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Delayed measles vaccination of toddlers in Canada: Associated socio-demographic factors and parental knowledge, attitudes and beliefs

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ABSTRACT

Delaying vaccination increases the period of vulnerability of children against vaccine-preventable diseases. We used a nationally representative sample of Canadian two-year-old children to explore factors associated with delays in the uptake of the first dose of measles-containing vaccine, recommended in Canada for children at 12 months of age. Distribution of delays was determined using data from the 2013 Childhood National Immunization Coverage Survey. Logistic regression was used to examine sociodemographic factors and knowledge, attitudes and beliefs (KAB) associated with the two outcomes of interest: delays of one to six months (vaccination at 13 to 18 months of age) and delays of seven to 18 months (vaccination at 19 to 23 months of age). Overall, 69% (95% confidence interval [CI] 67-71) of children received their first valid dose on time. Twenty-nine percent (95% CI 27-31) and 11% (95% CI 9-12) of children were unvaccinated before turning 13 and 16 months of age, respectively. Factors associated with delays of one to six months were being a girl, being born outside Canada, and the jurisdiction of residence. Being from a single-parent family, being born outside Canada and the jurisdiction of residence were associated with delays of seven to 18 months, suggesting that potential barriers might be at play. Associations between KAB and vaccination delays indicate that vaccine hesitancy could contribute to measles vaccination delays in Canada. Barriers in accessing vaccination services and the role of vaccine hesitancy in timely vaccination must be better understood to reduce vaccination delays in toddlers in Canada.

Introduction

Vaccination coverage is an important indicator of the level of protection of the population against vaccine-preventable diseases (VPD),¹ and coverage monitoring is used to measure the performance of vaccination programs and the compliance of the population with public health recommendations.² However, vaccination rates do not take into account timeliness in the uptake of vaccines, a factor of particular importance for prevention of highly transmissible diseases such as measles.²

Delaying childhood vaccines extends the period of vulnerability of children to VPD³ and is a predictor for an incomplete vaccination status at a later age.⁴⁻⁸ The National Advisory Committee on Immunization (NACI) recommends that two doses of the measles-mumps-rubella (MMR) vaccine or the measles-mumps-rubella-varicella (MMRV) vaccine be given to children before school entry: one dose between 12 and 15 months of age and another one at or after 18 months of age. All provincial and territorial vaccination schedules recommend a first dose of MMR or MMRV at 12 months of age, whereas timing of the second dose varies among provinces and territories with doses given at 18 months, 36 months or between four and six years of age. **ARTICLE HISTORY**

Received 31 October 2017 Revised 31 October 2017 Accepted 28 November 2017

KEYWORDS

Canada; children; measles; MMR; immunization; vaccination; delays; timely

Previous research showed that, in jurisdictions within or comparable to Canada, timely vaccination is associated with socio-demographic characteristics of the family and/or factors related to the healthcare system^{7,9-12} and parental knowledge, attitudes and beliefs (KAB) regarding vaccination.^{13,14} Associations between parental KAB and vaccination delays may indicate vaccine hesitancy, which refers to "delay in acceptance or refusal of vaccination despite availability of vaccination services"¹⁵ according to one of its definition. The "Three Cs" model proposed by a World Health Organization working group states that vaccine hesitancy is influenced by factors that can be grouped into three broad categories: complacency, confidence and convenience.¹⁵

This study is, to our knowledge, the first insight on vaccination delays in Canada using nationally representative data aimed at better defining population subgroups at risk for late vaccination.^{4,16} In Canada in 2013, no written proof of a dose of measles-containing vaccine was found in 10.3% (95% CI 8.9–11.6) of two-year-old children.¹⁷ Sporadic outbreaks of measles still occur in Canada and the majority of the recent pediatric cases were unvaccinated.¹⁸ Delayed vaccination may contribute to under-immunization in children, but the extent

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of delayed measles vaccination in two-year-old children in Canada is unknown.

In this study, we used data from the 2013 Childhood National Immunization Coverage Survey (cNICS 2013) to examine the distribution of delays in the uptake of the first dose of measles vaccine in two-year-old children in Canada, and to explore socio-demographic factors and KAB associated with delayed measles vaccination in this age group.

Results

A 63.5% response rate was obtained for the survey, yielding a sample of 5513 two-year-old children. Among them, measles vaccination information was not available for 1909 (35%) children. The analyses were thus carried out on a sample of 3604 two-year-old children, described in Table 1.

As shown in Table 2, 69.1% (95% CI 66.9–71.4) of toddlers in Canada received their first dose of measles vaccine on time at 12 months of age, leaving 29.1% (95% CI 26.9–31.4) of children not vaccinated at the recommended age. The proportion of children vaccinated with one- to three-month delays was 18.5% (95% CI 16.6–20.3). This group is considered delayed as per provincial and territorial vaccination schedules but not as per NACI recommendation. Noticeably, the proportion of unvaccinated children before turning 16 and 19 months of age

Table 1. Description of the analyzed sample, N = 3604.

Variable	%
Sex	
Female	48.0
Male	52.0
Province or region of residence	
Atlantic	5.0
Quebec	28.0
Ontario	38.2
Manitoba	3.2
Saskatchewan	2.6
Alberta	12.1
British-Columbia	10.6
Territories	0.3
Education of responding parent	
Secondary or less	24.4
Post-secondary	31.5
University graduate	42.2
Don't know/refusal/not stated/not a parent	1.9
Total household income	
0 – \$39,000	19.7
\$40,000 - \$59,999	13.9
\$60,000 - \$79,999	16.3
\$80,000 – \$99,999	14.9
\$100,000 or more	34.6
Don't know/refusal/not stated	0.6
Marital status of responding parent	
Married / common law	87.2
Widowed/divorced/separated/single	12.1
Don't know/refusal/not stated/not a parent	0.7
Child born outside Canada	06.0
NO	96.2
Yes Not stated	3.0
Not stated	0.8
Responding parent born outside Canada	(0.4
NU Voc	09.4 20 2
Not stated/respondent not shild's parent	29.2 1 F
Not stated/respondent not child's parent	1.5

¹Percentages are weighted

were 10.7% (95% CI 9.0-12.3) and 7.1% (95% CI 5.9-8.3), respectively.

Table 3 presents unadjusted (OR) and adjusted odds ratio (aOR) for associations between socio-demographic characteristics and the two outcomes of interest: delays of one to six months (vaccination at 13 to 18 months of age) and delays of seven to 18 months (vaccination between 19 and 30 months of age). Important variations across Canada's provinces and territories were found, with children from Manitoba, Saskatchewan, Alberta, British-Columbia and the territories presenting higher odds of vaccination delays compared with children from the Atlantic Provinces. Among the total number of toddlers for whom measles vaccination dates were available, the provincial or regional proportion of children vaccinated on time varied from 52% to 74% and the provincial or regional proportion of children presenting vaccination delays ranging from one to six months varied between 18% and 33%. After adjustment for covariates, these delays were less likely to occur in boys (aOR 0.78, 95% CI 0.61-0.99), with 24.35% (95% CI 21.45-27.25) of girls getting vaccinated with one- to six-month delays compared to 19.87% (95% CI 17.16-22.57) of boys. In the same model, children born abroad had higher odds of vaccination delays compared to children born in Canada (aOR 2.33 95% CI 1.13-4.80). The proportion of children immunized at 12 months of age was 69.8% (95% CI 57.4-72.1) for those born in Canada compared to 45.5% (95% CI 30.5-60.4) for those born outside Canada. The proportion of children born outside Canada whose vaccination was delayed one to 18 months was estimated at 46.7% (95% CI 31.7-61.8) as opposed to 24.4% (95% CI 22.3-26.5) in children born in Canada.

In the analysis of delays greater than six months, a partially different set of associated factors was obtained. The proportion of children with seven- to 18-month delays varied between 1 and 5% and occurred more frequently in those residing in Quebec, Manitoba, Saskatchewan and the territories compared to residents of Atlantic provinces. Among the children of married or common-law parents, 2.4% (95% CI 1.6-3.1) had sevento 18-month delays compared to 6.3% (95% CI 2.2-10.4) of children from unmarried parents. In children born outside Canada, this proportion was 13.7% (95% CI 3.5-24.0) compared to 2.7% (95% CI 1.9-3.5) for children born in the country. When adjusting for the province or region of residence, having a divorced, separated, widowed or single responding parent compared to those married or in a common-law relationship (aOR 3.17 95% CI 1.37-7.35) and being born outside of Canada (aOR 7.83, 95% CI 2.72-22.54) were factors significantly associated with seven- to 18-month delays. Interestingly, education level of the responding parent and household income were not associated with any of the outcomes studied.

Some KAB were associated with vaccination delays as depicted in Table 4. Not believing that childhood vaccines are safe had the strongest and the most statistically significant association (OR 0.48, 95% CI 0.26–0.87) with vaccination delays of one to six months. Confidence in the safety of childhood vaccines was also inversely associated with seven- to 18-month delays (OR 0.29, 95% CI 0.09–0.91). Among the factors statistically associated with these delays, agreeing with alternative

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Table 2. Distribution of delays for the first dose of measles-containing vaccine in two-year-old children in Canada, N = 3604.

Age at first dose of measles vaccine	Percentage (95% CI) ¹	Cumulative percentage (95% Cl) ¹
11 months of age (Invalid) 12 months of age (On time) 13 to 15 months of age (Delayed 1 to 3 months) 16 to 18 months of age (Delayed 4 to 6 months) 19 to 24 months of age (Delayed 7 to 12 months) 25 to 30 months of age (Delayed 13 to 18 months)	$1.74 (1.06-2.41)^{2}$ $69.14 (66.87-71.41)$ $18.46 (16.60-20.33)$ $3.55 (2.59-4.52)$ $2.08 (1.34-2.82)^{2}$ $0.92 (0.50-1.33)^{2}$ $4.11 (2.21, 5.01)$	70.88 (68.64–73.12) 89.34 (87.82–90.86) 92.89 (91.70–94.09) 94.97 (94.00–95.94) 95.89 (94.99–96.79)
Not vaccinated at 30 months of age	4.11 (3.21–5.01)	

¹All percentages are weighted

²Coefficient of variation between 16.5 and 33%; interpret with caution

practices for replacing vaccination presented the strongest association (OR 3.60, 95% CI 1.77–7.33). Parents believing that alternative practices such as homeopathy or chiropractic could replace vaccination were thus more than three times more likely to delay their child's measles vaccine seven to 18 months, compared to parents disagreeing with these practices. This association was also found to one to six months delays (OR 1.45, 95% CI 1.03–2.05). Parents feeling they had enough information about vaccination were less susceptible to delay their child's vaccine seven to 18 months compared to parents who were voicing a need for more information (OR 0.42, 95% CI 0.22–0.81). Finally, expressing concerns regarding MMR safety was marginally associated with seven- to 18-month delays, although this association did not reach statistical significance (OR 1.82, 95% CI 0.99–3.35).

Discussion

This analysis is, to our knowledge, the first nationally representative study of vaccination delays in Canada. In this study, approximately 70% of children in Canada have received their first valid dose of measles vaccine at 12 months of age in accordance with provincial and territorial vaccination schedules. Moreover, this study allowed identifying population subgroups at risk of delaying their child's first dose of measles vaccine.

For both vaccination delays outcomes, some geographic variations were observed and may result from the diverse delivery systems in Canadian jurisdictions. Accessibility to vaccination services may also vary across provinces and territories e.g. reduced accessibility in remote areas. Being born outside Canada was the factor most strongly associated with both vaccination delay outcomes. This subpopulation was also shown

Table 3. Sociodemographic characteristics associate	d with delayed measles vaccination and od	Ids ratios calculated by logistic regression, $N = 3385$.
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	One- to six-month vaccination delays $n = 798$		Seven- to 18-month vaccination delays $n = 96$	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Sex				
Male	0.78 (0.62-0.99)	0.78 (0.61–0.99)	1.24 (0.68–2.24)	
Female	Reference	Reference	Reference	
Province or region of residence				
Quebec	1.08 (0.82-1.42)	1.05 (0.79–1.38)	2.85 (1.31–6.21)	3.02 (1.32–6.95)
Ontario	1.20 (0.89–1.62)	1.19 (0.88–1.61)	1.94 (0.75–5.01)	2.11 (0.77–5.78)
Manitoba	2.58 (1.90-3.49)	2.53 (1.86–3.43)	3.28 (1.29-8.38)	3.37 (1.22–9.36)
Saskatchewan	1.65 (1.19–2.29)	1.61 (1.16–2.23)	3.57 (1.42-8.94)	4.13 (1.63–10.46)
Alberta	1.64 (1.20–2.25)	1.65 (1.20–2.27)	1.75 (0.55–5.58)	1.93 (0.56–6.63)
British Columbia	1.68 (1.24–2.26)	1.68 (1.24–2.26)	2.33 (0.86-6.27)	2.59 (0.89–7.52)
Territories	2.14 (1.67–2.74)	2.14 (1.67–2.75)	4.13 (1.98-8.61)	4.67 (2.12–10.28)
Atlantic	Reference	Reference	Reference	Reference
Education of the responding parent				
Secondary or less	1.03 (0.75–1.41)		2.08 (1.01-4.28)	
Post-secondary	0.98 (0.73-1.31)		1.40 (0.64-3.06)	
University graduate	Reference		Reference	
Total household income				
0 – \$39,000	1.01 (0.71–1.44)		1.97 (0.84–4.62)	
\$40,000 – \$59,999	0.92 (0.63–1.36)		1.57 (0.65–3.81)	
\$60,000 – \$79,999	1.02 (0.72–1.46)	1.06 (0.39–2.88)		
\$80,000 – \$99,999	1.02 (0.71–1.49)		0.37 (0.09–1.61)	
\$100,000 or more	Reference		Reference	
Single responding parent ¹				
Yes	1.37 (0.93–2.04)		3.18 (1.33-7.60)	3.17 (1.37–7.35)
No	Reference		Reference	Reference
Child born outside Canada				
Yes	2.33 (1.13–4.80)	2.33 (1.13–4.80)	7.83 (2.71–22.64)	7.83 (2.72–22.54)
No	Reference	Reference	Reference	Reference
Responding parent born outside Canada				
Yes	1.00 (0.76–1.31)		1.33 (0.72–2.47)	
No	Reference		Reference	

¹Single responding parent refers to widowed, divorced, separated or single parents, as opposed to married or living in a civil or common-law relationship.

Table 4. KAB associated with dela	ed measles vaccination and	d odds ratios calculated by	simple logistic r	egression, $N = 3385$
				<u>,</u>

	One- to six-month vaccination delays n = 798 Seven- to 18-month vaccination	
Childhood vaccines are safe ¹	Unadjusted 0 0.48 (0.26–0.87)	DR (95% CI) 0.29 (0.09–0.91)
Childhood vaccines are effective ¹	0.52 (0.14–1.87)	ns ²
Childhood vaccines are important ¹	0.50 (0.18–1.43)	ns ²
Understand how vaccines work ¹	0.85 (0.46–1.58)	0.75 (0.17–3.32)
Important to immunize against measles ¹	0.72 (0.45–1.16)	0.41 (0.15–1.11)
Enough info about immunization Yes No	0.87 (0.64–1.18) Reference	0.42 (0.22–0.81) Reference
Alternative practices can eliminate the need for vaccination ¹	1.45 (1.03–2.05)	3.60 (1.77–7.33)
Concerned about potential side effects ¹	1.19 (0.91–1.55)	1.63 (0.82–3.22)
Vaccines can cause the disease they are meant to prevent ¹	1.00 (0.76–1.31)	1.37 (0.71–2.65)
Concerned about MMR safety Very concerned/concerned Somewhat concerned/not concerned at all	1.23 (0.95–1.58) Reference	1.82 (0.99–3.35) Reference

¹OR compares responding parents who strongly or somewhat agree with the statement to responding parents who somewhat or strongly disagree with the statement. ²Data not shown; frequencies too low in certain categories for conducting analyzes

as more likely to be incompletely vaccinated against pertussis in a separate analysis conducted using the same survey data.¹⁷ One of the plausible explanations for this finding is that the routine vaccination schedule for infants can be different in the child's country of origin. For instance, the first dose of monovalent measles vaccine is routinely recommended at nine months of age in several African, Eastern Mediterranean, South East Asian and Western Pacific countries¹⁹ and in our analysis, doses given prior to 12 months of age were considered invalid and second doses received after 12 months of age would have been considered delayed, which was the case for only 4% children, who were not all born outside Canada. Vaccination delays could also result from reduced accessibility to vaccination services in their country of origin or to barriers in accessing health services after immigration.²⁰ On the other hand, a classification error in the vaccination status of immigrant children could have produced a biased association between the child's immigration status and vaccination delays. As the outcome was determined according to vaccination dates in the child's vaccination record, erroneous classification of immigrant children's vaccination as "late" because of missing information could lead to an overestimation of the association.

In terms of factors specifically associated with delays ranging from one to six months, girls were statistically more likely to be late for their measles vaccine, but the association might be of little population significance given the small difference in proportions. Associations of gender with vaccinations delays in toddlers are sparse in the literature, but do exist.²¹

Factors associated with vaccination delays more than six months were slightly different, with the province or region of residence, having a single parent or being born outside Canada as significant factors. The higher odds of delays in children from single parents are consistent with several other studies^{4,9-11} and may reflect that single parents may experience

difficulty in conciliating familial and work responsibilities. The associations between seven- to 18-month delays and jurisdiction of residence, marital status of the responding parent and immigration status of the child raise questions related to barriers limiting accessibility to vaccination services. The variables measured through cNICS 2013 provide limited insight on these issues. Finally, we did not observe relations between income or education level and timeliness of measles-containing vaccine administration, as opposed to a study on measles non-vaccination in the same sample of two-year-old children in which associations were found between low levels of parental education and medium household income and non-vaccination.¹⁷

Several KAB were associated with vaccination delays, supporting the concept that vaccine hesitancy contributes to this comportment.¹⁵ The marginal association of the importance of measles vaccination with delays could suggest complacency towards vaccines. Knowledge about vaccine safety as a factor associated with vaccination delays could reflect a lack of confidence in vaccines, and the belief that alternative practices can replace vaccine could be associated with mistrust in health care providers. In a study on vaccine delays where the outcome was self-reported, Smith et al.¹⁴ also found an association with perceived safety of vaccines, among other findings. According to the 3C's model, convenience refers to factors such as availability, affordability, accessibility, quality of service, convenience and ability to understand the information, in terms of language and health literacy, affecting the decision to get vaccinated.¹⁵ The perceived lack of information identified as a factor associated with delays could be linked to health literacy and thus not be a facilitating element in the decision of giving one's child their vaccine. A study based on delays in the province of Quebec, Canada, also identified a self-reported lack of information as one of the predictors of delay.²² In contrast with our results, studies on parental KAB and late vaccination identified

believing in vaccine effectiveness as a determinant of vaccination delays.^{14,22} Because the analysis was based on vaccination dates, the potential for misclassification from missing or incomplete information in vaccination records was reduced compared to analyses based on measles vaccination status (unvaccinated vs vaccinated),¹⁷ as they were restricted to children with measles vaccine doses and dates properly recorded.

This study had limitations. An important fraction of the sample could not be analyzed due to missing information on vaccination dates. In terms of KAB analysis, lack of statistical power due to low number in certain categories limited the analysis of certain factors associated with important vaccination delays (i.e. the strongest associations did not reach statistical significance). Some factors known to be associated with vaccination delays were not measured, thus limiting our ability to identify an exhaustive list of factors associated with vaccination delays and potentially leaving uncontrolled confounding. Not being the first-born child of the family^{2,4,11,22,23} or having more than one or two children^{6,9,10,24} and not having an up-to-date vaccination status at an earlier age^{4,6-8} are factors commonly found associated in studies of vaccination delays. These variables were not collected as part of cNICS 2013 but could have been of interest from a vaccination promotion perspective. Residual confusion might result from the use of broad categories, often necessary to ensure analyses were performed with a minimal number of observations. The potential information bias relative to the association between being born outside Canada and vaccination delays was highlighted above. Finally, although the sampling frame is estimated to be representative of children from Canada,²⁵ exclusions were applied and participation was limited to respondents able to communicate in French or in English, which could have excluded immigrants, those most likely to have difficulty in accessing vaccination services.

In conclusion, although most children in Canada received their first dose of measles-containing vaccine on time, vaccination delays occurred in our sample of two-year-old children, from which delays of one to three months were the most frequent. Factors associated with vaccination delays, all durations combined, were child's gender, immigration status as well as jurisdiction of residence, and parental marital status and KAB. Barriers in accessing vaccination services need to be better understood to promote timely vaccination. Vaccine hesitancy and its contribution to vaccination delays should be further studied.

Methods

cNICS 2013 is described elsewhere.²⁶ Briefly, cNICS is a nationally representative cross-sectional study conducted approximately every two years for measuring childhood vaccination coverage in Canada. The list of children for whom the Canadian Child Tax Benefit was claimed was used as a sampling frame. On-reserve First Nations were excluded. Stratified sampling, based on age of children and province or territory of residence, was used. Parents were contacted by telephone and those who responded that their child was ever vaccinated were asked to read the vaccination record of their child and respond to questions on their socio-demographic characteristics and KAB. Information on vaccination from health care providers in addition to parents' responses was obtained for about a third of the sample. In this study, only children in the age group used to measure coverage by two were considered; they were aged 30 to 41 months at the time of the survey.

The age at measles vaccination (in months) was derived in calendar time from birth and measles vaccination dates. The analysis included 3604 children for whom information on measles vaccination was available. Doses received after 30 months of age were not considered as the youngest children from the sample were 30 months old at the time of the survey. Overall, 4% of children got their first dose of measles-containing vaccine prior to their first birthday and the majority of them were vaccinated at 11 months of age. For children whose first dose was given before 11 months of age, the second dose was referred to as a first valid dose. Children were classified in various age at vaccination categories: 11 months of age (invalid), 12 months of age (on time), 13 to 18 months of age (one- to six-month delays) or 19 to 30 months of age (seven- to 18-month delays). Children who were immunized at 11 months of age were excluded from regression analyses (i.e. were not included in the delays or reference groups).

Measles vaccination delays were defined according to Canadian vaccination schedules in accordance with the *National Eligible, Due and Overdue Guidelines for Immunization Registries*²⁷ and published literature. Doses received one month or greater after the scheduled age were considered delayed.^{11,12,23,24} For descriptive statistics, doses were categorized as being received without delay, delayed one to three months, delayed four to six months, delayed seven to 12 months, delayed 13 to 18 months, not vaccinated or not stated. The latest, namely children from which the dates at vaccination could not be calculated for various reasons, were excluded from analyzes. Important delays were empirically defined as a delay of more than six months after the recommended age.¹¹

Delays in the first valid dose of measles vaccine were dichotomized and yielded two dependent variables used in distinct logistic regression models: important vaccination delays of seven to 18 months (vaccine received when children aged 19 months or greater) vs. on-time vaccination as the reference group (vaccine received when children aged 12 months) and 'shorter" vaccination delays of one to six months (vaccine received when children is aged between 13 months and 18 months of age) vs. on-time vaccination as the reference group (vaccine received when children aged 12 months). 2491 children were vaccinated on time, 798 children were vaccinated with one- to six-month delays and 96 were vaccinated with seven- to 18-month delays. This yields a sample size of 3385 children for the logistic regression analysis, which excludes children who were unvaccinated at 30 months of age and children vaccinated prior to 12 months of age.

Logistic regressions were carried out separately for sociodemographic characteristics and KAB. For models comprising socio-demographic characteristics, simple and multiple logistic regressions were performed, whereas for models of KAB, only simple logistic regressions models were used due to correlation among variables. Independent variables were selected for the multiple logistic models based on the statistical significance (p<0.1 for inclusion) and were backwardly excluded if the p value exceeded 0.1 in the multiple model. Socio-demographic variables are listed in Table 1. Provinces and territories of residence were grouped into regions when sample size was suboptimal (Atlantic: Newfoundland and Labrador, Prince Edward Island, Nova Scotia, New Brunswick; territories: Northwest Territories, Yukon, Nunavut). Imputation by the nearest neighbour method²⁸ was used to account for missing values for household income (n = 1523, 28%). To account for the survey design, variance for all presented estimates was calculated using the Bootstrap method with 1000 replications.²⁹ OR and proportions presented for the analytical sample were weighted to account for the sampling method. All analyzes were performed using SAS Enterprise Guide 5.1 and SAS 9.3.

Ethics

cNICS was not considered health research as it was conducted by Statistics Canada as part of its mandate to "collect, compile, analyze, abstract and publish statistical information relating to the commercial, industrial, financial, social, economic and general activities and conditions of the people of Canada". Participants volunteered in the survey and data was kept confidential. Authors of this study had no access to any identifiable records.

Disclosure of potential conflicts of interest

The authors have no potential conflicts of interest to disclose.

Acknowledgments

The authors thank all survey participants. cNICS was developed jointly by the Special Survey Division, Statistics Canada, and the Centre for Immunization and Respiratory Infectious Diseases, Public Health Agency of Canada. We are also grateful to Dr Sarah Wilson for advice as well as to Joy Pulickal, Lyne Cantin and Rhonda Kropp for reviewing the manuscript.

Funding

cNICS was funded by the Public Health Agency of Canada.

Contributors

SP and NLG designed the study with input from GDS and MK. SP conducted the analysis and wrote the manuscript. All authors contributed to the manuscript, reviewed and approved the manuscript.

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