July 7, 2016 • Volume 42-7

CCDR

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Public Health Agency of Canada
Agence de la santé publique du Canada

Canada

CCDR
CANADA COMMUNICABLE DISEASE REPORT

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.

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ISSN 1481-8531 Pub.150005

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CAN WE STOP MEASLES?

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Measles surveillance in Canada: 2015

Sherrard L[1*], Hiebert J[2], Cunliffe J[1], Mendoza L[2], Cutler J[1]

Abstract

Background: Measles has been eliminated in Canada since 1998. Every year, the Public Health Agency of Canada presents epidemiologic evidence to the Pan American Health Organization (PAHO) to verify that measles elimination continues in Canada.

Objective: To describe measles activity in Canada for 2015 as updated evidence for continued measles elimination status.

Methods: Measles surveillance data were captured by the Canadian Measles and Rubella Surveillance System (CMRSS) and the Measles and Rubella Surveillance (MARS) pilot project and assessed for distribution by demographics and risk factors. Outbreak characteristics were summarized and genotypic and phylogenetic analyses were conducted and described. Surveillance data for 2015 were evaluated against PAHO's essential criteria for measles elimination status.

Results: In 2015, the incidence of measles in Canada was 5.5 cases per 1,000,000 population, with 196 cases across four provinces. The majority of cases (87.2%, n=171) were not immunized and both age-specific incidence rates and case counts were highest among those aged 10 to 14 years (29.5 cases per 1,000,000 population, n=55). This was due in large part to a sizeable outbreak in a non-immunizing religious community. Overall, 10.7% (n=21) of cases were hospitalized. Genotype information was available for 100% of measles events (4/4 outbreaks and 6/6 sporadic cases). Canada met or partially met most of PAHO's criteria for verification of measles elimination.

Conclusion: Although importations and areas of low immunization coverage continue to challenge Canada's elimination status, surveillance data for 2015 provides strong evidence that measles elimination has been maintained.

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Suggested citation: Sherrard L, Hiebert J, Cunliffe J, Mendoza L, Cutler J. Measles surveillance in Canada: 2015. Can Comm Dis Rep 2016;42:139-45.

Introduction

Measles is one of the most infectious diseases known. Before vaccines against measles became widely available, the disease was a significant cause of death and disability worldwide, leading to an estimated 2.6 million deaths every year (1).

In Canada, measles has been a nationally notifiable disease since 1924, except between 1959 and 1968. Enhanced, case-based surveillance of measles is coordinated by the Centre for Immunization and Respiratory Infectious Diseases and the National Microbiology Laboratory (NML) at the Public Health Agency of Canada, through the Canadian Measles and Rubella surveillance system (CMRSS) and the Measles and Rubella Surveillance (MARS) pilot project. Enhanced surveillance of measles is necessary to provide sufficient evidence for measles elimination.

The elimination of measles is defined as the absence of endemic measles transmission in a defined geographic area for 12 months or more, in the presence of a well-performing surveillance system (2). The elimination of measles in Canada has been described as an important and attainable public health objective since at least 1980 (3). During the 1992 Consensus Conference on Measles, Canada set the goal of achieving measles elimination by 2005 (4). This was revised at the 1994 XXIV Pan American Sanitary Conference, where Canada and other member states agreed to eliminate measles in the Americas by 2000 (5). Following the implementation of a two-dose routine immunization program against measles, the last endemic case in Canada was reported in 1997 and measles elimination status was achieved one year later (6).

Despite this success, Canada's elimination status continues to be challenged by importations of measles from other countries, where the disease remains endemic. In order to verify measles elimination status on an ongoing basis, Canada submits surveillance data to the Pan American Health Organization (PAHO). The objective of this report is to provide an epidemiologic summary of measles activity reported in Canada for the 2015 epidemiologic year.

Methods

Surveillance data: On a weekly basis, measles cases meeting the national case definition (7) were reported by provinces and territories to PHAC via CMRSS or MARS (n=10 and 3, provinces and territories respectively), including zero-reporting. Non-nominal, non-identifying case data were extracted and submitted to PAHO. Confirmed measles cases with rash onset during the 2015 epidemiologic year (January 4, 2015 to January 2, 2016) were included in this report.

Genotyping: All measles virus genotyping was performed at PHAC's NML. The World Health Organization (WHO) standardized genotyping: sequencing of 450 nucleotides of the nucleoprotein (N) gene (the N-450), with the addition of the full length haemagglutinin (H) gene (8) was attempted on all reverse transcription-polymerase chain reaction (RT-PCR) confirmed measles cases. The clinical specimens (respiratory and/or urine) were referred to the NML by provincial laboratories and were RT-PCR-confirmed in the provincial laboratories or at the NML. Measles N-450 and H gene sequences were aligned with WHO genotype reference sequences (9) and maximum parsimony phylogenetic trees were generated using MEGA6 software (10). Genotypes were assigned by maximum homology of the N-450 sequences to the WHO genotype reference sequences (9). Sequences were also deposited in the WHO measles nucleotide surveillance database (MeaNS, http://www.who-measles.org) and compared to so called "named strains" as well as sequences deposited by other members of the global measles laboratory network (9,11).

Data management and validation: Measles surveillance data were managed using Microsoft Access 2010. A data validation process was conducted in March 2016, with the four provinces that reported measles cases in 2015. This included querying for blank fields, identifying illogical field entries and confirming values with reporting jurisdictions.

Analysis: SAS Enterprise Guide 5.1 (12) was used to perform descriptive epidemiologic analyses, for categorical variables (counts, proportions) and continuous values (medians, ranges). Incidence rates were calculated using Statistics Canada July 1, 2015 population estimates. The distribution of measles cases by demographics (e.g., age, gender, location), risk characteristics (e.g., immunization status, hospitalization, source of exposure) and genotype were assessed. Outbreak characteristics were summarized and surveillance data were evaluated against the essential criteria for the maintenance of measles elimination status, as described by PAHO (13).

Immunization status was defined in accordance with the routine, publicly-funded immunization schedule (14). Cases that were age-ineligible for routine immunization (i.e., aged less than one year or born before 1970) were classified as up-to-date, regardless of reported status. Those born after 1970 and aged seven years or more were defined as up-to-date with two doses. For those aged one to six years, either one or two doses were defined as up-to-date, depending on the recommended schedule in the reporting jurisdiction.

This routine public health surveillance activity was exempt from research ethics board approval.

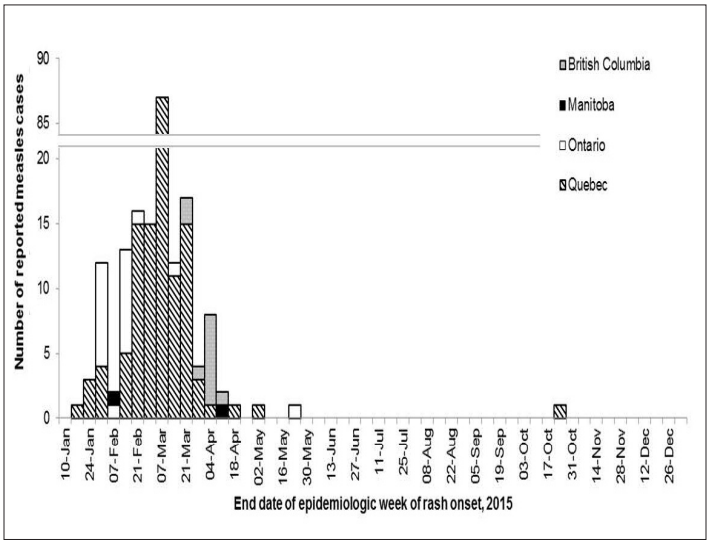
Results

Overview

In 2015, the incidence of measles in Canada was 5.5 cases per 1,000,000 population, with a total of 196 reported cases. These data include one case of measles in an international traveller, who was not reflected in the denominator. All cases were either laboratory-confirmed (29.1%, n=57) or epidemiologically linked to a laboratory-confirmed case (70.9%, n=139).

The majority of cases (99.5%, n=195) were reported between epidemiologic weeks 1 and 20, ending January 10 and May 23, 2015, respectively. A maximum of 87 (44.4%) cases were reported during a single week, occurring during an outbreak in Quebec (week 9, ending March 7) (**Figure 1**).

Figure 1: Number of reported measles cases, by epidemiologic week of rash onset and reporting province or territory, Canada, 2015



Age, gender and location

Information on age, gender and reporting province or territory was available for every case reported in 2015. Cases ranged in age from one month to 55 years, with a median age of 13.9 years. The most frequently reported age group was 10 to 14 years (28.1%, n=55), followed by those aged 15 to 19 years (19.9%, n= 39) and five to nine years (17.9%, n=35). Incidence rates were also highest for these groups, at 29.5, 18.6 and 17.9 cases per 1,000,000 population respectively (**Table 1**). There were no cases reported among those aged 60 years and older. Approximately half of the reported cases (55.1%, n=108) were male. Four Canadian provinces reported measles cases in 2015: British Columbia, Manitoba, Ontario and Quebec. Incidence was highest in Quebec, followed by British Columbia, Manitoba and Ontario (19.7, 2.3, 1.5 and 1.5 cases per 1,000,000 population respectively).

Table 1: Confirmed measles cases and incidence rates (per 1,000,000 population) by age group, gender and reporting province or territory[1], Canada, 2015

Age group	M	F	BC	MB	ON	QC	CA	Overall incidence rate
<1 year	2	3	0	1	0	4	5	12.9
1 to 4 years	12	6	0	0	4	14	18	11.6
5 to 9 years	22	13	0	0	0	35	35	17.9
10 to 14 years	30	25	1	0	3	51	55	29.5
15 to 19 years	19	20	7	0	1	31	39	18.6
20 to 24 years	6	9	0	0	4	11	14	5.7
25 to 29 years	3	5	0	0	0	8	8	3.2
30 to 39 years	10	4	2	1	5	6	14	2.9
40 to 59 years	4	3	1[2]	0	3	3	7	0.7
60 years or more	0	0	0	0	0	0	0	0.0
Total	108	88	11	2	20	163	196	5.5
Incidence rate:	6.1	4.9	2.3	1.5	1.5	19.7	5.5	

Abbreviations: M, Male; F, Female; BC, British Columbia; MB, Manitoba; ON, Ontario; QC, Quebec; CA, Canada

[1] Only provinces and territories with confirmed cases were included. No cases of measles were reported in Alberta, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Prince Edward Island, Saskatchewan and Yukon.
[2] This count reflects one case of measles in a visitor to BC who was exposed on a flight to Canada and experienced the course of disease in Canada. This case is not reflected in BC's provincial case count.

Immunization

During 2015, the vast majority of cases (87.8%, n=172) were not up-to-date for age with measles-containing vaccine at the time of infection (**Table 2**). Similarly, the majority of cases (86.7%, n=170) had never received any documented doses of measles-containing vaccine. Nine cases of measles (five infants aged less than one year, four adults born before 1970) were age-ineligible for measles-containing vaccine, according to the current recommendations for routine immunization by the National Advisory Committee on Immunization (NACI). These cases were categorized as up-to-date, regardless of reported immunization history. Thus of the 16 cases described as up-to-date, only seven cases (or 3.6% of all reported cases) had previously received measles-containing vaccine.

None of the reported cases were born before 1957, the cut off used in some other countries such as the United States (15). One case in 2015 was indicated as having received three doses of measles-containing vaccine. However, the third dose was administered within one week of rash onset and presumably occurred after exposure to measles. Immunization status could not be assessed for 4.1% (n=8) of cases due to missing information.

Table 2: Immunization status of confirmed measles cases, by age group and completeness[1], Canada, 2015

Age group	Not Immunized		Immunized		Unknown	
	Not up-to-date	Up-to-date	Not up-to-date	Up-to-date	Unable to assess	Up-to-date
<1 year	0	5	0	0	0	0
1 to 4 years	17	0	0	1	0	0
5 to 9 years	35	0	0	0	0	0
10 to 14 years	51	0	4	0	0	0
15 to 19 years	33	0	1	4	1	0
20 to 24 years	14	0	0	1	0	0
25 to 29 years	8	0	0	0	0	0
30 to 39 years	5	0	3	1	5	0
40 to 59 years	0	2	1	0	2	2
60 years or more	0	0	0	0	0	0
TOTAL	163	7	9	7	8	2

[1] The current recommendation for routine immunization by NACI is that the first dose of measles-containing vaccine should be given at 12 to 15 months of age, with the second dose at 18 months, or any time thereafter prior to school entry (16). Age groups where there is no existing recommendation are considered up-to-date for age having received no doses of measles-containing vaccine. This includes infants less than one year of age, who are too young to receive measles-containing vaccine as part of the routine schedule. There is also no recommendation for most adults born before 1970, as they are generally presumed to be immune to measles through prior infection.

Hospitalization

Overall in 2015, hospitalization was indicated for 10.7% (n=21) of cases reported (**Table 3**). The highest number of hospitalizations occurred among those aged 20 to 24 years (n=5, 33.3%). In contrast, the highest proportion of hospitalizations occurred among those aged less than one year, where 60% (n=3) of cases were hospitalized. Almost all hospitalized cases (95.2%, n=20) reported no history of immunization, as most hospitalizations (76.2%, n=16) were linked to an outbreak in Quebec, in a non-immunizing religious community. Importantly, however, it was unknown whether 2.6% (n=5) of cases were hospitalized or not.

Molecular epidemiology

In 2015, 28.6% (n=56) of reported measles cases had specimens available for genotyping. However, genotypes were determined for all unique measles events which include outbreaks (n=4) and sporadic cases without secondary transmission (n=6).

The genotypes detected were B3 (n=23), D4 (n=17), H1 (n=11) and D8 (n=5) (**Figure 2**).

Table 3: Hospitalization status of confirmed measles cases by age group, Canada, 2015

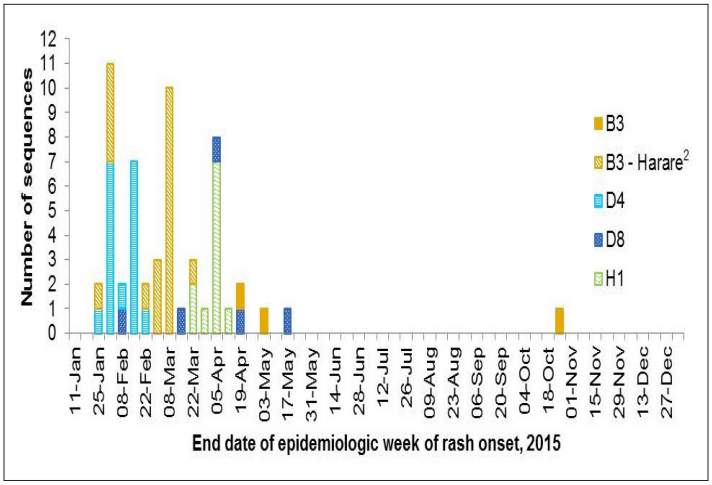
		Not hospitalized		Hospitalized		Unknown	
Age group	Total	N	%	N	%	N	%
<1 year	5	2	40.0%	3	60.0%	0	0.0%
1 to 4 years	18	18	100.0%	0	0.0%	0	0.0%
5 to 9 years	35	33	94.3%	2	5.7%	0	0.0%
10 to 14 years	55	53	96.4%	1	1.8%	1	1.8%
15 to 19 years	39	32	82.1%	3	7.7%	4	10.3%
20 to 24 years	15	10	66.7%	5	33.3%	0	0.0%
25 to 29 years	8	6	75.0%	2	25.0%	0	0.0%
30 to 39 years	14	11	78.6%	3	21.4%	0	0.0%
40 to 59 years	7	5	71.4%	2	28.6%	0	0.0%
60 years or more	0	0	-	0	-	0	-
Total	196	170	86.7%	21	10.7%	5	2.6%

Abbreviation: N, number

Nearly all of the genotype B3 viruses identified were identical to the MVi/Harare.ZWE/38.09 (GenBank JF973033) named strain (n=20) (**Figure 3**). All of these B3-Harare viruses were detected in measles cases associated with the Quebec outbreak (**Appendix**), which was linked to a large B3-Harare outbreak in the USA (17). Three additional cases had genotype B3 viruses identified. While all three were sporadic, travel-related cases (South Africa, Ethiopia and Tunisia), the two cases with travel history to the African region had identical N-450 sequences (matching the MVs/Kansas.USA/1.12, GenBank JX315576 named strain) (Figure 3). However these measles viruses were distinguishable by H gene sequencing (data not shown).

All genotype D4 viruses identified (n=17) had identical N-450 sequences (Figure 3), which were not identical to any named strain. All were associated with an outbreak in Ontario of unknown origin and for which epidemiological links could not be established between many of the cases (Appendix). Extended sequencing, including the H gene and the MF-NCR

Figure 2: Distribution of measles genotypes detected in 2015 (n=56) **by week of rash onset**[1]



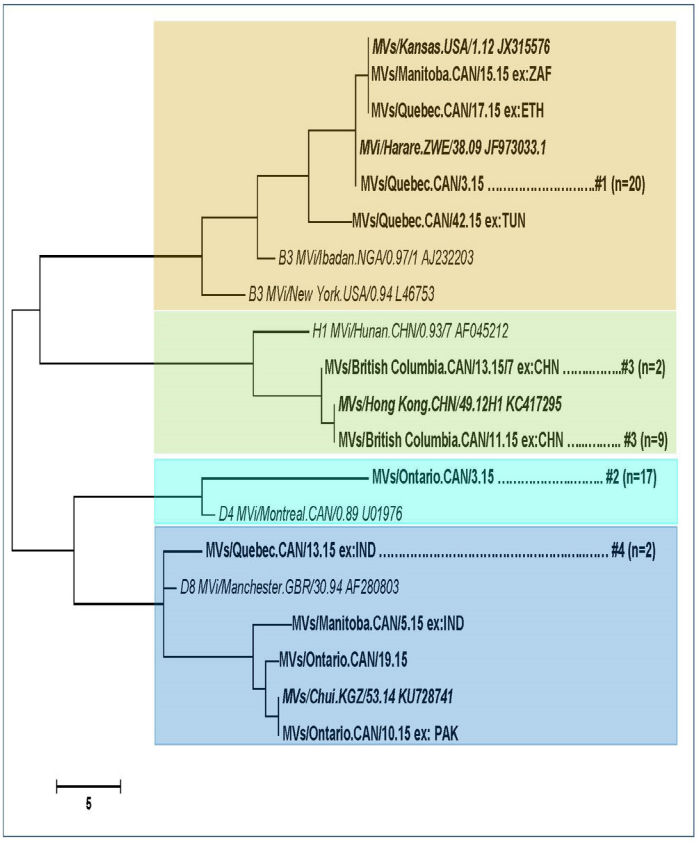
[1] Epidemiological weeks are assigned in accordance with WHO guidelines (9) with week one beginning on the first Monday of the year.
[2] Genotype B3 sequences identical to sequence variant MVi/Harare.ZWE/38.09 (GenBank accession number JF973033).

(the non-coding region between the matrix and fusion genes) was performed to better characterize this outbreak. A detailed description is forthcoming.

Genotype H1 viruses were identified in 11 measles cases, all of which had either travel history to China, where genotype H1 is endemic (11) or were linked to cases with travel to China (Appendix). Nine of the viruses were identical to the MVs/Hong Kong.CHN/49.12 named strain (GenBank KC417295) while the remaining two viruses differed by a single nucleotide but were identical to each other (Figure 3).

The remaining measles cases that were genotyped were all identified to be genotype D8 (n=5), four of which did not match any named strains (Figure 3). Two had identical N-450 sequences and were both from the same outbreak associated with travel to India (Appendix). The remaining three cases with genotype D8 viruses were sporadic cases and all had unique N-450 sequences. Two cases had a history of travel, to either India, where genotype D8 is endemic (11) or neighbouring Pakistan, while the third case was of unknown source. Globally, measles genotype D8 was the second most frequently reported genotype in 2015, based on submissions to the WHO measles nucleotide surveillance database (MeaNS) (18).

Figure 3: Phylogenetic tree of measles N-450 sequences detected in Canada in 2015 (n=56)



NOTE: Relevant WHO reference sequences (9) are shown in bold, italic font. Named strains, assigned in the WHO measles sequence database (MeaNS) (9), matching any Canadian sequences are shown in italics. Canadian sequences are shown in regular font and are identified by their WHO name which indicates province and week of rash onset. Cases with travel history are identified with "ex:<3 letter country code>." Outbreaks are represented by a single sequence and are tagged with their outbreak number (Appendix). The number of identical sequences identified in the outbreak is provided in brackets. The remaining sequences (without an outbreak number listed) are from sporadic cases (n=6). The scale bar indicates number of nucleotide differences between branches.

Canadian measles in the global context

Importations accounted for 4.6% (n=9) of cases in 2015. All imported cases were either adults (aged between 16 and 42 years) who were incompletely immunized for age (n=7), or children too young to be immunized according to the routine schedule (n=2). However, as giving measles-containing vaccine can be considered as early as six months of age when travelling outside of North America (16), these two children also represent missed opportunities for immunization.

Imported cases were exposed to measles during travel to most of the WHO regions: South-East Asian (n=2), Western Pacific (n=2), Eastern Mediterranean (n=2), African (n=2) and the Americas (n=1). No importations were reported from the European region. Two importations each were reported from both China and India. One importation per country was reported from Ethiopia, Pakistan, South Africa, Tunisia and the United States.

A total of four outbreaks were reported in 2015, involving 190 cases. The source of exposure for the index case was identified for three of four outbreaks, involving travel to the United States, China and India. The largest outbreak resulted from a single importation from the United States, totalling 159 cases (Appendix). Although the number of cases reported for each outbreak ranged from two to 159 (median: 15), outbreak duration was generally short, with a median of three generations (range: 2 to 6). Genotypes B3, D4, H1 and D8 (n=1, each) were identified. A source of exposure was not identified for 14 cases in 2015, all of which were reported by Ontario. Ten of these cases were described in detail elsewhere (19). Only one of these cases resulted in secondary spread (Appendix).

Maintenance of measles elimination

There are four criteria and indicators set out by PAHO, for the ongoing verification of measles elimination (**Table 4**). Canada met or partially met three of four indicators.

Discussion

There were 196 confirmed cases of measles reported in Canada in 2015 originating from all WHO regions except the European Region. The majority of these cases arose from a single importation associated with a popular tourist destination in the United States (17). This is the third highest total since elimination was achieved in 1998, following 2011 (n=725) and 2014 (n=418). Similar to 2014, most cases (81.1%, n=159) were in a non-immunizing religious community. Burden was highest among children, especially those aged five to 19 years, but also those aged five years or less. Most hospitalized cases were unimmunized. At least one case from every measles event (i.e., four outbreaks and six sporadic cases) was genotyped, with four genotypes were reported in 2015—B3, D4, H1 and D8. Every measles event was separate, as they all had a viral strain distinct from the others. After each event concluded, none of those viral strains were observed again in 2015. The presence of cases with unknown source suggests that not all cases of measles have been reported, however these were relatively few. All outbreaks were well contained given the median outbreak duration was three generations.

Table 4: Pan American Health Organization essential criteria for the verification of measles elimination

Criterion	Indicator	Description
Verify the interruption of endemic measles cases for a period of at least three years from the last known endemic case, in the presence of high-quality surveillance.	Zero cases of endemic transmission.	Criterion met. Canada achieved measles elimination status in 1998. Since then, molecular and epidemiological data continue to demonstrate that no viral strain has circulated for a period of one year or more in Canada (6,20,21,22).
Maintain high-quality surveillance sensitive enough to detect imported and import-related cases.	> 2 suspect cases per 100,000 population adequately investigated.	Criterion partially met. As only confirmed cases of measles are nationally notifiable in Canada, this indicator cannot be directly assessed. However, using data obtained by the Measles and Rubella Surveillance (MARS) pilot project, the national rate of measles-like illness investigation was estimated to be between 12 per 100,000 population (2006, non-outbreak year) and 19 per 100,000 population (2011, outbreak year) (23).
Verify the absence of endemic measles virus strains through viral surveillance.	Measles genotype assessed in 80% of outbreaks.	Criterion met. Genotype information was available for 100% of outbreaks reported in 2015.
Verify adequate immunization in the population.	95% of population cohorts aged 1 to 40 years have received a measles-containing vaccine.	Criterion not met. As a national immunization registry does not currently exist in Canada, this criterion cannot be directly assessed. However, the 2013 Childhood National Immunization Coverage survey estimated first dose measles-containing vaccine coverage among two year olds to be 89.6% and second dose measles-containing vaccine coverage among seven year olds to be 85.5% (24). This estimate reflects a change in methodology, as opposed to a decline in coverage, from previous years (e.g., 95.2% and 94.9%, 2011 [25]). Note that these are average values; coverage is heterogeneous and will be higher in some areas and lower in others.

For three of four criteria, Canada continues to meet or partially meet PAHO essential indicators for maintenance of measles elimination. One criterion previously met was not met in 2015: coverage with measles-containing vaccine. This likely reflects a change in methodology for estimating coverage, as opposed to a decrease in actual coverage. Notably, the 2016 federal budget announced $25 million over five years in new investments that will support improving immunization coverage in Canada (26).

Globally, measles elimination and eradication continues to be a public health priority, with all WHO regions striving to achieve elimination goals. Three targets for measles eradication were also endorsed at the World Health Assembly in 2010, aimed at increasing immunization coverage with measles-containing vaccine and reducing in morbidity and mortality worldwide by 2015 (27). Nevertheless there is still room for improvement, as both the global targets and the elimination goals were not achieved by 2015 (28).

Limitations

There are a number of limitations to these data that merit consideration. The indicators of a well-performing surveillance system established by PAHO are based on investigation of measles-like illness (i.e., suspected cases), whereas only confirmed cases are nationally notifiable in Canada. As such, these data can only indirectly address the PAHO criteria. In addition, information on mortality and detailed information on morbidity (e.g., length of hospitalization, sequelae) are not currently captured by CMRSS or MARS, limiting the ability to completely describe the burden of illness due to measles in Canada. Finally, as immunization status is a derived variable that is affected by differences in schedule across jurisdictions, it may be discriminating between individuals on a factor that does not completely describe their risk of being infected with measles.

Conclusion

Both in Canada and abroad, maintaining high immunization coverage with measles-containing vaccine remains a significant public health effort, as well as an essential component of a strategy for achieving and maintaining measles elimination. Although importations and areas of low immunization coverage continue to challenge Canada's elimination status, surveillance data provided strong evidence that measles elimination has been maintained.

Acknowledgements

The authors gratefully acknowledge the continued cooperation and efforts of provincial and territorial surveillance and laboratory partners for providing and validating data captured by CMRSS and MARS, for referring specimens for molecular surveillance (genotyping) and for their review of the report content.

The authors are also grateful to Dr. Alberto Severini, Jennifer Beirnes and Lisa Podhorodecki and NML staff in the Genomics Core Services for their contribution in generating the molecular data.

Conflict of interest

No conflict of interest to declare.

Funding

This work was supported by the Public Health Agency of Canada.

Appendix: Summary of measles outbreaks in Canada, ordered by earliest date of rash onset, 2015

No.	Province/ Territory	n	Days (Generations)	Genotype	Description
1	QC	159	72 (6)	B3– Harare[1]	The index case in this outbreak was exposed to measles during travel to a popular theme park in California, USA. Subsequent spread occurred in the non-immunizing religious community to which the index case belonged. Very few cases were reported outside of the religious community.
2	ON	18	23 (3)	D4	The primary case in this outbreak was not identified. Thirteen initial cases across four health units were identified. These cases had no epidemiologic link to each other, or to a known case. However, based on dates of rash onset and genotype results, it is presumed that they shared a common source of exposure. Only one of the cases resulted in secondary spread (to five household contacts).
3	BC	11	19 (2)	H1	Two cases of measles were reported among Canadians who were exposed during travel to China. These cases were communicable during the return flight to Canada. One measles case exposed during the flight was a visitor to BC and is not included in BC's provincial case count. Subsequent spread occurred among other passengers on the flight, or individuals who were epidemiologically linked to the flight.
4	QC	2	14 (2)	D8	The index case had a history of travel to India. One secondary case was reported, who was exposed to measles in a health-care setting.

Abbreviations: No., number; n, number of measle cases

[1] Identical to the MVi/Harare.ZWE/38.09 (GenBank JF973033) named strain.

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Exploring gaps in surveillance of a small measles outbreak in Toronto, Canada

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Abstract

In early 2015, an outbreak of 10 confirmed measles cases occurred in Toronto, Ontario. As part of the outbreak response, the Toronto Public Health staff conducted both traditional and supplementary case investigation activities. Despite this extensive effort, and unlike many previous measles outbreaks in Canada, neither the source case nor any confirmed epidemiologic links between cases were identified. The outbreak investigation brought to light potential gaps in the current measles surveillance and suggested approaches to future investigations: routine use of social media and other time-stamped resources to enhance case investigation; early and repeated targeted communication with primary care partners to improve case detection; and continued efforts to increase and maintain sufficient immunization coverage to interrupt transmission.

Suggested citation: Gournis E, Shane A, Shane E, Arthur A, Berger L. Exploring gaps in surveillance of a small measles outbreak in Toronto, Canada. Can Comm Dis Rep 2016;42:146-8.

Introduction

On January 28, 2015, Toronto Public Health was notified of a laboratory-confirmed measles case. Reports of nine additional confirmed cases soon followed. Molecular evidence supported the hypothesis that all the cases resulted from a single importation, but this could not be confirmed through epidemiologic evidence.

This article explores the gaps in measles detection and investigation identified while investigating this outbreak, describes the supplementary epidemiologic activities used to address these gaps, and considers the implications for future outbreak response activities.

The outbreak

A detailed description of the epidemiology and public health response to this outbreak will be provided elsewhere (*S. Thomas et al. Measles outbreak with unique genotyping*). To summarize, 10 confirmed and genotypically similar measles cases were reported to Toronto Public Health between January 28, 2015, and February 17, 2015. An incident management system was activated to manage and coordinate the outbreak response activities. All cases and contacts were investigated and managed as per *Ontario's Infectious Diseases Protocol* (1). This included follow-up of 1,548 contacts and hosting of 10 post-exposure prophylaxis clinics. No secondary cases were detected among contacts. Routine case investigation information did not reveal the source of the measles outbreak.

Supplementary epidemiologic investigations

As it became apparent that epidemiologic links between the cases were missing, Toronto Public Health epidemiologists conducted supplementary activities during the public health investigation. The purpose of these activities was to increase the completeness of the information about possible exposure provided by the cases in order to better understand and characterize measles transmission within the community. First, a subset of cases or their guardians were asked to use any social media information (e.g., Instagram posts) and online banking records from their respective accounts to help recall activities during the potential acquisition and transmission periods. Each supplementary phone interview took an additional two to three hours per case (including the time required to validate addresses). This led to a number of additional locations of interest beyond those ascertained in the initial interviews. In addition, the investigation used the social network visualization tool Pajek (2) to identify overlapping exposures. As the exposure list expanded and manual review became time-consuming and onerous, including social network visualization in the routine reporting cycle led to a quicker and more systematic method to identify potential epidemiologic links.

Gaps in detection

Despite using traditional and supplementary case investigation measures, there remained insufficient evidence to confirm the source of the outbreak or any epidemiologic links between cases. Given that the National Microbiology Laboratory characterized the cases as genotypically similar and likely due to a single importation event (*Personal communication, Alberto Severini, National Microbiology Laboratory, March 31, 2016*), a gap in case detection and investigation was evident. While missing the source case of an outbreak is

not uncommon in Canada, a small and contained community outbreak of measles with no identified epidemiologic links between cases is unusual (3).

Several hypotheses could explain these findings. It is possible that people with measles never presented to the health care system. Alternatively, they may have presented but were not identified as suspect measles cases and not tested appropriately. In both these scenarios people may have experienced attenuated, or subclinical, symptoms, possibly as a result of secondary vaccine failure (4), and did not meet the classical clinical or laboratory case definition for measles. It is also possible that the traditional and supplementary epidemiologic case investigation processes and tools used in this investigation were insufficient to identify the common exposure(s) given the high transmissibility of the virus, the mobility of the population and the urban environment in which the cases resided. The social media-facilitated reinterviews were only conducted using a subset of cases. Had these methods been applied to all 10 cases additional links may have been found.

Discussion

Despite routine and enhanced investigations of an outbreak of measles limited to 10 laboratory-confirmed cases in Toronto, Ontario, neither the source nor any confirmed epidemiologic links were identified. It is important to consider the implications of these findings for measles surveillance and Canada's elimination efforts.

In order to sufficiently document Canada's measles elimination status, it is essential to minimize the number of sporadic or unknown source cases and ensure thorough investigation and understanding of transmission events. While it has been suggested that subclinical cases may be less infectious than clinical cases, detection of all cases remains important in order to understand outbreak and transmission dynamics (5).

Although Canada experiences few and small outbreaks of measles, the resources required to manage these outbreaks are considerable, specifically in terms of follow-up of persons under investigation, suspect cases and contact management in the context of high vaccine coverage (6). For example, after the outbreak was declared, Toronto Public Health received many reports of persons under investigation that did not meet the outbreak case definition yet required substantial public health and laboratory resources to rule out. Finding a balance between an acceptable level of surveillance sensitivity required to characterize and interrupt transmission and the appropriate allocation of resources required to maintain that level of sensitivity is a key challenge, especially in areas with high and homogeneous immunization coverage.

The gaps identified in this summary suggest there are important opportunities to improve case identification and epidemiologic investigation of measles. The resources for any additional activities need to be weighed against what is already required to meet the current measles outbreak investigation standards.

To improve the ability to accurately describe the epidemiology of measles among confirmed cases, continued emphasis on the collection of comprehensive exposure (both acquisition and transmission) information during case interviews is needed. This could include routinely asking cases to review time–stamped resources (e.g., bank and credit card statements or social media sites) to help remind them of their activities and locations during their exposure and communicability periods and using social networking visualization to deal with the complexity of this added information.

To address the potential gap in sensitivity identified through this outbreak investigation, early, repeated and active communication with primary care and emergency department networks during measles outbreaks may help reinforce the key signs and symptoms that trigger appropriate laboratory testing procedures. This was done during the 2015 outbreak via alerts and communications with primary care providers. If fewer reports of persons under investigation are received because physicians know whom to report and test, public health resources could be reallocated to additional epidemiologic activities. To improve detection of measles cases during non-outbreak periods (i.e., in order to detect source cases), it is important to remind health care providers that symptoms may be attenuated in previously immunized people and to consider travel history from measles-endemic areas to inform the differential diagnosis.

Continued efforts to increase immunization coverage and access to electronic records confirming immunization status may allow public health to both rely on herd immunity to interrupt measles transmission following an importation and shift the balance of public health resources from contact management to persons under investigation as well as suspect and confirmed cases.

Conclusion

Despite routine and supplementary case investigation activities, Toronto Public Health could not confirm any epidemiologic links between the 10 outbreak cases. The gaps in case detection and investigation revealed by this unusual outbreak can inform future outbreak response activities.

Acknowledgements

We would like to acknowledge all the staff at Toronto Public Health who contributed to the investigation and management of this outbreak, the team at Public Health Ontario who helped coordinate the provincial investigation and response, and the staff at the National Microbiology Laboratory for their work and information on the phylogenetic characterization of the cases.

Conflict of interest

None.

Funding

None.

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Summary of the National Advisory Committee on Immunization's Updated Recommendations on Human Papillomavirus (HPV) vaccines: Nine-valent HPV vaccine and clarification of minimum intervals between doses in the HPV immunization schedule

Tunis MC[1], Deeks SL[2,3], on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Human papillomavirus (HPV) infections are the most common sexually transmitted infections, and in the absence of vaccination it is estimated that 75 percent of sexually active Canadians will have an HPV infection at some point in their lives. Quadrivalent (HPV4) and bivalent (HPV2) vaccines have been authorized for use in Canada since 2007 and 2010, respectively. Canada's National Advisory Committee on Immunization (NACI) has previously recommended HPV4 vaccination in males and females according to a three-dose (0, 2, 6 months) or a two-dose (0, 6 months) immunization schedule, or HPV2 vaccination for females according to a three-dose (0, 1, 6 months) or a two-dose (0, 6 months) immunization schedule, depending on the age and health status of the recipient. In February 2015, a nine-valent (HPV9) vaccine (Gardasil®9, Merck Canada, Inc.) was authorized for use in Canada for the prevention of HPV types 6-, 11-, 16-, 18-, 31-, 33-, 45-, 52- and 58-related cancers and anogenital warts (AGW) in females aged 9 to 45 years and males aged 9 to 26 years.

Objectives: To summarize evidence on the new HPV9 vaccine and make recommendations for its use in Canada, to review epidemiological data on the relative contribution to disease outcomes of the 5 additional genotypes covered in the HPV9 vaccine, and to clarify acceptable minimum intervals between vaccine doses in either a 2-dose or 3-dose HPV immunization schedule.

Methods: The NACI HPV working group performed literature reviews on the topics of HPV vaccine minimum dose intervals, and the HPV9 vaccine. Vaccine manufacturers provided additional data for review. All evidence was reviewed, rated, and a representative dataset for each trial was reported in evidence tables. A knowledge synthesis was performed, and NACI approved specific evidence-based recommendations, elucidating the rationale and relevant considerations.

Results: At the time of the review, only one published peer-reviewed study of HPV9 vaccine was available for inclusion, but information from additional unpublished studies in the form of presentations, posters, and abstracts were shared by the vaccine manufacturer to be appraised.

Based on the evidence available to date, the HPV9 vaccine is recommended on a three-dose schedule for females aged 9 to 26 years; females aged over 26 years who have not been vaccinated previously or who have not completed the vaccination series; and males aged 9 to 26 years. There is insufficient evidence at this time to recommend a two-dose immunization schedule with HPV9 vaccine, but a clinical trial to assess alternate dosing schedules for HPV9 vaccine is currently underway. The efficacy of HPV9 vaccine in preventing infection and disease related to HPV types 31, 33, 45, 52 and 58 in individuals previously immunized with HPV4 vaccine has not been assessed. In Canada, immunization against HPV types 16 and 18 with HPV2, HPV4 or HPV9 vaccine can prevent approximately 70% of anogenital cancers and 60% of high-risk precancerous cervical lesions. Immunization with either HPV4 or HPV9 vaccine can prevent approximately 90% of AGWs (HPV types 6 and 11). Immunization with HPV9 vaccine can prevent up to an additional 14% of anogenital cancers and up to 30% of high-risk precancerous cervical lesions caused by the additional five HPV types (31, 33, 45, 52 and 58) against which the vaccine protects. The disease burden associated with the five additional genotypes contained in HPV9 vaccine is not equally shared between the sexes, with the additional benefit primarily observed among females.

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In terms of the HPV immunization schedule, there is a paucity of published evidence supporting shortened or flexible minimum intervals for HPV vaccines, compared to ample evidence endorsing the recommended schedules as well as evidence supporting delays in the receipt of booster doses. Assumptions about the immunogenicity and efficacy of shortened 'flexibility range' minimum dose intervals rely heavily on the manufacturer's unpublished data on file and their Health Canada-approved recommendations included in the product monographs. The NACI recommendations and evidence grades based on these results are included below.

Conclusions: In addition to the HPV 6, 11, 16, and 18 strains that can be covered by other HPV vaccines, the HPV9 vaccine is expected to provide further protection by preventing infection and disease related to HPV types 31, 33, 45, 52 and 58. Protecting against these additional strains may prevent up to an additional 14% of anogenital cancers and up to 30% of high-risk precancerous cervical lesions in Canada. Efforts should be made to administer HPV vaccines at the recommended intervals. When an abbreviated schedule is required, minimum intervals between HPV vaccine doses should be met including a minimum interval of 24 weeks between the first and last dose in either a 2-dose or 3-dose schedule. Please note that NACI is currently reviewing evidence for a 2-dose HPV9 vaccine immunization schedule.

Suggested citation: Tunis MC, Deeks SL, on behalf of the National Advisory Committee on Immunization (NACI). Summary of the National Advisory Committee on Immunization's Updated Recommendations on Human Papillomavirus (HPV) vaccines: Nine-valent HPV vaccine and clarification of minimum intervals between doses in the HPV immunization schedule. Can Comm Dis Rep 2016;42:149-51.

Introduction

The review of the literature on human papillomavirus (HPV) vaccines: Nine-valent HPV vaccine and the National Advisory Committee on Immunization's (NACI) current HPV vaccine recommendations are published in the full NACI statement (1) and the HPV chapter of the *Canadian Immunization Guide* (2).

Recommendation no.1

NACI concludes that any of the currently authorized HPV vaccines in Canada can be used according to the recommended HPV immunization schedules – NACI recommendation evidence grade A or B (Table 1).

HPV immunization may be completed with HPV2, HPV4 or HPV9 vaccines in females and HPV4 or HPV9 vaccines in males, according to the immunization schedules summarized in Table 1, below. Where possible, the same vaccine should be used to complete the series. If completion of the series with the same vaccine is not possible, the HPV2, HPV4 or HPV9 vaccine may be used to complete the series in females, and the HPV4 or HPV9 vaccine may be used to complete the series in males. The HPV9 vaccine among immunocompetent 9 to 26 years old is expected to provide similar protective efficacy against genotypes contained in the HPV4 vaccine. HPV2, HPV4 and HPV9 vaccines all protect against HPV types 16 and 18, which are responsible for approximately 70% of anogenital cancers. In addition, HPV9 vaccine protects against the additional five HPV types not contained in HPV4 vaccine (HPV 31, 33, 45, 52 and 58).

HPV9 protects against 5 additional HPV genotypes responsible for approximately 14% of anogenital cancers. HPV4 and HPV9 also protect against HPV genotypes 6 and 11, which cause over 90% of AGWs. At the population level, if all persons recommended for the vaccine receive it, and there is 100 % long-term efficacy, immunization with HPV9 vaccine in Canada can potentially prevent annually up to 320 additional cases of anogenital cancers (300 in females and 20 in males). Adverse events following immunization with HPV vaccines primarily include mild to moderate injection site-related pain, erythema and swelling. These local adverse events are more common in HPV9 vaccine recipients compared to recipients of the HPV4 vaccine.

NACI will reassess the grading of this recommendation as new evidence emerges.

Table 1: Recommended Immunization Schedule with Human Papillomavirus Vaccines

Recommended groups	Recommended immunization schedule	Vaccine(s) and NACI evidence grade
Healthy (immunocompetent, non-HIV infected) Females 9-14 years of age (and healthy females >15 years of age in whom the first dose was administered between 9-14 years of age)	2- or 3-dose schedule	HPV2 or HPV4 (Grade A)
	3-dose schedule	HPV9 (Grade B)
Healthy (immunocompetent, non-HIV infected) Females >15 years of age	3-dose schedule	HPV2 or HPV4 (Grade A) or HPV9 (Grade B)
Healthy (immunocompetent, non-HIV infected) Males 9-14 years of age (and healthy males >15 years of age in whom the first dose was administered between 9-14 years of age)	2- or 3-dose schedule	HPV4 (Grade B)
	3-dose schedule	HPV9 (Grade B)
Healthy (immunocompetent, non-HIV infected) Males >15 years of age	3-dose schedule	HPV4 or HPV9 (Grade B)
Immunocompromised individuals and immunocompetent HIV-infected individuals	3-dose schedule	HPV2, HPV4 or HPV9 in females; HPV4 or HPV9 in males Grade I

Abbreviations: HPV, human papillomavirus; HIV, human immunodeficiency virus

Recommendation no. 2

NACI concludes that there is insufficient evidence at this time to recommend a 2-dose immunization schedule with HPV9 vaccine – NACI Recommendation Evidence Grade I.

A phase III clinical trial to study the safety and immunogenicity of a 2-dose immunization schedule with HPV9 vaccine is currently under way. The goal of the 37-month study is to establish whether the investigational 2-dose regimens of 0, 6 months and 0, 12 months in boys and girls 9 to 14 years of age are safe and immunogenic, with an antibody response non-inferior to that observed in females 9 to 26 years of age who received the standard 3-dose regimen of the vaccine.

NACI will review and reassess this recommendation as new evidence emerges.

Recommendation no. 3

NACI concludes that there is insufficient evidence at this time to recommend, at a population level, the re-immunization with HPV9 vaccine of individuals who have completed an immunization series with another HPV vaccine - NACI Recommendation Evidence Grade I.

Unpublished data suggest that re-immunization with HPV9 vaccine after completion of a series with HPV4 produces lower immunogenicity to the five additional HPV genotypes (clinical significance unknown) and higher incidences of local injection site adverse events; efficacy has not been assessed.

While not recommended at a population level, individuals who have been vaccinated with HPV4 vaccine and who wish to take advantage of the additional protection provided by HPV9 vaccine may be vaccinated with HPV9 vaccine. There is insufficient evidence at this time to determine whether fewer than 3 doses of HPV9 vaccine conveys protection against the additional five HPV types in prior HPV4 vaccine recipients.

NACI will review and reassess this recommendation as new evidence emerges.

Recommendation no. 4

NACI concludes that there is good evidence that the minimum interval between the first and last doses in either a 2-dose or 3-dose HPV immunization schedule should be 24 weeks (6 months) – NACI Recommendation Evidence Grade A.

NACI recommends that, whenever possible, the recommended intervals between doses of HPV2 vaccine (0, 1, 6 months in a 3-dose schedule or 0 and 6 months in a 2-dose schedule), HPV4 vaccine (0, 2, 6 months in a 3-dose schedule or 0 and 6 or 12 months in a 2-dose schedule) and HPV9 vaccine (0, 2 and 6 months) should be respected. When an abbreviated schedule is unavoidable, the minimum intervals in a 3-dose schedule (as summarized in Table 1) between the first and second doses of HPV vaccine is 4 weeks (1 month), the minimum interval between the second and third doses of HPV vaccine is 12 weeks (3 months), and the minimum interval between the first and third doses is 24 weeks (6 months).The minimum interval between the first and second dose in a 2-dose schedule with either HPV2 or HPV4 is 24 weeks (6 months).

Conflict of interest

None.

Funding

The work of NACI is supported by the Public Health Agency of Canada.

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1. National Advisory Committee on Immunization's Updated Recommendations on Human Papillomavirus (HPV) Vaccines: 9-valent HPV vaccine and clarification of minimum intervals between doses in the HPV immunization schedule. http://www.healthycanadians.gc.ca/publications/healthy-living-vie-saine/human-papillomavirus-9-valent-vaccine-update-recommendation-mises-a-jour-recommandations-papillome-humain-vaccin-nonavalent/index-eng.php.
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Yellow Fever in Angola and the Democratic Republic of Congo

Source: Public Health Agency of Canada. Travel Health Notice. **Yellow Fever in Angola and the Democratic Republic of Congo.** June 15, 2016. http://www.phac-aspc.gc.ca/tmp-pmv/notices-avis/notices-avis-eng.php?id=162

Yellow fever is a serious and occasionally fatal disease. It is caused by a virus which is spread to humans by infected mosquitoes. Symptoms can include fever, chills, headache, muscle pain (mostly back pain), yellowing of the skin and eyes (jaundice), loss of appetite, nausea and vomiting. All unvaccinated travellers are at high risk if going to a destination where yellow fever occurs.

The Ministries of Health in Angola and Democratic Republic of Congo (DRC) are both reporting outbreaks of yellow fever. The outbreak in Angola was first reported in December 2015 where it began in an urban area (Luanda) and subsequently spread through the country. The majority of confirmed cases in DRC were travellers returning from Angola, however, several infections were locally acquired as well. Cases have also been reported in travellers returning to Kenya and China from Angola. The World Health Organization indicates that there is a risk for further spread of the disease because of the large international communities in Angola and the frequent travel with neighbouring and overseas countries.

People who have never been vaccinated against yellow fever should consider not travelling to Angola and the DRC. The Public Health Agency of Canada recommends that travellers get vaccinated against yellow fever and protect themselves from mosquito bites when travelling to Angola and the DRC.

The governments of Angola and the DRC require that travellers age 9 months or older be vaccinated for yellow fever and show proof of vaccination on an International Certificate of Vaccination or Prophylaxis to enter the country.

There is currently a shortage of the yellow fever vaccine in Canada. It is important for travellers to contact a designated Yellow Fever Vaccination Centre well in advance of their trip to ensure that the vaccine is available.

Recommended practices for the prevention of endoscopy-related infections

Source: Public Health Agency of Canada. Disease Prevention and Control Guidelines. **Recommended Practices for the prevention of endoscopy-related infections**. May 24, 2016. http://www.phac-aspc.gc.ca/nois-sinp/notice-avis/endo-2016-eng.php

Recommendations: The Agency has consulted the Infection Prevention and Control Expert Working Group (with expertise in infectious diseases, medical microbiology, infection prevention and control, healthcare epidemiology and public health).

1. At this time, the Agency is not recommending enhanced reprocessing procedures for duodenoscopes nor periodic microbiologic surveillance cultures of endoscopes.

2. The Agency reminds users of the importance of adherence to current infection prevention and control guidelines, standards and requirements to prevent endoscopy-related infections. This includes following the manufacturer's instructions for reprocessing devices.

3. For more information on reprocessing duodenoscopes, please refer to the Agency's *Infection Prevention and Control Guideline for Flexible Gastrointestinal Endoscopy and Flexible Bronchoscopy*, or consult your endoscope manufacturer, the Canadian Association of Medical Device Reprocessing or your provincial/territorial Ministry of Health.

4. Any case of patient infection or other serious side effects with the use of endoscopes should be reported to Health Canada.

CCDR

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