Vaccine 37 (2019) 3123–3132

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Characteristics of immunized and un-immunized students, including non-medical exemptions, in Ontario, Canada: 2016–2017 school year

Sarah E. Wilson [a,b,c,*], Jillian Murray [a], Andrean Bunko [a], Steven Johnson [a], Sarah A. Buchan [a,b,c], Natasha S. Crowcroft [a,b,c,d], Vinita Dubey [b,e], Lawrence C. Loh [b,f], Melissa MacLeod [g], Christina Taylor [h], Shelley L. Deeks [a,b]

[a] Public Health Ontario, Toronto, Ontario, Canada
[b] Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[c] ICES, Toronto, Ontario, Canada
[d] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada
[e] Toronto Public Health, Toronto, Ontario, Canada
[f] Peel Public Health, Mississauga, Ontario, Canada
[g] Southwestern Public Health, Woodstock, Ontario, Canada
[h] Huron County Health Unit, Clinton, Ontario, Canada

ARTICLE INFO

Article history:
Received 19 February 2019
Received in revised form 9 April 2019
Accepted 10 April 2019
Available online 24 April 2019

Keywords:
Immunization
Non-medical exemptions
Medical-exemptions
Vaccine hesitancy
Vaccine acceptance
Immunization policy

ABSTRACT

Background: Our objectives were: (1) to quantify and describe un-immunized students in Ontario, Canada and assess the extent to which these students have exemptions; and (2) to quantify and describe students with non-medical exemptions (NMEs), including what proportion have up-to-date immunizations.

Methods: We examined Ontario students 7 to 17 years-of-age in the 2016–2017 school year using information within a centralized immunization repository. We identified and described students with different immunization/exemption classifications by age, sex, school type, geography and area-level material deprivation using descriptive and multivariable logistic regression analyses. Finally, we assessed the immunization status of students with NMEs, by antigen.

Results: We found that students could be recorded as un-immunized with or without an NME, or be immunized with an NME. From a cohort of 1.65 million students, 2.9% of students had zero vaccine doses recorded, and of these 68% had no exemption of any kind. A total of 2.4% of students had an NME. Of these, 39% were un-immunized and 61% had received ≥1 vaccine. Among all students with NMEs, 19–48% had up-to-date immunizations, varying by antigen. Factors associated with increased odds of having a NME and being un-immunized included: attendance at private and 'other' schools, rural residence, and geography. Older age and greater area-level deprivation were associated with a reduced odds.

Conclusions: Our assessment revealed that Ontario students with NMEs cannot be assumed to be un-immunized and at risk for all vaccine-preventable diseases. Conversely, not all un-immunized students had NMEs suggesting that future studies of un-immunized children in Ontario must consider additional factors beyond NME status alone. Other jurisdictions that use NME data to inform research and surveillance of vaccine hesitancy and risks for VPD outbreaks may wish to undertake a similar assessment to determine how well student NMEs correlate with student immunization status.

1. Introduction

In jurisdictions with school-entry immunization requirements that allow for medical and non-medical exemptions (NMEs), population-based systems that record both immunizations and exemptions can be used as a routine data source to monitor trends in vaccine confidence and to assess the impact of policy interventions to limit exemptions and/or improve vaccine coverage. Studies from the United States (US) have demonstrated an increase in children with NMEs over time [1–4], spatial clustering of under-immunized children [5] and those with NMEs [6,7], the spatial relationship between geographic areas with high levels of NMEs

* Corresponding author at: Public Health Ontario, 480 University Avenue, Suite 300, Toronto, ON M5G 1V2, Canada.
E-mail address: sarah.wilson@oahpp.ca (S.E. Wilson).

https://doi.org/10.1016/j.vaccine.2019.04.033
0264-410X/

and risk of vaccine-preventable disease (VPD) outbreaks [8–11] and the influence of state policies on exemptions [12–15].

Among Canada's 13 provinces and territories, Ontario is one of only two jurisdictions with legislation outlining comprehensive school-entry immunization requirements. Immunizations and exemptions are submitted to local Public Health Units (PHUs) by parents/guardians and recorded in a centralized, population-based information system, the Digital Health Immunization Repository (DHIR). Previous analyses of Ontario students found that non-medical exemptions (specifically to measles-containing vaccine) increased over an eleven year period, while medical exemptions declined over the same time, resulting in little overall change in total exemptions [16]. A number of changes have occurred in the Ontario immunization context following our earlier analyses. These include additional vaccines required for school-entry (implemented in September 2014) [17], a new requirement for parents seeking an NME to attend a mandatory in-person education session (effective September 2017) [18], and the implementation of the DHIR between 2013 and 2016. Prior to the implementation of the DHIR, analyses of immunization exemptions in Ontario were limited to aggregate data provided by individual PHUs [16]. In contrast, the availability of DHIR data, now permits more detailed analyses using record-level data.

The goals of this study were to address unanswered questions about Ontario children and their immunization and exemption status that were not previously feasible to assess using aggregate data and to establish a baseline for future monitoring of immunization exemptions. Our specific objectives were to: (1) quantify and describe un-immunized students in Ontario and assess the extent to which these children have exemptions; and (2) quantify and describe students with non-medical exemptions (NMEs), including what proportion have up-to-date immunizations.

2. Methods

2.1. Study population and setting

Ontario is Canada's most populous and ethnically diverse province with 13.5 million residents. Under the *Immunization of School Pupils Act* (ISPA), students must be immunized against nine VPDs (measles, mumps, rubella, diphtheria, tetanus, pertussis, polio, meningococcus and varicella) or submit a statement of medical or religious/conscientious (non-medical) exemption. Students may face school suspension if ISPA requirements are not met [17]. The ISPA was first established in 1982 and originally applied to six VPDs, with requirements for pertussis, invasive meningococcal disease, and varicella (for those born on/after 2010) coming into force in 2014.

Prior to September 2017, a notarized Statement of Conscience or Religious Belief was required to obtain an exemption [19]. As of September 2017, parents seeking an NME must also attend a mandatory education session held by their local PHU [18]. This requirement was not applicable to the students assessed as part of our analyses. To obtain a medical exemption under the ISPA, a Statement of Medical Exemption must be completed and signed by a physician or nurse practitioner indicating the rationale for the exemption as being "detrimental to health" or on the basis of laboratory confirmation of immunity for select diseases [20]. Within the DHIR, the former are classified as medical exemptions; the latter are captured under a distinct classification specific to prior immunity.

In Ontario, immunizations are publicly-funded and administered primarily by community-based healthcare providers, with the exception of three school-based adolescent immunization programs. Parents provide student immunization information to their local PHU at the time of school enrollment or as otherwise requested, for subsequent recording within the DHIR. Separate from the process of reporting of immunizations, enrollment lists for publicly-funded school boards are uploaded into the DHIR to establish a population-based record for all students in Ontario.

To address our study objectives we created a population-based analytic cohort using data extracted from the DHIR, comprised of all students aged 7 to 17 years of age who attended school in Ontario in the 2016–2017 school year.

2.2. Data management, definitions and descriptive analysis

2.2.1. Identification of un-immunized students and students with exemptions

Vaccine doses recorded in the DHIR were used to identify two groups of students: immunized (i.e., those with at least one dose of any vaccine) and un-immunized (i.e., those with no doses of vaccine of any kind). Within these two groups, students were further described by exemption status (yes/no) and those with exemptions were further categorized by type: medical, non-medical, prior immunity and administrative. Only the first three exemption types are recognized under the ISPA, while administrative exemptions are applied at the discretion of local PHUs to address operational issues [21]. The total number of students with exemptions, irrespective of vaccine status in the DHIR, was also calculated by exemption type.

2.2.2. Student characteristics

Demographic and education data from the DHIR were used to describe students on the basis of gender, age group (7–10, 11–13, 14–17 years) and school-board type (public, private, other). The "other" school board type is a classification in the DHIR that represents a variety of school types (including home schools, religious schools, specialty schools such as sports academies, and some private schools that are allocated to this category at the discretion of individual PHUs). Residential postal code was used to assign students to Dissemination Areas (DAs); DAs are the smallest standard geographic unit for which Canadian Census data are disseminated. Using 2016 census data, students were characterized by population density based on their DA of residence (rural: population < 1000; small/medium population centres: population range: 1000 to < 100,000; urban: population $\geq$ 100,000), PHU and PHU Region. We also assigned students to quintiles of material deprivation using the 2011 Ontario Marginalization Index (ON-Marg), based on residential DA [22]. A descriptive analysis using PHU Region (at the time of data extraction, 36 PHUs comprised 7 PHU geographic regions) and the other characteristics noted above was carried out focussed on students within four categories of immunization and exemption information: (i) students with at least 1 vaccine dose and no exemptions, (ii) students with zero vaccine doses and no exemptions, (iii) students with an NME and zero vaccine doses; and (iv) those with an NME and at least 1 vaccine dose.

To characterize the geographic variability in immunization exemptions we mapped the proportions of students with an NME and zero vaccine doses and those with an NME and $\geq$ 1 vaccine dose by PHU, separately.

2.2.3. Antigen-level non-medical exemptions and immunization status

Among all students with an NME, we further described exemptions at the antigen level (i.e. the number of students with an NME to one antigen only, to at least one antigen and to all eight ISPA antigens). Within each group of students with an NME to a specific antigen, we categorized students according to immunization status (up-to-date (UTD), under-immunized or un-immunized). Students were categorized as UTD, by antigen, if they received the recom-

mended number of vaccine doses for their age, after considering minimum ages and intervals and vaccine interactions (if applicable), as specified elsewhere [23]. In Ontario, there are two publicly-funded meningococcal immunization programs. In recognition of the two programs and ISPA requirements, we assessed students 7 to 11 years of age for receipt of meningococcal C-containing vaccine (MCC) and assessed students aged 12 to 17 years for receipt of quadrivalent meningococcal conjugate vaccine (MCV4). Students were classified as under-immunized if they had received at least one dose of a relevant vaccine but were not UTD. For one dose programs (such as rubella), under-immunized students reflect those who have received an invalid dose (e.g. given before the first birthday).

2.3. Statistical analysis

Unadjusted and adjusted odds ratios (ORs and aORs) with 95% confidence intervals (CI) were calculated using multivariable logistic regression to assess the association between student characteristics (gender, age, school board, area-type, PHU region and material deprivation) for three different outcomes: students with an NME who had received ≥ 1 vaccine dose, students with an NME who were un-immunized, and students with zero vaccine doses and no exemptions. Each of the three outcomes were assessed in separate models and compared to a reference group of immunized students ($\geq$1 vaccine dose) with no type of exemption recorded in the DHIR. Only students with complete covariate information were included in the models.

2.4. Ethics, consent and privacy statements

The study was approved by Public Health Ontario's (PHO) Ethics Review Board. Similar to other studies using routine surveillance data, subjects were not contacted to receive expressed consent. All analyses occurred at PHO using SAS Version 9.4 (SAS Institute, Cary, NC) and ArcGIS Version 10.3 (Environmental Systems Research Institute, Redlands, CA).

3. Results

3.1. Un-immunized students and those with exemptions: Numbers and characteristics

The study cohort consisted of 1,651,729 students. A total of 47,820 students (2.9%) were un-immunized in the DHIR (i.e. zero doses of any vaccine recorded) (Fig. 1A). The majority (68%) of these students had no exemption of any type in the DHIR

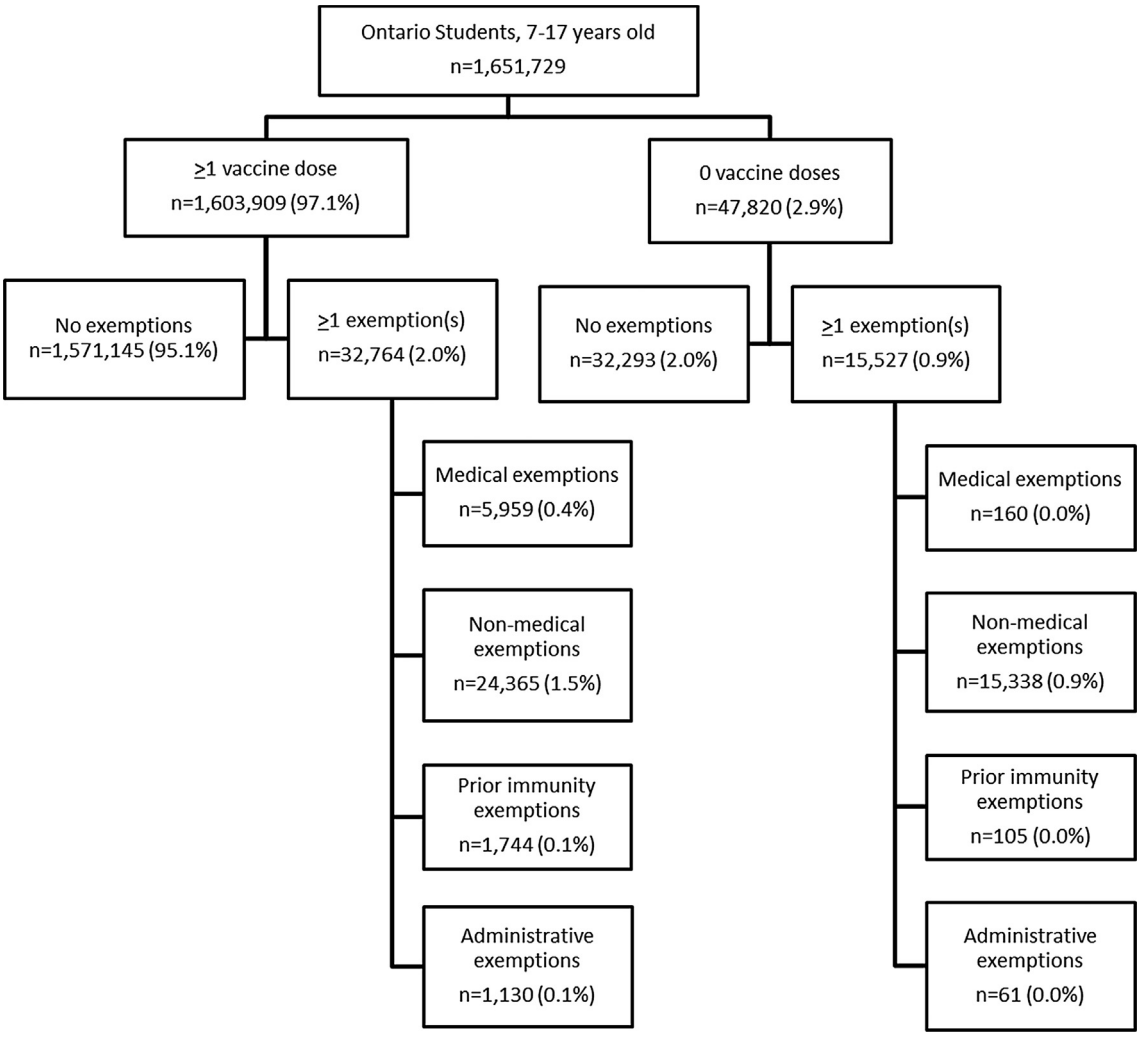

Fig. 1A. Flowchart of student immunization and exemption information* categorized into groups of interest: 2016–17 school year *Note: Exemption types are not mutually exclusive.

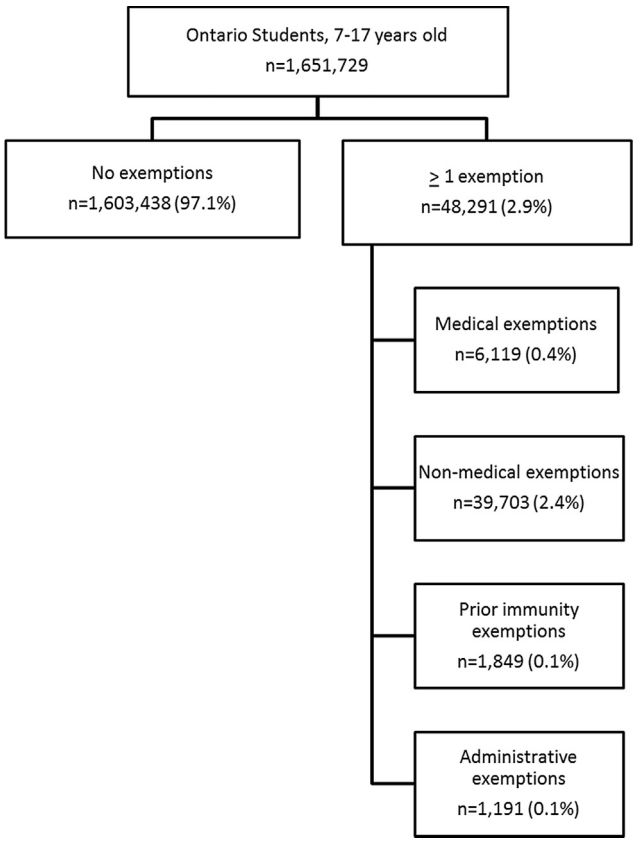

Fig. 1B. Flowchart of student exemption status and exemption classification: 2016–17 school year.

(n = 32,293); the remaining 15,527 students had an exemption, of which 99% were NMEs (n = 15,338).

The total number of students with an NME in the 2016–2017 school year was 39,703 (2.4%) (Fig. 1B). Of these, 39% were un-immunized and 61% had received ≥ 1 vaccine. Few students had medical exemptions (n = 6,119), less than 0.4% of the total cohort.

The characteristics of students assigned to one of four classifications incorporating immunization and exemption information, are presented in Table 1. Thirty-six percent of immunized (≥1 vaccine dose recorded in the DHIR) children without exemptions were in the 7–10 year age strata, as compared to 47% un-immunized children with an NME and 44% of un-immunized children without any form of exemption, respectively. A greater proportion of un-immunized children attend private schools (12–16%), regardless of exemption status, as compared to 4% of children who are immunized and without exemptions. Differences were also noted by area-type. A greater proportion of un-immunized children without exemptions live in urban areas (83%), as compared to 69% of immunized children without exemptions. In contrast, a greater proportion of un-immunized children with an NME live in rural areas (25%), as compared to 14% of immunized children without exemptions. Just under half (47–49%) of children with NMEs, regardless of immunization status, reside in neighbourhoods assigned to the two most affluent quintiles. In contrast, 52% of un-immunized students without exemptions live in neighbourhoods in the two most deprived quintiles.

3.2. Geographic variability

The geographic variability in NMEs across Ontario is described by PHU Region in Table 1 and further by PHU in Figs. 2A and 2B. The proportions of students with an NME (with and without vac-

Table 1
Student characteristics by immunization and exemption status, for students aged 7 to 17 years in Ontario, Canada, 2016–2017 school year.

	Immunized, no exemptions (n = 1,571,145)	Immunized, with NME (n = 24,365)	Un-immunized with NME (n = 15,338)	Un-immunized, no exemptions (n = 32,293)	Groups of Interest Combined* (n = 1,643,141)
Gender	# (%)	# (%)	# (%)	# (%)	# (%)
Female	767,020 (49)	11,489 (47)	7501 (49)	15,106 (47)	801,116 (49)
Male	803,994 (51)	12,872 (53)	7829 (51)	17,157 (53)	841,852 (51)
Missing	131 (<1)	4 (<1)	8 (<1)	30 (<1)	173 (<1)
Age (years)					
7–10	566,051 (36)	7384 (30)	7283 (47)	14,220 (44)	594,938 (36)
11–13	423,645 (27)	6424 (26)	3718 (24)	6836 (21)	440,623 (27)
14–17	581,449 (37)	10,557 (43)	4337 (28)	11,237 (35)	607,580 (37)
School Board					
Publicly-funded	1,503,124 (96)	22,362 (92)	12,974 (85)	27,062 (84)	1,565,522 (95)
Private	62,456 (4)	1620 (7)	1912 (12)	5050 (16)	71,038 (4)
Other	5565 (<1)	383 (2)	452 (3)	181 (1)	6581 (<1)
Area Type					
Urban	1,090,088 (69)	14,270 (59)	8294 (54)	26,704 (83)	1,139,356 (69)
Small/Med population centre	264,686 (17)	5000 (21)	3208 (21)	2963 (9)	275,857 (17)
Rural	215,076 (14)	5046 (21)	3775 (25)	2587 (8)	226,484 (14)
Missing	1,295 (<1)	49 (<1)	61 (<1)	39 (<1)	1,444 (<1)
PHU Region					
Central East	520,290 (33)	6699 (27)	4223 (28)	12,088 (37)	543,300 (33)
Central West	320,462 (20)	6408 (26)	3709 (24)	5564 (17)	336,143 (20)
Eastern	200,733 (13)	2957 (12)	1674 (11)	1431 (4)	206,795 (13)
North East	56,866 (4)	1093 (4)	467 (3)	101 (<1)	58,527 (4)
North West	24,842 (2)	386 (2)	179 (1)	136 (<1)	25,543 (2)
South West	179,871 (11)	4122 (17)	3029 (20)	2988 (9)	190,010 (12)
Toronto	266,189 (17)	2646 (11)	1978 (13)	9840 (30)	280,653 (17)
Missing	1892 (<1)	54 (<1)	79 (1)	145 (<1)	2,170 (<1)

Table 1 (*continued*)

	Immunized, no exemptions (n = 1,571,145)	Immunized, with NME (n = 24,365)	Un-immunized with NME (n = 15,338)	Un-immunized, no exemptions (n = 32,293)	Groups of Interest Combined* (n = 1,643,141)
Quintiles (Q) of Material deprivation					
Q1 (most affluent)	299,700 (19)	5588 (23)	3468 (23)	3519 (11)	312,275 (19)
Q2	330,274 (21)	5940 (24)	3945 (26)	5063 (16)	345,222 (21)
Q3	311,538 (20)	5015 (21)	3577 (23)	6661 (21)	326,791 (20)
Q4	301,064 (19)	4020 (16)	2309 (15)	6102 (19)	313,495 (19)
Q5(most deprived)	321,747 (20)	3653 (15)	1923 (13)	10,560 (33)	337,883 (21)
Missing	6822 (<1)	149 (1)	116 (1)	388 (1)	7475 (<1)

* This group of students represents the sum of Groups 1A, 1B2, 2B2, and 2A.

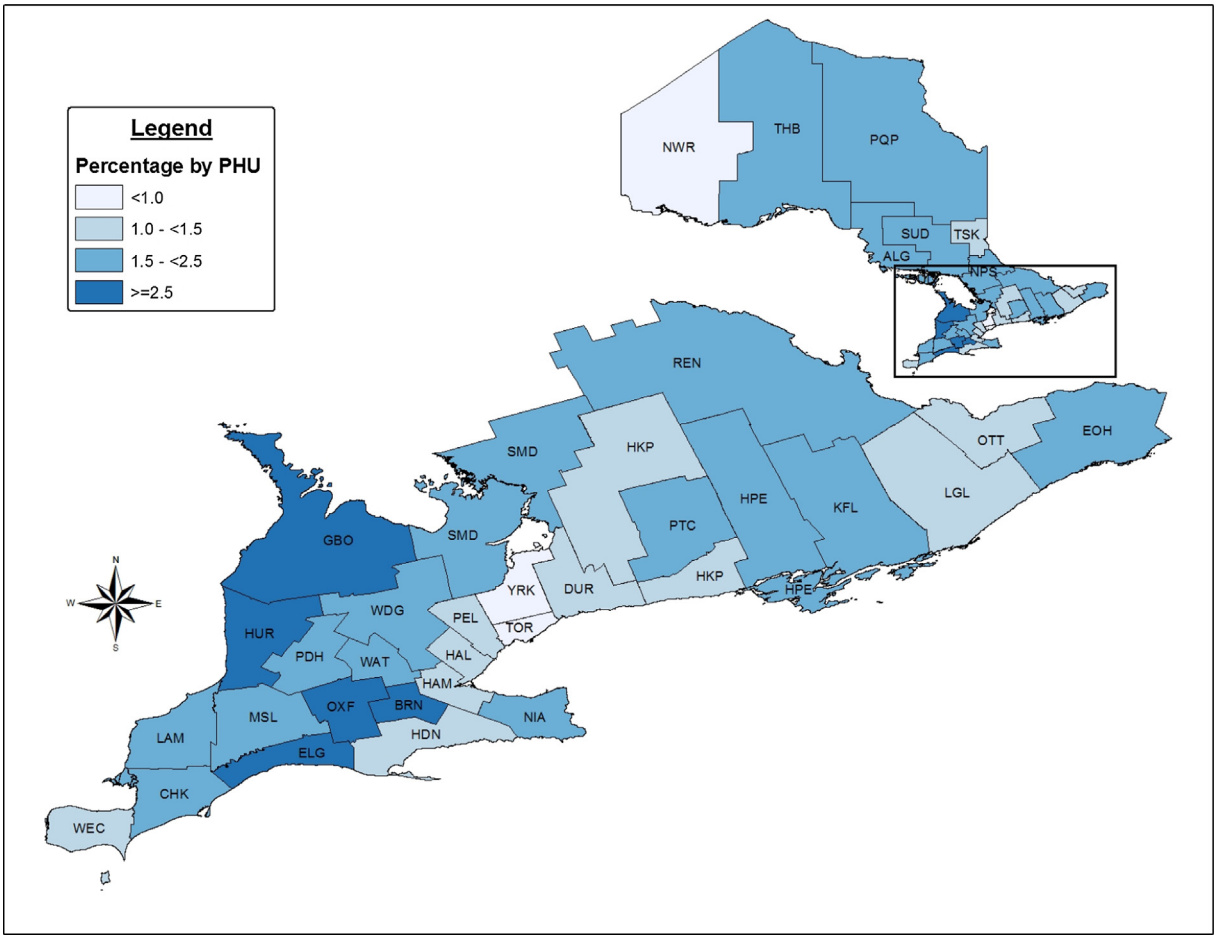

Fig. 2A. Percentage of students aged 7–17 years with an NME and at least one vaccine dose, by Public Health Unit: 2016–2017 school year.

cine doses in the DHIR) varied substantially by PHU and were highest among a small group of neighbouring PHUs located in the southwest of Ontario.

3.3. Multivariable logistic regression

Factors associated with increased odds of having an NME and being un-immunized included: attendance at private (aOR 3.29, 95% CI 3.13–3.46) or 'other' (aOR 7.30, 95% CI 6.56–8.12) schools, living in a rural area (aOR 1.95, 95% CI 1.87–2.04) or small-medium population centre (aOR 1.46, 95% CI 1.40–1.53), and living in the South West (aOR 1.64, 95% CI 1.56–1.72), Central West (aOR 1.29, 95% CI 1.23–1.35) regions, as well as Toronto (aOR 1.16, 95% CI 1.10–1.23) (Table 2). The odds of having an NME and being un-immunized decreased with age (aOR for those aged 14–17: 0.59, 95% CI 0.57–0.61) and decreased with neighbourhood-level deprivation (aOR for those living in the most deprived quintile (Q5): 0.66, 95% CI 0.62–0.69). Similar associations were found in the analysis of children with an NME and receipt of ≥ 1 vaccine, with the exception of age where the odds were higher for older age groups compared to 7–10 year olds (aOR for those age 14–17: 1.41, 95% CI 1.37–1.45), sex (aOR for males: 1.07, 95%CI 1.04–1.10) and differences noted by PHU Region.

Finally, un-immunized children with no exemptions had many similarities to children with no immunizations and an NME with several notable exceptions. Using the same reference group for comparison (students with at least one vaccine dose and no exemptions), un-immunized children with no exemptions were less likely to reside in small-medium population centres and rural centres (aOR for rural centres: 0.72, 95% CI 0.69–0.75; aOR for

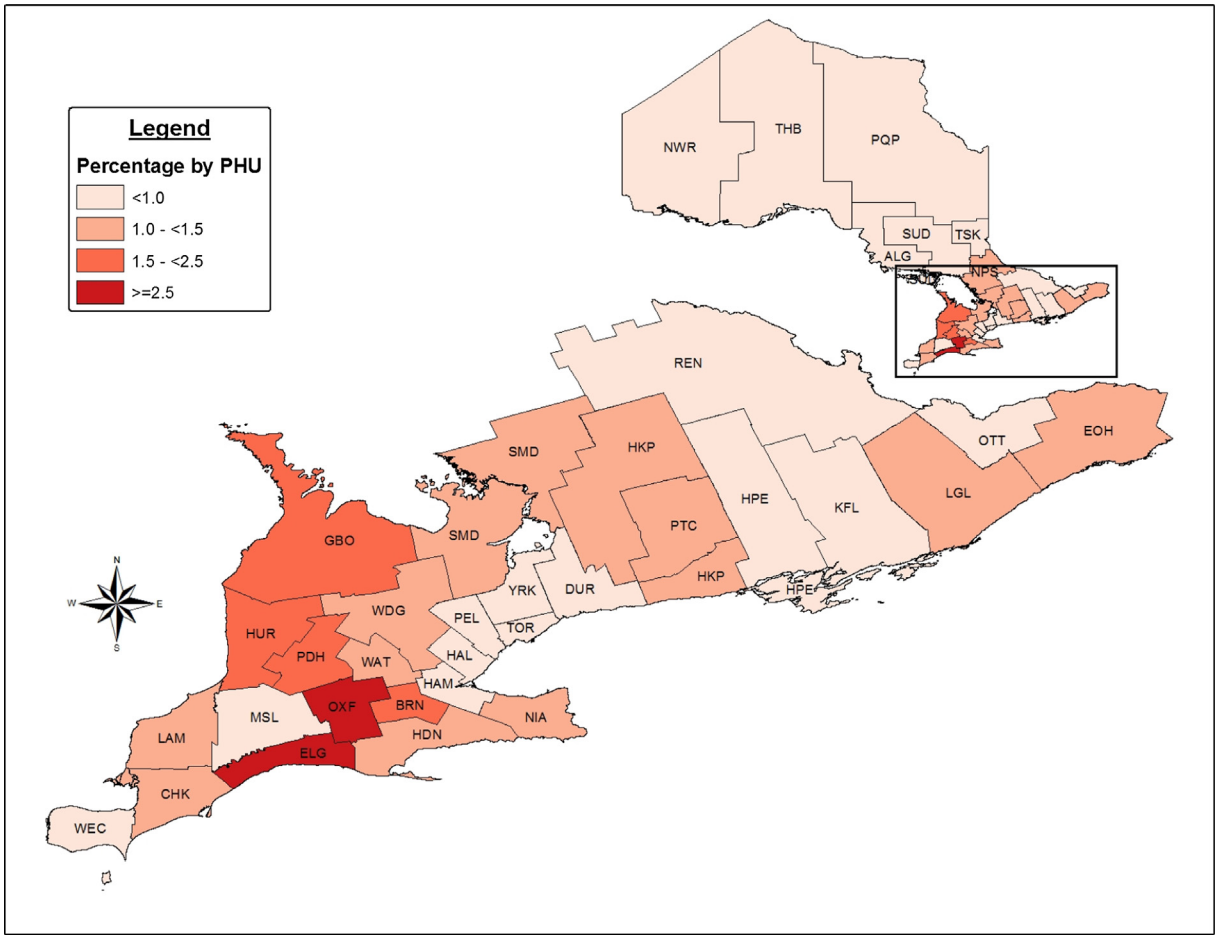

Fig. 2B. Percentage of students aged 7–17 years with an NME and zero vaccine doses, by Public Health Unit: 2016–2017 school year.

small/medium centre: 0.70, 95% CI 0.67–0.73), were more likely to reside in neighbourhoods characterized by material deprivation (aOR for those living in the most deprived quintile (Q5): 2.43, 95% CI 2.33–2.53) and more likely to be male (aOR 1.09, 95% CI 1.06–1.11).

3.4. Antigen-level non-medical exemptions and immunization status

Among the 39,703 students identified as having an NME, 91% (n = 35,984) had an NME to all eight ISPA antigens that were applicable to the birth years included within the study cohort (Table 3). Only 2.6% (n = 1025) had an NME for only one antigen. Of these students, 89% (n = 913) had their single NME recorded for meningococcal vaccines. Among all children with an NME, 19–48% were up-to-date for their immunizations, varying by specific antigen (Fig. 3). With the exception of children with an NME for meningococcal vaccines, for which 77% of children were un-immunized, the proportion of children who were un-immunized for specific antigens ranged from 44 to 52%.

4. Discussion

Our study provides the first estimates of un-immunized children in Ontario, Canada and provides more detailed characterization of students with NMEs than a previous analysis from our team that was limited by aggregate data and focussed only on NMEs to measles-containing vaccines [16]. Our findings indicate that 2.4% students aged 7–17 in the 2016–2017 school year had an NME to at least one antigen, and that the overwhelming majority (>90%) had an NME to all eight antigens applicable to the study cohort. When NMEs were examined at an antigen level, approximately half of children had some degree of protection to VPDs for which they had NMEs recorded, with the exception of exemptions for meningococcal disease where 77% of students with an NME were un-immunized. The proportion of fully un-immunized students in Ontario likely falls between 0.9% and 2.9%.

Uncertainty remains regarding the precise number of un-immunized students in Ontario as it is unclear whether the 32,293 students in the DHIR who have neither immunizations, nor exemptions (of any kind) reflect fully un-immunized children, or children who have yet to be assessed by local PHUs who may be up-to-date, partially immunized or un-immunized. Our descriptive and multivariable analyses suggest this may be a distinct group of students, as they differ from un-immunized children with an NME in many ways, including being less likely to live in rural and smaller centres and more likely to live in neighbourhoods characterized by material deprivation. These factors would support the hypothesis that these are students who are new to Ontario (and possibly new to Canada), who have yet to be assessed under the *Immunization of School Pupils Act*. Approximately 29% of Ontario's population is foreign-born and the largest proportion of newcomers to Canada settle in the province, particularly in urban and suburban areas comprising the Greater Toronto Area (GTA) (population 5.9 million). For example, in several GTA municipalities outside the city centre of Toronto, approximately half of the population is born outside of Canada [24]. Children who settle in Ontario after the local PHU has completed its ISPA assessment and enforcement activities

Table 2
Association between student characteristics and three different immunization and exemption classifications, 2016–2017 school year.

	Un-immunized with NME * (n = 15,214)		Immunized, with NME* (n = 24,212)		Un-immunized, no exemptions* (n = 31,879)	
Gender	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.00 (0.97–1.03)	0.99 (0.96–1.03)	1.07 (1.04–1.10)	1.07 (1.04–1.10)	1.09 (1.06–1.11)	1.09 (1.06–1.11)
Age (years)						
7–10	Ref	Ref	Ref	Ref	Ref	Ref
11–13	0.68 (0.66–0.71)	0.67 (0.64–0.70)	1.17 (1.13–1.21)	1.16 (1.12–1.20)	0.64 (0.62–0.66)	0.63 (0.61–0.65)
14–17	0.58 (0.56–0.60)	0.59 (0.57–0.61)	1.40 (1.36–1.44)	1.41 (1.37–1.45)	0.75 (0.74–0.77)	0.75 (0.73–0.77)
School Board						
Publicly-funded	Ref	Ref	Ref	Ref	Ref	Ref
Private	3.49 (3.33–3.67)	3.29 (3.13–3.46)	1.75 (1.66–1.84)	1.76 (1.67–1.85)	4.51 (4.37–4.66)	4.63 (4.48–4.78)
Other	9.96 (8.99–11.02)	7.30 (6.56–8.12)	4.94 (4.43–5.51)	4.14 (3.70–4.64)	1.75 (1.49–2.06)	2.61 (2.22–3.08)
Area Type						
Urban	Ref	Ref	Ref	Ref	Ref	Ref
Small/Med population centre	1.60 (1.53–1.66)	1.46 (1.40–1.53)	1.44 (1.40–1.49)	1.22 (1.18–1.26)	0.46 (0.44–0.47)	0.70 (0.67–0.73)
Rural	2.33 (2.24–2.42)	1.95 (1.87–2.04)	1.80 (1.74–1.86)	1.50 (1.45–1.56)	0.45 (0.43–0.47)	0.72 (0.69–0.75)
PHU Region						
Central East	Ref	Ref	Ref	Ref	Ref	Ref
Central West	1.42 (1.36–1.49)	1.29 (1.23–1.35)	1.55 (1.50–1.61)	1.48 (1.43–1.53)	0.73 (0.70–0.75)	0.78 (0.76–0.81)
Eastern	1.03 (0.97–1.09)	0.89 (0.84–0.94)	1.14 (1.09–1.19)	1.04 (1.00–1.09)	0.30 (0.28–0.32)	0.35 (0.33–0.37)
North East	1.02 (0.92–1.12)	0.86 (0.78–0.95)	1.48 (1.39–1.58)	1.32 (1.23–1.41)	0.08 (0.06–0.09)	0.11 (0.09–0.13)
North West	0.93 (0.80–1.08)	0.62 (0.53–0.72)	1.20 (1.08–1.34)	0.94 (0.84–1.04)	0.24 (0.20–0.28)	0.28 (0.23–0.33)
South West	2.08 (1.98–2.18)	1.64 (1.56–1.72)	1.78 (1.71–1.85)	1.57 (1.51–1.64)	0.71 (0.68–0.74)	0.85 (0.81–0.88)
Toronto	0.92 (0.87–0.97)	1.16 (1.10–1.23)	0.77 (0.74–0.81)	0.88 (0.84–0.92)	1.59 (1.55–1.63)	1.23 (1.20–1.27)
Quintiles (Q) of Material deprivation						
Q1 (most affluent)	Ref	Ref	Ref	Ref	Ref	Ref
Q2	1.03 (0.99–1.08)	1.03 (0.99–1.08)	0.97 (0.93–1.00)	0.99 (0.95–1.02)	1.31 (1.25–1.37)	1.29 (1.23–1.35)
Q3	0.99 (0.95–1.04)	1.05 (1.00–1.10)	0.86 (0.83–0.90)	0.93 (0.89–0.97)	1.83 (1.75–1.90)	1.72 (1.65–1.79)
Q4	0.66 (0.63–0.70)	0.79 (0.75–0.83)	0.72 (0.69–0.75)	0.85 (0.82–0.89)	1.73 (1.66–1.81)	1.51 (1.45–1.58)
Q5 (most deprived)	0.52 (0.49–0.55)	0.66 (0.62–0.69)	0.61 (0.58–0.64)	0.77 (0.74–0.80)	2.80 (2.70–2.91)	2.43 (2.33–2.53)

* Reference is immunized children (>=1 dose) with no exemptions recorded in the DHIR (Group 1).

Table 3
Number of antigen-specific NMEs per student, among Ontario students with at least one NME: 2016–2017 school year.

Number of antigen-specific NMEs among students with at least one NME	Number of students	% of all students with at least one NME (n = 39,703)
1	1025	2.6
2	68	0.2
3	759	1.9
4	661	1.7
5	315	0.8
6	169	0.4
7	722	1.8
8	35,984	90.6

will have a student record in the DHIR but no immunization information until the next immunization screening and enforcement period begins, the frequency of which varies considerably by PHU. These factors suggest that the true proportion of fully un-immunized children in Ontario may be closer to 0.9% than 2.9%. We plan to reassess the immunization status of these children in the future, by examining immunizations recorded in the DHIR in the 2017–18 school year. Further work, including record linkage to other sources of immunization data (i.e. physician billing data) could also help to clarify the true immunization status of these students.

Whether the proportion of un-immunized students in Ontario is 0.9% or 2.9%, or somewhere in between, these estimates are in line with recent estimates of un-immunized children from individual Canadian provinces [25,26] and from a large Canadian coverage survey [27]. The 2013 childhood National Immunization Coverage Survey (cNICS) surveyed parents of children aged 2, 7, and 17, in addition to 12–14 year-old girls. A total of 1.5% (95% 1.2–1.7) were fully un-immunized. Similar to our findings, this varied inversely with age with a higher proportion of two-year children being un-immunized (i.e. 2.7% of children at age 2, 95% CI 2.1–3.4%), relative to older children [27].

We found similar age-related trends in our multivariable regression analyses, with a 40% reduced odds of being un-immunized (with an NME) among older children (aOR 0.59, 95% CI 0.57–0.61), relative to the youngest age strata of 7–10 years. We found the opposite for the outcome of having a NME and at least one vaccine dose recorded. A 40% increase in the odds of this outcome was observed for students age 14–17 (aOR 1.41, 95% CI 1.36–1.45), relative to the youngest students. One explanation for these findings could be a cohort effect, mediated by increasing vaccine hesitancy among parents of younger children. A further possibility is that parents might become more open to accepting immunizations for their children over time and as their children grow older, and immunize children for whom NMEs were previously submitted. This latter hypothesis is in keeping with our findings that many children with NMEs were partially immunized, or even up-to-date for immunizations associated with the antigen-specific NMEs recorded with the DHIR. These findings are consistent with other studies reporting on the immunization status of children with exemptions [28–31]. For example, using data from the 2013–2014 United States National Immunization Survey-Kindergarten, Smith et al. found that 96% of children whose parents had requested an exemption had received at least one vaccine dose [28]. Children with exemptions had received on average 22 vaccine doses of any type, as compared to 28 doses among children without an exemption; 43 to 55% of children were UTD, when examined by vaccine. In Australia, Beard et al. found that 12–23% of children with a recorded vaccine objection were fully vaccinated, varying by age. A further potential explanation for why so many children in Ontario with NMEs are immunized may be

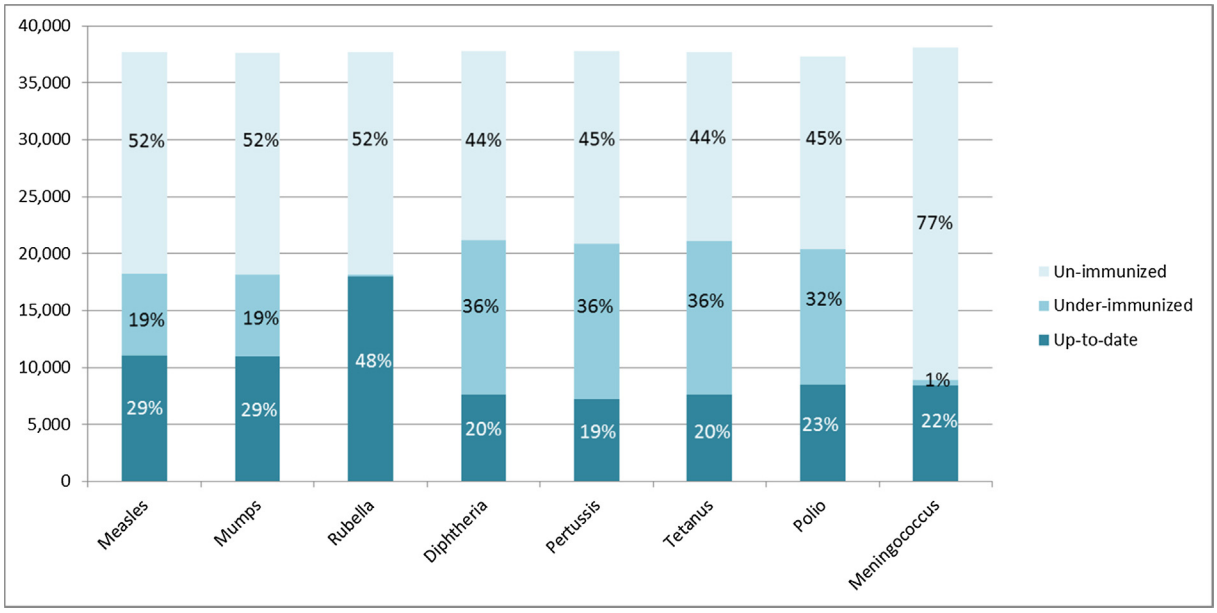

Fig. 3. Antigen-specific immunization status of Ontario students, among students with NMEs: 2016–2017 school year.

related to the form used in Ontario. The form was revised in 2017 to request that parents specify to which antigen(s) the NME was requested [19]. Previous versions on the form did not ask for this information and exemptions may have been entered in the DHIR across all ISPA antigens in the absence of further details.

Our finding that attendance at private and 'other' schools is associated with increased odds of having an NME (regardless of immunization status) is in line with US literature which has found increased rates of NMEs at private, charter and Waldorf schools [1,32,33]. The high aOR for having an NME and being un-immunized observed for "other" schools at 7.09 (95% CI 6.37–7.89) may be explained by the use of this school board type to capture religious schools and home schooled children. Ontario has several religious communities in the southwest of the province that are known to be non-accepting of immunization, and some have been associated with outbreaks of VPDs [34,35]. This likely explains the significant aORs observed for rural and small/medium population centres and South West and Central West PHU Regions among children with NMEs, regardless of immunization status. We also found that private and 'other' school attendance was significantly associated with increased odds of having no immunizations or exemptions recorded in the DHIR. This likely reflects variability in local implementation of the ISPA, for example by focussing on students attending publicly-funded school boards, although this requires further confirmation. Finally, we found that male gender was associated with increased odds of having an NME and at least one vaccine dose (aOR 1.07, 95%CI 1.04–1.10) as well as being un-immunized and without exemptions (aOR 1.09, 95% CI 1.06–1.11). Owing to the small size of the aORs and the population-based nature of this study, it is unclear if these findings represent a true, gender effect that is small in magnitude, or a chance finding. Further work examining whether a child's gender influences parental decision-making on immunization would be helpful in interpreting these findings.

The strengths of this study include the use of a population-based immunization repository, capturing all Ontario students and enabling legislation supporting the routine collection of immunization and exemption information. The transition to a centralized immunization repository in Ontario has facilitated the analysis of data at an individual-level, including the ability to integrate area-level and individual-level characteristics, including immunization status. However, there are several limitations that deserve mention. Children attending school but younger than seven years of age were excluded from our assessment for several reasons. Age seven is a recommended age milestone used in Canada for the surveillance of immunization coverage, as it allows the assessment of the receipt of pre-school booster doses given between four and six years-of-age [36]. It is also an age milestone commonly used by PHUs to initiate ISPA assessment and enforcement activities. As a consequence, we may have under-estimated the true proportion of children with NMEs and the proportion of un-immunized children, especially in light of the age-specific trends noted in our analysis. In addition, we did not examine exemptions to varicella in our analyses as this ISPA requirement applies only to children born in 2010 and after, birth years outside our analytic cohort. Other studies have found varicella to be one of the most commonly refused vaccines among parents who have requested NMEs [29,37]. The future monitoring of NMEs in Ontario will need to consider this in the interpretation of future trends. A final limitation of our work is the use of PHU and PHU Region as the spatial resolution for the maps and multivariable regression analyses, respectively. We plan to address this in a future study that will assess geospatial clustering of un-immunized children and those with NMEs using 2016 Canadian Census geographies to provide a more detailed understanding of the distribution of exemptions and un-immunized children at a smaller-area level in Ontario.

5. Conclusions

Using a centralized, population-based immunization repository we calculated that among Ontario students aged 7 to 17 in the 2016–2017 school year, 2.4% had at least one NME and that the vast majority of students had exemptions recorded for all VPDs noted in the relevant legislation. Despite this, 61% of students had at least one vaccine dose in the DHIR and about 50% were partially immunized or up-to-date, varying by antigen. Further work remains to be done to better determine if these findings reflect an artefact of data collection or relate in any way to changes in vaccine decision-making over time. A future study would also be helpful to examine and distinguish between age and cohort effects, and

to better understand the temporal sequence between the dates of individual immunization events and the date(s) associated with the submission of NMEs. Finally, we also found that a number of students, comparable in size to those with NMEs, had no immunization/exemption information recorded in the DHIR and that these children were more likely to live in more deprived neighbourhoods. This requires further study and additional data sources to confirm their true immunization status and to better understand the health equity findings to inform future solutions.

Conflict of interest

All authors declare that there are no conflicts of interest.

Acknowledgements

The project team thanks Fatima Campos, Ping Chapman, Jastej Dhaliwal, and Alicia Palmer from Peel Public Health for helpful discussions regarding local IPSA implementation and DHIR data, and gratefully acknowledges the support of Karen Hay and colleagues form the Digital Health Solutions and Innovation team of the Ontario Ministry of Health and Long-Term Care and Jocelyn Cortes from the Immunization Policy and Programs Section of the Ontario Ministry of Health and Long-Term Care.

Funding source

This project was funded by Public Health Ontario.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.033.

References

[1] Richards JL, Wagenaarb BH, Van Otterlooa J, Gondaliaa R, Atwell JE, Kleinbaum DG, et al. Nonmedical exemptions to immunization requirements in California: a 16-year longitudinal analysis of trends and associated community factors. Vaccine 2013;31:3009–13. https://doi.org/10.1016/j.vaccine.2013.04.053.

[2] Shaw J, Mader EM, Bennett BE, Vernyi-Kellogg OK, Yang YT, Morley CP. Immunization mandates, vaccination coverage and exemption rates in the United States 2018;5(6):ofy130. https://doi.org/10.1093/ofid/ofy130.

[3] Wang E, Clymer J, Davis-Hayes C, Buttenheim A. Nonmedical exemptions from school immunization requirements: a systematic review. Am J Public Health 2014;104(11):e62–84. https://doi.org/10.2105/AJPH.2014.302190.

[4] Olive JK, Hotez PJ, Damania A, Nolan MS. The state of the antivaccine movement in the United States: a focused examination of nonmedical exemptions in states and counties. PLoS Med 2018;15(6). https://doi.org/10.1371/journal.pmed.1002578.

[5] Lieu TA, Ray GT, Klein NP, Chung C, Kulldorff M. Geographic clusters in underimmunization and vaccine refusal. Pediatrics 2015;135(2):280–9. , https://pediatrics.aappublications.org/content/pediatrics/135/2/280.full.pdf.

[6] Carrel M, Bitterman P. Personal belief exemptions to vaccination in California: a spatial analysis. Pediatrics 2015;136:80–8. , https://pediatrics.aappublications.org/content/pediatrics/early/2015/05/26/peds.2015-0831.full.pdf.

[7] Jones M, Buttenheim A. Potential effects of California's new vaccine exemption law on the prevalence and clustering of exemptions. Am J Public Health 2014;104(9):e3–6. , https://ajph.aphapublications.org/doi/full/10.2105/AJPH.2014.302065.

[8] Aloe C, Kulldorff M, Bloom BR. Geospatial analysis of nonmedical vaccine exemptions and pertussis outbreaks in the United States. Proc Natl Acad Sci USA 2017;114:7101–5. https://doi.org/10.1073/pnas.1700240114.

[9] Atwell JE, Van Otterloo J, Zipprich J, Winter K, Harriman K, Salmon DA, et al. Nonmedical vaccine exemptions and pertussis in California, 2010. Pediatrics 2013;132:624–30. https://doi.org/10.1542/peds.2013-0878.

[10] Omer SB, Enger KS, Moulton LH, Halsey NA, Stokley S, Salmon DA. Geographic clustering of nonmedical exemptions to school immunization requirements and associations with geographic clustering of pertussis. Am J Epidemiol 2008;168:1389–96. https://doi.org/10.1093/aje/kwn263.

[11] Feikin DR, Lezotte DC, Hamman RF, Salmon DA, Chen RT, Hoffman RE. Individual and community risks of measles and pertussis associated with personal exemptions to immunization. JAMA 2000;284(24):3145–50. , https://jamanetwork.com/journals/jama/fullarticle/193407.

[12] Navin MC, Kozak AT, Clark EC. The evolution of immunization waiver education in Michigan: a qualitative study of vaccine educators. Vaccine 2018;36(13):1751–6. https://doi.org/10.1016/j.vaccine.2018.02.046.

[13] Michigan Department of Health and Human Services. Immunization status of school children in Michigan, https://www.michigan.gov/documents/mdch/School_Summary_2014_483316_7.pdf; 1 September 2017 [accessed 28 December 2018].

[14] Delamater PL, Leslie TF, Yang YT. Change in medical exemptions from immunization in California after elimination of personal belief exemptions. JAMA 2017;318(9):863–4. https://doi.org/10.1001/jama.2017.9242.

[15] Omer SB, Richards JL, Ward M, Bednarcz RA. Vaccination policies and rates of exemption from immunization, 2005–2011. N Engl J Med 2012;367(12):1170–1. https://doi.org/10.1056/NEJMc1209037.

[16] Wilson SE, Seo CY, Lim GH, Fediurek J, Crowcroft NS, Deeks SL. Trends in medical and nonmedical immunization exemptions to measles-containing vaccine in Ontario: an annual cross-sectional assessment of students from school years 2002/03 to 2012/13. CMAJ Open 2015;3(3):E317–23. https://doi.org/10.9778/cmajo.20140088.

[17] Immunization of School Pupils Act, RSO 1990, c. I.1., https://www.ontario.ca/laws/statute/90i01.

[18] Government of Ontario. Vaccines for children at school, https://www.ontario.ca/page/vaccines-children-school; 18 September 2015 [updated 5 July 2018; accessed 13 July 2018].

[19] Government of Ontario. Central forms repository: statement of conscience or religious belief – Immunization of School Pupils Act, http://www.forms.ssb.gov.on.ca/mbs/ssb/forms/ssbforms.nsf/GetFileAttach/014-4897-64E~1/$File/4897-64E.pdf; 2017 [accessed 13 July 2018].

[20] Government of Ontario. Central forms repository: statement of medical exemption – Immunization of School Pupils Act, http://www.forms.ssb.gov.on.ca/mbs/ssb/forms/ssbforms.nsf/GetFileAttach/014-4895-64E~1/$File/4895-64E.pdf; 2013 [accessed 13 July 2018].

[21] Ontario. Ministry of Health and Long-Term Care. Panorama data standards and best practices. Toronto, ON: Queen's Printer for Ontario; 2017.

[22] Matheson FI; Ontario Agency for Health Protection and Promotion (Public Health Ontario). 2011 Ontario marginalization index: technical document, https://www.publichealthontario.ca/en/DataAndAnalytics/Documents/Technical_Document_2011_ON-Marg.pdf; 2017 [accessed 2019 Feb 13].

[23] Ontario Agency for Health Protection and Promotion (Public Health Ontario). Technical annex: Immunization coverage report for school pupils in Ontario, 2013-14, 2014-15 and 2015-16 school years, https://www.publichealthontario.ca/en/eRepository/Immunization_Coverage_Report_Technical_Annex_2013-16.pdf; 2017 [accessed 2019 Feb 13].

[24] Ontario. Ministry of Finance. 2016 census highlights: factsheet 8, https://www.fin.gov.on.ca/en/economy/demographics/census/cenhi16-8.html; 2017 Nov 21 [accessed 2019 Feb 13].

[25] BC Centre for Disease Control (BCCDC). Immunization uptake in children by the second birthday, 2007-2017, http://www.bccdc.ca/resource-gallery/Documents/Statistics%20and%20Research/Statistics%20and%20Reports/Immunization/Coverage/2Year-Old-Coverage-2007-2017-Birth-Cohorts.pdf; 2018 [accessed 2019 Feb 13].

[26] Institut National de Santé de Publique du Québec. Enquête sur la couverture vaccinale des enfants de 1 ans et 2 ans au Québec en 2012, https://www.inspq.qc.ca/pdf/publications/1651_EnquCouvVaccinEnfants1Et2Ans2012.pdf; 2013 [accessed 2019 Feb 13].

[27] Public Health Agency of Canada. Vaccine coverage in Canadian children: results from the 2013 Childhood National Immunization Coverage Survey (CNICS), http://publications.gc.ca/collections/collection_2017/aspc-phac/HP40-156-2017-eng.pdf; 2017 [accessed 2019 Feb 13].

[28] Smith PJ, Shaw J, Seither R, Lopez A, Hill HA, Underwood M, et al. Vaccine exemptions and the kindergarten vaccination coverage gap. Vaccine 2017;35:5346–51. https://doi.org/10.1016/j.vaccine.2017.08.036.

[29] Salmon DA, Moulton LH, Omer SB, DeHart MP, Stokley S, Halsey NA. Factors associated with refusal of childhood vaccines among parents of school-aged children: a case-control study. Arch Pediatr Adolesc Med 2005;159(5):470–6. https://doi.org/10.1001/archpedi.159.5.470.

[30] Beard FH, Hull BP, Leask J, Dey A, McIntyre PB. Trends and patterns in vaccination objection, Australia, 2002–2013. Med J Aust 2016;204(7):275. https://doi.org/10.5694/mja15.01226.

[31] Buttenheim AM, Sethuraman K, Omer SB, Hanlon AL, Levy MZ, Salmon D. MMR vaccination status of children exempted from school-entry immunization mandates. Vaccine 2015;33:6250–6. https://doi.org/10.1016/j.vaccine.2015.09.075.

[32] Birnbaum MS, Jacobs ET, Ralston-King J, Ernst KC. Correlates of high vaccination exemption rates among kindergartens. Vaccine 2013;31(5):750–6. https://doi.org/10.1016/j.vaccine.2012.11.092.

[33] Brennan JM, Bednarczyk RA, Richards JL, Allen KE, Warraich GJ, Omer SB. Trends in personal belief exemption rates among alternative private schools: Waldorf, Montessori, and holistic kindergartens in California, 2000–2014. Am J Public Health 2017;107(1):108–12. https://doi.org/10.2105/AJPH.2016.303498.

[34] Hahne S, Macey J, van Binnendijk R, Kohl R, Dolman S, van der Veen Y, et al. Rubella outbreak in the Netherlands, 2004–2005: high burden of congenital infection and spread to Canada. Pediatr Infect Dis J 2009;28:795–800. https://doi.org/10.1097/INF.0b013e3181a3e2d5.

[35] Deeks S, Lim G, Walton R, Fediurek J, Lam F, Walker C, et al. Pertussis: prolonged pertussis outbreak in Ontario originating in an under-immunized religious community. Can Commun Dis Rep 2014;40(3):42.
[36] Government of Canada. National standards for immunization coverage assessment: recommendations from the Canadian Immunization Registry Network, https://www.canada.ca/en/public-health/services/publications/healthy-living/national-standards-immunization-coverage-assessment-recommendations-canadian-immunization-registry-network.html; 2015 [accessed 2019 Feb 13].
[37] Salmon DA, Sotir MJ, Pan WK, Berg JL, Omer SB, Stokley S, et al. Parental vaccine refusal in Wisconsin: a case-control study. WMJ 2009;108(1):17–23.