaccines that were approved at that time, including polio, measles, tetanus, pertussis, diphtheria and smallpox. Although the Committee has evolved over the years, its focus has remained on providing guidance on an ever-increasing number of products: twenty-four, according to the recent updates to the *Canadian Immunization Guide*.

With the changing vaccine landscape, including immunization programs and practices, the membership of the Committee has evolved to include expanded expertise, such as immunology. The work of the Committee has had to adapt, with more complex and extensive evidence and the establishment of a published evidence-based methodology. Over the past 50 years, the success and accomplishments of NACI have been in large part due to the efforts of its chair and members, who have dedicated countless hours of work to committee activities and products. NACI's Technical advisory groups are recognized globally as a valuable resource, benefiting immunization practices and programs across Canada and internationally. NACI is a committee of which PHAC and indeed Canada can be truly proud.

Introduction

The National Advisory Committee on Immunization (NACI) will celebrate its fiftieth anniversary in October of 2014. This paper provides an account of NACI's formation, history and work over the past 50 years. The Committee was constituted in 1964 as the National Advisory Committee on Immunizing Agents by the then Department of National Health and Welfare and reported to the federal, provincial, territorial Dominion Council of Health. Over the last fifty years, NACI has provided evidence-based advice on vaccines authorized for use in Canada as well as immunization practices and schedules, through meticulous and pain-staking review and invoking the best judgement of some of the most knowledgeable professionals in paediatrics, nursing, infectious disease, immunology and public health in Canada. NACI has been a model for other policy and expert advisory committees in Canada and is highly regarded as the authority on immunization practice in this country.

Early beginnings

NACI held its first meeting in October of 1964 and was chaired by the highly respected Canadian virologist, Dr. Andrew Rhodes of the University of Toronto. A technical group had been convened to discuss the implementation of the polio vaccine in Canada several years earlier and it was Dr. Rhodes' vision that there was a need for a group to provide ongoing advice regarding polio and other new vaccines of the era, such as the measles vaccine. A presentation was made to the Dominion Council of Health (the group of Deputy Ministers that guided health programs in Canada) in April, 1963 and the constitution of a committee "in the capacity of an Advisory Committee on Vaccines" was approved. In 1977, the name was changed to the National Advisory Committee on Immunization (NACI), which reflected the fact that the Committee made recommendations on vaccines as well as immunization practices and programs.

"The purpose of the Committee was [is] two-fold: first, to advise and to make recommendations on immunizing agents to the Minister through the Dominion Council of Health, as requested by Council or its Chairman; and second, to propose to Council aspects of immunizing agents that appear to warrant special consideration..." While the terms of reference of NACI have been updated on many occasions over the years, these two purposes still reflect the spirit of the Committee's fundamental work.

Dr. Rhodes' vision was clearly astute. In 1964, there were only a handful of vaccines. Smallpox vaccine had been used for decades, pertussis vaccine since 1918, diphtheria vaccine since the 1920s and tetanus vaccine since the 1940s (1). Polio and measles vaccines were new. Today, the online edition of the *Canadian Immunization Guide* (2) provides guidance on twenty-four vaccines and many more are anticipated. In addition, from time to time, NACI provides advice on the establishment of universal programs, such as hepatitis B vaccine for children and has provided guidance on best practice in immunization, from how to do a proper intramuscular (IM) injection, to communicating effectively to vaccine recipients. Further, in the future, NACI may be asked to provide guidance on other elements such as the cost-effectiveness of various vaccine programs. The scope of the work of NACI has expanded hugely over the last fifty years and it is difficult to imagine how health professionals and those responsible for implementing vaccines programs would manage without its guidance. The health system is fortunate to have an eminent body like NACI to provide unbiased and comprehensive advice on immunization.

NACI members and leadership

The membership of NACI has evolved over the years. Original members were leading names in virology, bacteriology and paediatrics, along with both federal and provincial public health administrators. In 1980, a local public health practitioner was added. Experts in infectious diseases were invited to join and an immunologist was recommended as early as 1976 (NACI now has an immunologist as a standing member). Starting in the 1970s, various professional organizations involved in immunization practice were invited to appoint liaison representatives, who not only provide a link to those other organizations but also bring a wealth of knowledge and experience to the proceedings of NACI. Some examples of these professional organizations are listed in **Table 1**.

Table 1: Liaison organizations represented on NACI over the past several decades

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| <ul style="list-style-type: none"> • Advisory Committee on Epidemiology • Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, Atlanta • Association of Medical Microbiology and Infectious Disease Canada • Canadian Association for Immunization Research and Evaluation • Canadian Immunization Committee • Canadian Infectious Disease Society • Canadian Medical Association • Canadian Nursing Coalition for Immunization • Canadian Paediatric Society • Canadian Public Health Association • Canadian Occupational Health Nurses Association • College of Family Physicians of Canada • Community and Hospital Infection Control Association • Council of Chief Medical Officers of Health • Committee to Advise on Tropical Medicine and Travel • Society of Obstetricians and Gynaecologists of Canada |
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NACI has been led by a series of distinguished health professionals who have served as its chair and who provided visionary leadership to NACI's work and discussions (**Table 2**). Sadly, the longest-serving chair, Dr.

Michael Dixon, passed away in November 2013, less than one year before NACI's fiftieth anniversary. Dr. Dixon served as chair for seventeen years, 1972-1989.

Table 2: Chairs of the National Advisory Committee on Immunization

1964 - 1966	Dr. Andrew Rhodes, Toronto, ON
1968 - 1969	Dr. Edward Bynoe, Ottawa, ON (acting)
1972 - 1989	Dr. J. Michael S. Dixon, Edmonton, AB
1989 - 1993	Dr. Susan Tamblyn, Stratford, BC
1993 - 1998	Dr. David Scheifele, Vancouver, BC
1998 - 2003	Dr. Victor Marchessault, Ottawa ON (passed away March 31, 2003)
2003 - 2007	Dr. Monika Naus, Vancouver, BC
2008 - 2011	Dr. Joanne Langley, Halifax, NS
2011 - 2014	Dr. Bryna Warshawsky, London, ON
2014 -	Dr. Ian Gemmill, Kingston, ON

The work of NACI

NACI's work has primarily focused on publishing guidance on vaccines and immunization practice through both statements on new vaccines or new indications for established vaccines and its main reference for the use of vaccines in Canada, the *Canadian Immunization Guide*. Statements on vaccines are needed whenever a new vaccine is authorized for use to support decision-making with credible, evidence-based guidance. NACI's statements have addressed this need since its inception in 1964. Statements are developed by first conducting an exhaustive review of the literature and then by writing guidance based on the best evidence, using a standard format (3).

Formerly, statements were written by individual members, but more recently, as the complexity of immunizing products has increased and the proliferation of similar products to protect against the same illnesses has occurred, working groups have been established to provide a broader mechanism to address this complex task. It is important to understand that recommendations of NACI are not based simply on product monographs, but all evidence that is available on a given vaccine. With the increasing complexity of immunizing products, there has also been a similar increase in the volume and complexity of epidemiological and clinical data that NACI assesses and grades to formulate its recommendations. Statements are thoroughly debated and thoughtfully crafted. In addition, readers of statements benefit from the good judgement of the members, who consider feasibility, practicability and a clear focus on what constitutes the best practice for recipients of vaccines. Once the lead author and the working group have agreed on the most reasonable, evidenced-based recommendations, the statement is discussed by all members of NACI for final approval. Over the years, statements have been made on new vaccines, on new developments in the literature about various vaccines and on vaccine-related issues, such as thimerosal.

The *Canadian Immunization Guide* (CIG) was first published in 1979 as the *Guide to Immunization for Canadians*, and has been revised every four years on average. The guide provided "comment and advice on the usage of all licensed immunizing agents for infectious diseases available in Canada at the time of writing" (4). The Committee believed "that this booklet would [will] help in the attainment of a greater degree of uniformity of immunization policy and practice in Canada than has been achieved in the past". The first edition was 92 pages in English version and 104 pages in French. The seventh edition, published in 2006, was almost 400 pages in length, and provides advice not only on specific vaccines, but on issues ranging from the use of various vaccines in special populations, to vaccine safety. With the increasing complexity of the practice of immunization and the fast rate of

change in knowledge and with the advances in technology that facilitated an electronic version of the CIG, NACI undertook to develop an online edition which is easily edited and updated. The work on the online edition was completed in early 2014 and schedules for both ad hoc changes, precipitated by changes in knowledge and routine reviews over a cycle of four years are being developed.

Conclusion

NACI has been an institution in vaccinology in Canada for half a century. It has provided reliable and forward-thinking advice that goes beyond the legal requirements of a product monograph. It has outlived the Council that created it. It has been a resource to the Public Health Agency of Canada (PHAC) and its predecessors longer than most committees and it continues to thrive. The professionals who have served on NACI have contributed countless hours to ensure that Canadian health professionals have the best possible advice on immunization practice, and consider their appointment to this distinguished committee an honour. In fact, it is considered one of the premier committees in the health system in Canada and it has set the standard for providing evidence-based guidance.

The need and role for such technical advisory committees is recognized at a global level. Without the guidance of NACI over the years, the immunization system in Canada would likely be more chaotic and far less harmonized than it is. The World Health Organization recommends the establishment, support and strengthening of national advisory committees on immunization as a key element to improving immunization programmes and establishing priorities and introducing new vaccines and immunization technologies (5). On the fiftieth anniversary of NACI, it is time to celebrate its contributions over the last half century and to thank the many professionals who have given their time and thoughtful attention to issues on immunization on behalf of us all and all of the committed people at PHAC and its predecessors who have supported NACI. It is a committee of which PHAC and indeed Canada can be truly proud.

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