

# Measles in Canada Between 2002 and 2013

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**Background.** In 1994, Canada committed to eliminate measles by the year 2000. This report presents the epidemiology of measles in Canada between 2002 and 2013 and its implications in sustaining measles elimination.

**Methods.** Cases included individuals reported to the Canadian Measles and Rubella Surveillance System with confirmed measles.

**Results.** In Canada, 1171 cases of measles were reported between 2002 and 2013 (incidence 0.29 cases per 100 000 population). The annual number of cases ranged from 6 to 752. The majority of cases were unvaccinated (63%) or had an unknown vaccination status (19%). The median age of cases was 14.4 years (range, <1 to 63 years) globally and 14 years when excluding the 2011 outbreak in Quebec where 68% of the 678 cases were 10 to 19 years old. With the exclusion of this outbreak, the incidence was highest in infants (1.0 per 100 000), lower but fairly similar between 1 and 19 years of age (0.2 to 0.4 per 100 000), and there was a substantial decline between 20 and 39 years of age (0.1 per 100 000). There was a significant trend towards a greater annual number of importations over the period. Although importations resulted in no transmission sustained for  $\geq 12$  months, 5 chains of transmission had  $>30$  cases. The effective reproductive number between 2002 and 2013 was estimated at 0.86 (95% confidence interval, .81–.92).

**Conclusions.** Canada has maintained elimination between 2002 and 2013, but additional efforts are needed to reduce the proportion of unimmunized individuals and respond to importation events.

**Keywords.** elimination; epidemiology; measles; vaccine.

In 1994, Canada committed to the objective of measles elimination by 2000 [1]. In Canada, a single dose of the live-attenuated measles vaccine administered at the age of 12 months had been recommended since the early 1970s [2]. Despite good vaccine coverage, large epidemics in mostly vaccinated children occurred between 1989 and 1994 [3–7]. Because immunogenicity studies had also shown that a second dose administered to children who did not respond to a first dose mounted a good response [8–10], the National Consensus Conference on Measles in 1993 and the National Advisory Committee on Immunization in 1996 recommended the routine administration of a second dose and

catch-up programs to administer a second dose to all children and adolescents previously vaccinated under the 1-dose program [11, 12].

Between 1996 and 1998, provinces implemented routine 2-dose vaccination programs and catch-up campaigns targeting school-age children and adolescents [1]. A review of the measles epidemiology in Canada between 1996 and 2001 demonstrated that despite a few importations and 12 to 199 cases annually, endemic transmission had been interrupted since 1997 [1]. With elimination defined as the interruption of endemic measles virus transmission for a period  $\geq 12$  months in presence of high-quality surveillance, Canada (1) showed that all reported clusters lasted  $\leq 26$  weeks and (2) demonstrated that elimination had been maintained between 2002 and 2011 [13]. This article presents the epidemiology of measles in Canada between 2002 and 2013 and discusses the implications for sustaining measles elimination.

## METHODS

### Surveillance and Data Collection

Measles has been a reportable disease in Canada since 1924. As recommended by the Pan American Health

Received 24 November 2014; accepted 09 April 2015.

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#### Open Forum Infectious Diseases

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DOI: 10.1093/ofid/ofv048

Organization, Canada initiated a national enhanced measles surveillance program in 1998. Integration with rubella and congenital rubella syndrome/infection occurred in 2006 and 2007, respectively, with addition of these diseases to the national surveillance system. Each case reported through the Canadian Measles and Rubella Surveillance System is reviewed, and only confirmed cases are added to the national database (see below). Data include information on clinical description, age, any epidemiologic link to confirmed cases, travel history, vaccination status, and measles genotype.

### Case Definition

Measles cases were defined as either laboratory-confirmed or clinically confirmed [13]. Laboratory-confirmed cases were characterized by either isolation of measles virus from an appropriate clinical specimen, detection of measles virus RNA, a 4-fold or greater rise in measles-specific antibody titer between acute and convalescent sera, or positive serologic test for measles immunoglobulin (Ig)M antibody using a recommended assay. Clinically confirmed cases were defined by fever ( $\geq 38.3^{\circ}\text{C}$ ), a generalized maculopapular rash for at least 3 days, and either cough, coryza, or conjunctivitis and must be epidemiologically linked to a laboratory-confirmed case. Potential cases with recent immunization with a measles-containing vaccine (MCV) were excluded.

### Measles Virus Genotyping

Measles virus genotyping was performed at the National Microbiology Laboratory (NML), Public Health Agency of Canada (PHAC) on appropriate clinical specimens (respiratory specimens, urines, and viral isolates) collected from suspect measles cases. RNA was extracted using either the RNeasy Mini kit (Qiagen), QIAamp Viral RNA kit (Qiagen), or the MPLC Total Nucleic Acid Isolation Kit – High Performance (Roche) automated on the MagNA Pure LC 2.0 (Roche). The World Health Organization (WHO) standardized genotyping region [14], and the 450 nucleotides encoding the carboxyl-terminus of the measles nucleoprotein was amplified by one-step reverse transcription-polymerase chain reaction ([RT-PCR] OneStep RT-PCR kit; Qiagen). Amplicons were purified and sequenced by the Genomics Core Services section at the NML. Contigs were prepared using SeqMan Pro (DNASTAR) software. The resulting sequences were aligned with WHO genotype reference sequences [15] using MegAlign (DNASTAR) software and genotypes determined by highest homology.

### Importation Status

Imported measles cases were defined as persons exposed outside Canada during the 7 to 21 days before disease onset. Import-linked cases had a documented epidemiologic link to an imported case. With measles elimination, all cases are either imported or a secondary spread. Cases were grouped into chains of transmission

(which sometimes included only the imported case) on the basis of epidemiological investigations. Chains with no known epidemiologic link to importation and no genotype information were most likely due to secondary spread from imported measles cases through an undetected link or chain of transmission. To correct for this bias, we assumed that for each of these chains, only the imported case was missed by surveillance.

### Vaccination Status

Where available, vaccination status was assessed from registries. Otherwise, it was obtained from written documentation (vaccination booklet) presented by cases and was sometimes confirmed by providers on an ad hoc basis. The vaccination status variable was derived based on age at onset and current Canadian immunization recommendations [16]. To be valid, the first dose had to be administered at  $\geq 12$  months of age and the second at least 1 month later. Cases with 1 reported MCV dose were considered up-to-date if they were between the ages of 12 months and 6 years (the second MCV dose is recommended between 18 months and before school entry [6 years]). Cases  $< 1$  year of age were considered too young for their first dose, and those born before 1970 were assumed to be naturally immune and not recommended to be vaccinated.

### Descriptive and Statistical Analyses

Associations between categorical variables were calculated with  $\chi^2$  or Fisher exact tests. To gain insight on the status of measles elimination in Canada, we estimated the effective reproduction number ( $R$ ) using the proportion of imported cases and the distribution of the size of the chains of transmission [17]. Approximate 95% confidence intervals (CIs) were calculated by use of the profile likelihood. For the calculations based on the proportion of imported cases, the CIs were truncated at a value of 1, because the method is conditional on outbreaks becoming extinct. Cases were grouped into chains of transmission on the basis of links found during the investigations.

## RESULTS

### Measles in Canada Between 2002 and 2013

Between 2002 and 2013, 1171 confirmed cases of measles were reported to PHAC for an overall incidence of 0.29 cases per 100 000 population (Table 1). The annual number of cases varied between 6 and 752, and the incidence ranged from 0.02 to 2.19 per 100 000 population (median, 0.05 per 100 000) (Figure 1). There were fewer cases between 2002 and 2006 ( $< 20$  cases/year) compared with 2007 and 2013 ( $> 60$  cases annually in 5 of the 7 years). Half of the cases were laboratory confirmed, and the other half were clinical cases with an epidemiological link to a laboratory-confirmed case (Table 1). Males were slightly more affected than females (53% vs 47%). Measles affected 8 of the 10 provinces and none of the 3 territories. The median age

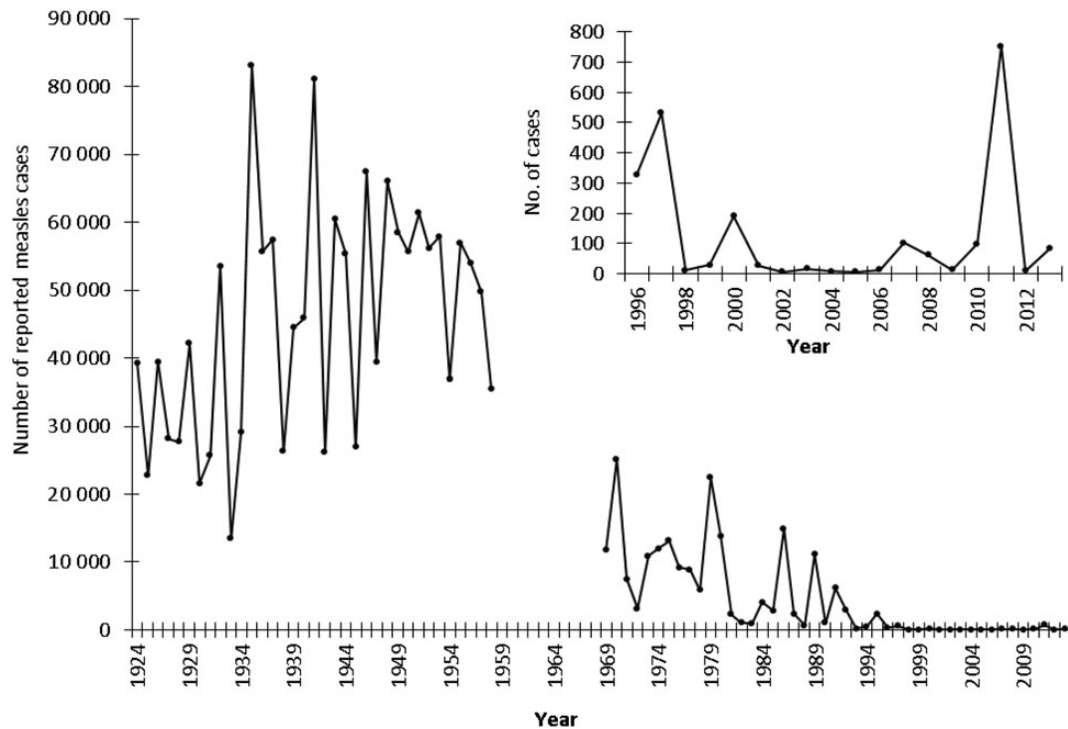
**Table 1. Characteristics of Confirmed Measles Cases in Canada 2002–2013 (n = 1171)**

	Total N (%)	Hospitalized <sup>a</sup> N (%)	2002 N	2003 N	2004 N	2005 N	2006 N	2007 N	2008 N	2009 N	2010 N	2011 N	2012 N	2013 N
Total	1171	151 (13%)	7	16	8	6	13	102	62	14	99	752	9	83
<b>Diagnosis Type<sup>b</sup></b>														
Laboratory confirmed	583 (50%)	118 (78%)	7	12	8	5	9	52	34	6	82	306	9	53
Epi-linked	584 (50%)	33 (22%)	0	0	0	1	4	50	28	8	17	446	0	30
<b>Sex<sup>c</sup></b>														
Male	624 (53%)	79 (52%)	3	6	1	0	7	51	37	9	50	412	3	45
Female	545 (47%)	72 (48%)	4	8	7	6	6	51	25	5	49	340	6	38
<b>Age group (years)</b>														
<1	56 (5%)	13 (23%)	0	3	2	1	4	0	4	0	11	26	1	4
1–4	128 (11%)	22 (19%)	2	3	4	1	3	14	6	1	12	63	2	17
5–9	127 (11%)	8 (6%)	1	1	0	0	1	35	9	3	6	61	1	9
10–14	320 (27%)	19 (6%)	0	0	0	2	0	25	9	2	5	260	0	17
15–19	271 (23%)	29 (11%)	0	1	0	1	2	6	4	7	11	227	1	11
20–29	94 (8%)	16 (17%)	2	3	0	0	1	7	6	0	18	40	2	15
30–39	125 (11%)	29 (23%)	1	3	2	1	1	13	16	1	22	57	2	6
40 and up	50 (4%)	15 (30%)	1	2	0	0	1	2	8	0	14	18	0	4
<b>Hospitalization<sup>a</sup></b>														
Yes	151 (13%)	151 (13%)	1	4	2	2	2	13	6	2	19	90	2	8
No	967 (83%)	Not applicable	6	5	6	4	10	86	54	12	74	632	6	74
<b>Vaccination status</b>														
Unvaccinated	740 (63%)	98 (13%)	3	8	6	5	8	72	36	10	43	477	5	67
1 dose	98 (8%)	13 (13%)	0	0	0	0	2	12	1	0	14	64	2	3
2 doses	109 (9%)	4 (4%)	0	0	0	0	0	5	0	0	7	93	0	4
Unknown	224 (19%)	36 (16%)	4	8	2	1	3	13	25	4	35	118	2	9
<b>Importation Status</b>														
Imported	99 (9%)	31 (21%)	4	9	5	3	5	5	6	4	10	29	7	12
All others	1072 (92%)	120 (79%)	3	7	3	3	8	97	56	10	89	723	2	71

<sup>a</sup> Hospitalization information is missing for 55 cases (7 in 2003; 1 in 2006; 3 in 2007; 2 in 2008; 6 in 2010; 30 in 2011; 1 for 2012; and 1 for 2013).

<sup>b</sup> Diagnosis type is missing for 4 cases in 2003.

<sup>c</sup> Sex is missing for 2 cases in 2003.



**Figure 1.** Number of confirmed measles cases by year, Canada, 1924–2013. Measles was not nationally notifiable between 1959 and 1968.

of cases was 14.4 years (range, <1 to 63 years) globally and 14 years when excluding the 2011 outbreak in Quebec where 68% of the 678 cases were 10 to 19 years old [18]. With the exclusion of this outbreak, the incidence during the study period was highest in infants (1.0 per 100 000), lower but fairly similar between 1 and 19 years of age (0.2 to 0.4 per 100 000), and there was a substantial decline between 20 and 39 years of age (0.1 per 100 000) (Table 2). Only 4% (50) of cases were adults born before 1970.

Among the 1171 cases, 63% ( $n = 740$ ) were unvaccinated, 19% ( $n = 224$ ) had an unknown vaccination status, 8% ( $n = 98$ ) had received only 1 dose, and 9% ( $n = 108$ ) had received 2 doses (Table 2). Among the 740 unvaccinated cases, 70 (9%) were not eligible for vaccination either because they were <12 months of age (49 cases [7%]) or because they were born before 1970 and considered naturally immune (21 cases [3%]). Among the 98 cases who had received only 1 dose of vaccine, 22% were adults ( $n = 22$ ) born after 1983 but before the implementation of the 2-dose program in 1996–1997, and another 17% [17] were between 1 and 6 years of age and may have been too young to have received their second dose.

Overall, 13% of cases were hospitalized (Tables 1 and 2). Outcome data are not collected through national measles surveillance, so specific information on severity of illness is not known. There was a significant association between age group and hospitalization status ( $P < .001$ ). Cases in the youngest and older age groups were more likely to be hospitalized: 22%

of adults 20 years and older and 19% of children <5 years were hospitalized, compared with 8% among children 5 to 19 years. The risk of hospitalization was significantly lower ( $P < .05$ ) among cases who received 2 doses (3.7%) than those who were unimmunized (13%), those who received 1 dose (13%), or those with unknown immunization history (16%) (Table 2).

Laboratory-confirmed cases were more likely than epi-linked cases to have unknown immunization history (25% vs 13%) but less likely to have received 2 doses (6% vs 13%) (Table 2). The distribution of immunization status was similar between male and female cases. Among cases younger than 20 years old, 12% had an unknown immunization status compared with 42% in adults 20–39 years old ( $P < .001$ ). The percentage of cases who had received 2 doses increased from 4% in those aged 1–4 years and 6% in those 5–9 years to 13% in 10–14 years and 18% in those 15–19 years old. The percentage of unimmunized cases was similar among imported and not imported cases (67% vs 63%), but 2-dose recipients were less frequent (3% vs 10%, respectively), and cases with unknown immunization status were more frequent (24% vs 19%).

#### Chains of Transmission and the Effective Reproductive Number

Between 2002 and 2013, there were 130 chains of transmission (Table 3). The imported case was identified in 93 (72%) of the chains but was missing for 37 chains. Because these 37 chains occurred in areas of the country or periods with no known

**Table 2. Characteristics of Measles Cases by Vaccination Status, Canada 2002–2013**

	Number of Doses				Total	
	Unvaccinated N = 740 n (Row%)	1 Dose N = 98 n (Row%)	2 Doses N = 109 n (Row %)	Unknown N = 224 n (Row %)	All <sup>a</sup> N = 1171 n (Incidence)	Excl. QC2011 <sup>a</sup> N = 493 n (Incidence)
<b>Diagnosis Type<sup>b</sup></b>						
Laboratory confirmed	338 (58)	61 (10)	36 (6)	148 (25)	583 (0.15)	334 (0.08)
Epi-linked	400 (68)	37 (6)	73 (13)	74 (13)	584 (0.15)	155 (0.04)
<b>Sex<sup>c</sup></b>						
Male	382 (61)	45 (7)	67 (11)	130 (21)	624 (0.32)	244 (0.12)
Female	356 (65)	53 (10)	42 (8)	94 (17)	545 (0.27)	247 (0.12)
<b>Age (years)</b>						
<1	49 (88)	2 (4)	0 (0)	5 (9)	56 (1.30)	44 (1.02)
1–4	92 (72)	18 (14)	5 (4)	13 (10)	128 (0.74)	71 (0.41)
5–9	109 (86)	5 (4)	7 (6)	6 (5)	127 (0.57)	70 (0.31)
10–14	235 (73)	9 (3)	41 (13)	35 (11)	320 (1.31)	72 (0.30)
15–19	160 (59)	14 (5)	48 (18)	49 (18)	271(1.03)	55 (0.21)
20–29	48 (51)	10 (11)	7 (7)	29 (31)	94 (0.17)	65 (0.12)
30–39	25 (20)	35 (28)	1 (1)	64 (51)	125 (0.23)	76 (0.14)
40 and up	22 (44)	5 (10)	0 (0)	23 (46)	50 (0.03)	40 (0.02)
<b>Importation status</b>						
Imported	66 (67)	6 (6)	3 (3)	24 (24)	99 (0.02)	98 (0.02)
All others	674 (63)	92 (9)	106 (10)	200 (19)	1072 (0.27)	395 (0.10)
Hospitalized	98 (65)	13 (9)	4 (3)	36 (24)	151 (0.04)	72 (0.02)

<sup>a</sup> For all cases or excluding the 678 cases of the 2011 outbreak in Quebec (Excl.QC 2011). Incidence per 100 000.

<sup>b</sup> Diagnosis type is missing for 4 cases in 2003.

<sup>c</sup> Sex is missing for 2 cases in 2003.

**Table 3. Distribution of Outbreak Size for Measles in Canada Between 2002 and 2013 and Estimates of the Reproduction Number (*R*) According to the Proportion of Imported Cases and Outbreak Size**

	Outbreak Size				Number of Cases		% of Imported Cases		Effective <i>R</i>	
	1 Case Total (NL) <sup>a</sup>	2 Cases Total (NL) <sup>a</sup>	≥3 Cases Total (NL) <sup>a</sup>	All Total (NL) <sup>a</sup>	Total (NL) <sup>a</sup>	Crude % (n/N)	Corrected <sup>a</sup> % (n/N)	From Corrected <sup>b</sup> % Imported	From Corrected <sup>b</sup> Outbreak Size	
2002	7 (3)			7 (3)	7 (3)	57% (4/7)	70% (7/10)	0.30 (0.07–0.78)	0 (0–0.19)	
2003	8 (1)		2 (1)	10 (2)	16 (5)	50% (8/16)	56% (10/18)	0.44 (0.20–0.83)	0.11 (0.02–0.34)	
2004	5 (1)		1	6 (1)	8 (1)	63% (5/8)	67% (6/9)	0.33 (0.08–0.86)	0.22 (0.04–0.69)	
2005	4 (2)	1		5 (2)	6 (2)	50% (3/6)	63% (5/8)	0.37 (0.09–0.97)	0.12 (0.01–0.55)	
2006	3	3 (1)	1 (1)	7 (2)	13 (6)	38% (5/13)	47% (7/15)	0.53 (0.24–0.99)	0.40 (0.16–0.81)	
2007	3 (1)		2 (1)	5 (2)	102 (97)	3% (3/102)	5% (5/104)	0.95 (0.78–1.0)	0.93 (0.76–1.13)	
2008	5 (1)	2	1 (1)	8 (2)	62 (54)	10% (6/62)	13% (8/64)	0.87 (0.67–1.0)	0.84 (0.64–1.09)	
2009	2		2	4	14	29% (4/14)	29% (4/14)	0.71 (0.36–1.0)	0.71 (0.36–1.25)	
2010	11 (3)	1 (1)	3 (2)	15 (6)	99 (85)	9% (9/99)	14% (15/105)	0.86 (0.69–1.0)	0.80 (0.64–0.98)	
2011	25 (1)	4 (3)	5 (2)	34 (6)	752 (20)	4% (28/752)	4% (34/758)	0.96 (0.89–1.0)	0.95 (0.88–1.02)	
2012	7 (1)	1		8 (1)	9 (1)	78% (7/9)	80% (8/10)	0.20 (0.03–0.62)	0.10 (0.01–0.44)	
2013	12 (5)	2	7 (5)	21 (10)	83 (26)	13% (11/83)	23% (21/93)	0.77 (0.61–0.97)	0.67 (0.51–0.85)	
Total	92 (19)	14 (5)	24 (13)	130 (37)	1171 (300)	8% (93/1171)	11% (130/1208)	0.89 (0.84–0.95)	0.86 (0.81–0.92)	

<sup>a</sup> Total (NL): Total number of outbreaks (outbreaks not linked to an imported case).

<sup>b</sup> Corrected for outbreaks not linked with an imported case. We assumed that for each of these outbreaks, only the imported case was missed, and we added these missed cases to both the numerator and denominator.

measles activity, they are not the result of endemic transmission but from an undetected importation. Assuming therefore that each chain originated from a different importation, there were on average 11 importations per year (range, 4–34) with  $\leq 10$  importations per year between 2002 and 2009, 15 in 2010, 34 in 2011, 8 in 2012, and 21 in 2013 ( $\chi^2$  for trend for the study period  $P < .001$ ). Among the 130 chains, 73 (54%) included only the identified imported cases and caused no secondary transmission. There were 24 chains with  $\geq 3$  cases including 5 with  $>30$  cases, which accounted for 81% of all cases and were described in detail elsewhere [13, 18–20]. These chains occurred in 2007 (Quebec: 94 cases, duration 24 weeks), 2008 (Ontario: 53 cases, 11 weeks), 2010 (British Columbia: 82 cases, 7 weeks), 2011 (Quebec: 678 cases, 26 weeks), and 2013 (Alberta: 42 cases, 6 weeks). The source of importation was not identified for the first 3 of these chains but was for the latter 2.

The 99 imported cases (93 chains because some chains had 2 coprimary imported cases) represent 8% (99 of 1171) of all reported cases. This result underestimates the real proportion of imported cases because 37 other chains had no source of importation detected. To correct for this bias, we assumed that for each of these chains, only the imported case was missed by surveillance, and we added these missed imported cases both to the numerator and denominator. The corrected proportion of imported cases is 11% [(99 imported cases detected + 37 imported cases undetected)/(1171 detected + 37 imported cases undetected)]. The effective  $R$  would be estimated at 0.92 for the uncorrected proportion and 0.89 (CI, 95% .84–.95) for the corrected proportion. When using the distribution of the size of all chains and again adding 1 imported case to chains with no identified imported cases,  $R$  was 0.86 (CI, 95% .81–.92) (Table 3).

### Measles Virus Genotypes

Between 2002 and 2013, the genotype of 349 measles viruses were identified. Genotype D4 was the most prevalent (177 of 349 [51%]), but 67% (119 of 177) of these were isolated during the 2011 outbreak in Quebec and were similar to a strain circulating in Europe that year. In other years, the D4 strains were imported from Europe, Pakistan, India, the United States, Bangladesh, or New Zealand. Genotypes D8 ( $n = 87$ , 25%) and H1 ( $n = 41$ , 12%) were the second most frequent: D8 was associated with the 2008 Ontario outbreak and the 2013 Alberta outbreak, whereas H1 was associated with the 2010 Vancouver outbreak. The other genotypes identified were B2 [1], B3 [21], D3 [1], D5 [6], D6 [1], D9 [11], and G3 [1]. The country of origin of importations was known for 96 of 99 imported cases (Table 4). Measles was most frequently imported from Europe (37.4% overall, 19.2% from France), followed by Southeast Asia (30% overall, 12% from Pakistan, and 11% from India). There were 7 importations from the United States, and 3 or fewer cases were imported from 19 other countries or regions (Table 4).

**Table 4. Country of Importation in the 93 Importations (99 Cases) With an Identified Imported Case**

WHO Region/Country	Total Number of Imported Cases (%)	Number of Cases With Genotype Identified	Genotype(s)
Total	99 (100)	63	
Africa	5 (5.1)	2	
Africa, unspecified	1 (1.0)	0	
Ethiopia	1 (1.0)	0	
Morocco	1 (1.0)	1	D8
Uganda	1 (1.0)	1	B3
Zambia	1 (1.0)	0	
Americas	10 (10.1)	8	
United States	7 (7.1)	1, 2, 1, 1	B3, D4, D8, D9
Mexico	2 (2.0)	2	D8 <sup>a</sup>
Cuba	1 (1.0)	1	D4 <sup>b</sup>
Eastern Mediterranean	1 (1.0)	0	
Somalia	1 (1.0)	0	
Europe	37 (37.4)	24	
Europe, unspecified	9 (9.1)	3, 2, 1	D4, D8, G3
Belgium	1 (1.0)	1	D4
England	1 (1.0)	1	D9
France	19 (19.2)	9, 1	D4, D5
Israel	1 (1.0)	0	
Italy	1 (1.0)	0	
The Netherlands	3 (3.0)	4	D8
Switzerland	1 (1.0)	1	D5
United Kingdom	1 (1.0)	1	B3
South East Asia	30 (30.3)	20	
Afghanistan	2 (2.0)	2	B3
Bangladesh	2 (2.0)	1, 1	D4, D8
India	11 (11.1)	2, 3	D4, D8,
Pakistan	12 (12.1)	4, 4	B3, D4
Sri Lanka	1 (1.0)	1	B3
Thailand	2 (2.0)	2	D8
Western Pacific	15 (15.2)	8	
Western Pacific, unspecified	2 (2.0)	1, 1	D5, H1
China	2 (2.0)	1	H1
Japan	3 (3.0)	1, 1	D5, H1
Malaysia	1 (1.0)	0	
New Zealand	1 (1.0)	1	D4
Vietnam	3 (3.0)	0	
Philippines	3 (3.0)	1, 1	B3, D9
Region/country unknown	3 (3.0)	1	B3

Abbreviations: UK, United Kingdom; WHO, World Health Organization.

<sup>a</sup> The traveler was exposed to a confirmed measles case who was a resident of the UK, where there was a documented increase in measles cases.

<sup>b</sup> The traveler was returning from the Caribbean but likely acquired measles at the Montreal airport [18].

## DISCUSSION

Between 2002 and 2013, a total of 1171 cases of measles have occurred in Canada for an overall incidence rate of 0.29 cases per 100 000 population. The maximum number of cases per year ranged from 6 to 752, with a trend towards higher number of cases and importations from 2007 onwards. The majority of cases were unvaccinated (63%) or had an unknown vaccination status (19%). There was a significant trend towards a greater annual number of importations over the period, with the exclusion of the 2011 Quebec outbreak, which affected mostly adolescents. The incidence was highest in infants (1.0 per 100 000) and lower but fairly similar between 1 and 19 years of age (0.2 to 0.4 per 100 000), suggesting a similar proportion of unvaccinated children in the numerous birth cohorts over the past 20–30 years. Although no transmission lasted  $\geq 12$  months, the effective reproductive number was estimated at 0.86 (0.81–0.92) for the entire period but at 0.95 for 2011.

The key elements needed to maintain elimination status include reaching high immunization coverage, minimizing vaccine failures, and effective public health management of cases and outbreaks in case of importations. It is estimated that at least 93% of the population needs to be immune to provide enough herd immunity to eliminate measles [21]. Heterogeneity and clustering of susceptibility narrow the margin between the level of immunity required to maintain elimination and that which allows sustained transmission. Among our cases, 63% were unimmunized and 19% had an unknown vaccination status, which is similar to the 65% and 20%, respectively, observed in the United States between 2001 and 2011 [22]. Despite representing a small proportion of the population, most unvaccinated individuals do so on religious grounds or for philosophical reasons and therefore often cluster, adding to the risk of large size outbreaks. Although the need to reduce the proportion of unvaccinated individuals in Canada is obvious, given the strong beliefs of these individuals or their family, it has been a difficult task. As an example, after the large 2011 outbreak in Quebec, a measles vaccination campaign was conducted in all schools of the province. Despite parents being advised that unvaccinated children would be excluded from school during outbreaks, 2.2% of students chose to remain unvaccinated (compared with 3.2% before the campaign) [23]. New strategies to address this group of parents need to be developed.

Overall, 17% of cases were known to be vaccinated (8% with 1 dose and 9% with 2 doses). Therefore, the contribution of vaccine failures to the vulnerability of the population has been limited during that period. However the accumulation of vaccinated but yet unprotected individuals over the years diminishes the margin of safety to maintain elimination. Ensuring the administration of the second dose is currently the most important intervention to minimize vaccine failures.

Importations are going to continue to occur until significant headway is made towards elimination in other jurisdictions. The genotype was identified for 349 cases. D4 was the most prevalent, but the majority of these cases occurred during the 2011 outbreak in Quebec and were genotypically linked to the virus causing the large epidemic in France at the same period [18, 24]. Genotypes D8 and H1 were the next most commonly reported. The genotype pattern seen in Canada reflects genotypes circulating in other endemic countries with no single genotype consistently seen in Canada. This lends further indication that elimination has been maintained between 2002 and 2013. The increased number of importation events since 2010 may be explained by the increase in epidemic measles activities in other parts of the world and particularly in Europe [24, 25]. Although Canadian travelers to developing countries often seek pretravel advice, very few would seek travel advice before traveling to Europe. Ensuring proper vaccination of travelers against measles to minimize the number of importations is necessary but will be challenging.

Among the estimated 130 distinct importations (93 where the imported cases were identified and 37 chains of transmission where it was not), half resulted in no secondary transmission, but 5 triggered outbreaks with  $>30$  cases, causing 81% of all cases. In the United States, between 2001 and 2013, 477 imported cases were reported, and many others had virological evidence of importation or had an unknown source [22, 26]. With approximately 5 times more importations than Canada, there were approximately the same total number of cases (1153 vs 1171), 83% resulted in no secondary spread [19], and only 3 outbreaks had 30 cases or more (Indiana 2005, 34 cases; Illinois 2008, 30 cases; New York 2013, 58 cases) [27–29]. The estimates of the effective reproductive number in the United States range between 0.62 and 0.66 [26, 30], substantially lower than the 0.86 found in Canada. All of these observations suggest a higher level of immunity and/or more efficient control measures in the United States. The effective  $R$  expresses the epidemic potential in a specific population and combines the contagiousness of the disease (duration of shedding and capacity to infect), the proportion of susceptible individuals, and the mixing patterns in the population. Outbreak control measures such as school exclusion, vaccination of exposed contacts, or quarantine of contacts without evidence of immunity do not reduce the risk of importation but can reduce  $R$  and the length of chains of transmission. An  $R$  hovering approximately 0.86 does not indicate that endemic transmission will resume in Canada in the short term, but 10% of importations are expected to result in outbreaks involving 25 cases or more [17]. In contrast, with an  $R = 0.65$ ,  $<1\%$  of importations in the United States are expected to trigger outbreaks of this size.

An important limitation of this study is its reliance on passive surveillance, which is known to underestimate the number of

cases, and despite great efforts since 1998, there is evidence of imperfect sensitivity of measles surveillance. For 37 (28%) of the 130 chains of transmission measles cases, the imported case was not identified, indicating that surveillance missed several cases. This could be due to initial cases of measles not presenting to healthcare personnel, cases being misdiagnosed because frontline physicians have little experience with measles or because of attenuated disease in individuals who are immunized or partially immunized. The underreporting is likely more substantial for vaccinated cases (imported or indigenous) because these cases can present with attenuated disease. Based on data gathered during the 2011 outbreak in Quebec, active investigation for cases and vaccination status in the most affected school found 43% more cases than reported to the passive surveillance system (110 vs 77), with a significant difference according to vaccination status: there was a 21% increase in unvaccinated cases but a 130% increase in fully vaccinated individuals [18]. Vaccinated cases may also remain IgM negative and, without an epidemiological link to a laboratory-confirmed case, would not be included in national case counts, if no other test (PCR, culture, or IgG) confirms a measles infection. In addition, visitors to Canada may not readily consult a Canadian physician when sick with measles. The diagnosis may be missed in mild cases, those consulting before rash onset, or even in cases with typical symptoms occurring outside an outbreak. To minimize the number of undiagnosed measles cases, it is essential to maintain a high suspicion index for frontline physicians and ensure their use of appropriate confirmatory tests. Another limitation of our current study is the absence of data at the national level, which would have allowed us to determine the proportion of cases due to visitors or those related to Canadians traveling. This variable has been added to the national surveillance system since 2011 and will be available in the future.

## CONCLUSIONS

Canada has successfully maintained elimination of measles between 2002 and 2013. Although more effective control measures coupled with better identification of imported cases may limit the size of outbreaks, it is the vulnerability of the population (reflected by the *R*) that poses the long-term challenge. Each year will add to the number and proportion of unprotected individuals in the entire population, slowly pushing the country towards the epidemic threshold. Maintaining elimination will require concerted efforts. For the public, this means getting immunized and seeking medical care when ill. Frontline providers will need (1) to maintain ongoing clinical suspicion to make the diagnosis and collect appropriate specimens and (2) to offer immunization to Canadians. For public health, the priorities will be to identify and vaccinate pockets of under-immunized individuals and to rapidly and adequately respond to new cases.

## Acknowledgments

**Potential conflicts of interest.** GDS has received research funds from GSK and has received travel fees reimbursement to attend an ad hoc advisory board for GSK. No other authors reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

**Funding.** This work has been supported by the Public Health Agency of Canada.

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