Trends in medical and non-medical immunization exemptions in Ontario: Annual cross-sectional assessment of students over eleven school years: 2002-03 to 2012-13.

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SW conceived of the study, directed the analyses, and drafted the article. CYS and GHL were involved in the acquisition of data and CYS executed the analyses presented. All authors substantially contributed to the interpretation of data, revised the manuscript critically for important intellectual content, gave final approval of the version to be published and agreed to act as guarantors of the work.

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Abstract

Background: Under Ontario legislation, for select vaccine-preventable diseases un- or under-immunized students must be vaccinated or provide a statement of exemption, otherwise risk school suspension. At the time of this assessment, these included measles, mumps, rubella, diphtheria, tetanus, and polio.

Methods: Exemptions data were obtained from the Immunization Records Information System (IRIS) for the school years of 2002-03 to 2012-13. Temporal trends were expressed for 7- and 17-year-olds by exemption classification (medical, prior immunity, religious/conscientious belief, total) at a provincial level, by school year and birth cohort. Regional analysis was conducted for 2012-13. Poisson distribution was used to examine the statistical significance of temporal trends using a two-sided test with an alpha of 5%. Exemptions for measles-containing vaccines were the focus of temporal trend analyses.

Results: For both 7- and 17-year-old students, religious/conscientious exemptions for measles-containing vaccines significantly increased over the study period (both age groups, $p< 0.001$) and medical exemptions decreased (both age groups, $p<0.001$). The trends were reproduced when examined by birth cohort. The proportion of Ontario students with any exemption classification (total exemptions) remained low (< 2.5%) over the period of analysis although considerable geographic variation was noted.

Interpretation: Ontario data suggest that non-medical exemptions have increased over the last eleven years, consistent with trends reported elsewhere. The trend towards increasing religious/conscientious exemptions coupled with declining medical exemptions explains why total exemptions have remained stable or decreased, at a provincial level. The prominent geographic variability in exemptions suggests that targeted interventions may be suitable for consideration.

Background

There is increasing concern about vaccine hesitancy in Canada. In a 2011 Canadian survey of parental attitudes toward vaccination, half of parents felt that newer vaccines are less safe than older vaccines and 43% indicated they were more concerned about vaccine safety than they were five years ago [1].There is limited literature to characterize vaccine hesitancy in Canada, although work is progressing in this area [2]. Investigators in the United States (US) have found evidence of increasing non-medical exemptions [3,4] which are presumed to reflect declining public confidence in immunization, and studies have linked geographical areas with high exemptions to vaccine-preventable disease (VPD) outbreaks [5,6]. In Ontario, there are communities who are known to be non-accepting of immunization on the basis of their religious beliefs. Several have been associated with recent VPD outbreaks [7,8].

In Ontario, the *Immunization of School Pupils Act* (ISPA) requires that public health units (PHUs) maintain and assess the immunization records of students [9]. For nine "designated diseases", students with incomplete immunizations must be vaccinated or provide a valid exemption statement, or else risk school suspension. Measles, mumps, rubella, diphtheria, tetanus, and polio have been long-standing designated diseases and in July 2014, varicella, invasive meningococcal disease and pertussis were added. The original 1982 legislation permitted only non-medical exemptions on religious grounds, but conscientious objections were added in a 1984 amendment [10]. Only New Brunswick has similarly comprehensive legislation pertaining to immunization requirements for school-entry [11].

Our objective was to describe immunization exemptions to measles-containing vaccine (MCV) among Ontario students over the last eleven school years, and to compare the direction

and magnitude of trends in non-medical and medical exemptions to trends observed elsewhere. We chose to focus on exemptions to MCV for two reasons. Firstly, we expected that there would be a greater number of medical exemptions as MCV is a live virus vaccine and certain immune-compromising conditions are medical contraindications to immunization [12]. We also anticipated that vaccine hesitant parents might be more concerned about MCV as compared to other vaccines, following the discredited hypothesis linking measles, mumps, rubella (MMR) vaccine to autism [13].

Methods

Processes for assessment of immunization coverage and exemptions in Ontario

Ontario is Canada's largest province (population size 13.5 million); it has 36 PHUs which vary greatly in their geographic and population size and density. Under the Ontario Public Health Standards, comprehensive immunization coverage assessment is conducted annually for all school pupils within each PHU [14]. Under the ISPA, local Medical Officers of Health (MOHs) maintain records of immunization and exemptions for all students [9]. If the appropriate immunization information (or exemption statement) is not received, students may be suspended until such documentation is provided. Between 1992 and 2014, the Immunization Records Information System (IRIS), a collection of provincially-supported, decentralized databases was used to support documentation and assessment. Over the course of 2013 and 2014, all PHUs transitioned with a sequenced implementation schedule to Panorama, a centralized provincial immunization repository. Exemptions were documented in IRIS by MMR vaccine until 2009-10, and from 2010-11 onwards by measles antigen.

To register a non-medical exemption, the "Statement of Conscience or Religious Belief" must be completed and signed by the parent or guardian, or student themselves if 16 years of age or older, and notarized [15]. The statement does not ask the individual to specify whether an exemption on the basis of conscience or religious belief (C/RB) is claimed, thus analyses cannot delineate between these two motivations. The "Statement of Medical Exemption" must be completed and signed by a physician or nurse practitioner. Medical exemptions are classified on the Statement as being either "detrimental to health" or on the basis of laboratory confirmation of immunity for select diseases [16]. Individuals with a medical exemption on the basis of prior immunity have a distinct exemption classification within IRIS. The collection, review and data entry of exemptions occurs at a local level. At least annually, PHUs provide immunization coverage and exemption data in the form of in-application reports from IRIS containing aggregate data by antigen and birth cohort to the provincial level, for the purposes of immunization coverage surveillance. These represent the data source of all analyses.

Study population and methodology

Due to the scope of the ISPA, this analysis represents a true population-based assessment of immunization exemptions in Ontario. We selected to focus on students 7 and 17 years of age, in accordance with Canadian guidelines on age cohorts for routine coverage assessment [17].

Immunization exemptions were reviewed by classification for the six VPDs cited by the ISPA at the time of immunization assessment for 2012-13, which occurred on June 30, 2013. For the 2012-13 school year, the proportion of 7-year-old students with any type of exemption, and by exemption classification, was determined for each antigen provincially. PHU-specific proportions among 7-year-olds were determined for non-medical and medical exemptions,

excluding prior immunity, for MCV. PHUs were rank-ordered in a non-nominal fashion from highest to lowest with regards to the proportion of 7-year-olds with a non-medical exemption to MCV. A number was assigned to each of the 36 PHUs based on their relative ranking with regards to the proportion of 7-year-old students with a non-medical exemption to MCV (ranked from highest to lowest), with this number preserved when assessing the distribution of PHUs with regards to medical exemptions. Due to limitations of IRIS, it was not possible to estimate the number of unique students with an exemption to any antigen in 2012-13 or previous school years.

Immunization exemptions among 7- and 17-year-old students for MCV over the school years of 2002-03 to 2012-13 were examined. Trends in exemptions were assessed for 7- and 17-year-olds at the provincial level by classification: medical (excluding prior immunity), prior immunity, and C/RB. We also examined trends in total exemptions defined as the sum of medical, prior immunity, and C/RB exemptions. We examined these by school year, examining 7- and 17-year old students separately over the period of 2002-03 to 2012-13. We also assessed temporal trends using a birth cohort approach which explored exemptions for 7- and 17-year old students, assessed by year of birth (1985 to 2005). For analyses of temporal trends in medical exemptions, we continued to examine students with prior immunity as a distinct classification. The statistical significance of temporal trends was assessed using a Poisson distribution, using a two-sided test with an alpha of 5%.

Following the transfer of surveillance functions to Public Health Ontario (PHO) in 2011, PHO has validated local coverage and exemptions data with PHUs before their inclusion in

reports and related analyses. Exemptions and coverage data prior to 2010-11 did not undergo this step. For the analyses reported here, PHU-specific exemption data from the time period pre-dating routine validation (2002-03 to 2010-11) were reviewed. For PHUs with small population sizes and for any PHU where the 17 year old cohort was smaller than 50% of the 7 year old cohort, further review was undertaken. The 17 year old birth cohort was assessed in relation to the size of the same cohort (i.e. same year of birth) in the previous school year, where available. If this was not available, the size of the birth cohort comprised of 16 year olds was reviewed for the same school year. We excluded PHU-specific data for a particular school year if the size of the 17 year old birth cohort was less than 60% of the comparator birth cohort.

Ethics statement

This project was assessed through PHO's ethics screening process [18] and was found to not require additional ethics review.

Results

The distribution of exemption classifications among 7-year-olds in Ontario in the 2012-13 school year, for ISPA designated diseases at the time of assessment, are represented in Figure 1. Total exemptions were highest against polio-containing vaccine (2.4%) and lowest against mumps and rubella (1.4%). Of the three categories of exemptions captured in IRIS, C/RB exemptions accounted for the greatest proportion of total exemptions, responsible for 89% of all exemptions registered in 2012-2013 in this age group (13,559/15,307). Provincial estimates obscure prominent variability by individual PHU, which ranged from 0.7 to 7.5% for exemptions due to C/RB (Figure 2A). Less variability was noted in medical exemptions (range 0% to 1.8%,

Figure 2B). PHUs with the highest proportions of non-medical exemptions differ from those with greater proportions of students with medical exemptions (Figure 2B).

Data cleaning of historical exemptions data on the basis of birth cohort size resulted in the exclusion of 69 PHU-specific estimates out of a total of 398 PHU-specific estimates for 17-year olds over the 11 years of analysis. The exclusions had no impact on the overall proportion of total exemptions across the study period for this age group: total exemptions were 1.8% with (26,586/1,476,321) and without (27,736/1,530,165) the above-noted exclusions. When assessed by trends across school years, C/RB exemptions increased among 17-year-olds, (0.6 to 1.1%, $p<0.0001$) with a more pronounced decrease in medical exemptions (0.8% to 0.2%, $p<0.0001$) resulting in a decrease in total exemptions over time (1.9% to 1.4%, $p<0.0001$) (Figure 3A). Similar trends were noted among 7-year-olds (Figure 3B).

The birth cohort approach revealed a doubling in the proportions of students with C/RB exemptions to MCV over a 20 year time period, from 0.6% among students born in 1985 to 1.5% for students born in 2005 ($p<0.0001$) and a significant decline in medical exemptions (0.8% for students born in 1985 to 0.2% for students born in 2005, $p<0.0001$) (Figures 4A, 4B). Over the 20 birth cohorts of interest, exemptions claimed on the basis of prior immunity to measles (natural infection) decreased from 0.5% to 0.1% ($p<0.0001$) (data not shown).

Interpretation

This is the first comprehensive assessment of immunization exemptions conducted in Canada. To our knowledge, only one previous study has examined Ontario exemptions; it examined exemptions data from only two school years, focused on the ratio of exemptions due to

C/RB as compared to medical exemptions, and did not explore PHU variability [19]. Our analysis provides important insight into trends of vaccine refusal within Canada's largest province and demonstrates that non-medical exemptions to MCV have significantly increased over time, although the absolute magnitude remains low provincially at less than 2%. As demonstrated by our more detailed assessment of the 2012-13 school year, regional variability is marked. Analyses at a smaller area level, such as individual schools, even among PHUs with 'low' levels of exemptions serve to further illustrate this [20], as does analysis of exemptions by income quintile [21]. We were not able to explore this further at the provincial level due to IRIS limitations.

The trends observed in non-medical exemptions are comparable, although in some cases smaller in magnitude, to what has been observed in the US. In a recent analysis of secular trends in personal belief exemptions among California kindergarten students, the state level exemption rate increased from 0.6% in 1994 to 2.3% in 2009, an average annual increase of 9.2% [4]. Analyses from Michigan found the mean non-medical exemption rate by census tract increased from 1.9% in 1991 to 5.2% in 2004 [5]. Regional variability in exemptions is well documented and in some US states more marked than what we observed, with some counties documenting non-medical exemption rates as high as 25% [3].

There are few studies in the literature examining medical exemptions [22,23] and none have examined temporal trends directly. Instead, their focus has been to assess the relationship between medical exemptions and state-level policies or intervention studies targeting providers [22,23]. There are several hypotheses for the significant decline in medical exemptions noted in our analyses including greater clinician awareness regarding true immunization contraindications

versus precautions and expanded expert guidance on immunization practice in this area [24]. In the 4th edition of the Canadian Immunization Guide, released in 1994, the National Advisory Committee on Immunization (NACI) recommended routine skin testing for any individual with an egg allergy, with guidance to administer MMR using a graded challenge under continuous observation for those with a positive skin test [25]. This recommendation was revised in 1998 following a literature review which found no evidence of increased risk of anaphylaxis associated with egg allergy [26]. This change could explain the notable drop in medical exemptions observed in the birth cohorts born between 1993 and 1995. An alternate explanation for the decline in medical exemptions is that Ontario parents may now be more aware of the ability to opt-out of immunization requirements through an exemption claimed on C/RB and may make fewer requests for medical exemptions. Because medical exemptions due to prior immunity are classified separately, declining numbers of children with naturally acquired measles antibody due to previous wild type infection in the post-measles elimination era cannot explain these trends.

The strengths of this assessment lie with the comprehensive scope of the ISPA and the time period captured by our analyses. The temporal trends in immunization exemptions described represent a true population-level assessment of exemptions among Ontario's school-aged population over 11 school years, representing children born over a 20 year period (1985 to 2005), during which notable shifts in public confidence in vaccination have occurred. However, this assessment has several limitations, which primarily relate to the lack of individual-level data available for analysis. Due to the nature of the IRIS reports available at the provincial level, PHU is the smallest geographic level by which exemptions are reported, obscuring spatial clustering at a smaller area level. Other limitations include an inability to examine exemptions across the range of ISPA antigens, in order to document the proportion of Ontario students with an

immunization exemption to at least one ISPA antigen. A further limitation was our inability to explore the individual immunization status of students with and without exemptions. Other studies have demonstrated that some students with immunization exemptions will have been immunized against the particular antigen [27,28]. In contrast, data from Australia, suggest that the proportion of children who have received no vaccines is approximately twice as high as the proportion of children who have a documented exemption [29]. Finally, due to the current wording of the ISPA, exemptions due to conscience and religious belief are captured together, preventing us from delineating trends for these separately. We presume the increase observed has been driven by conscientious objection, rather than secular trends in religious beliefs or significant population expansion of religious groups in Ontario who are known to be non-accepting of immunization.

Other investigators have found that for both medical and non-medical exemptions, US states with more stringent administrative criteria are more likely to have lower rates of medical and non-medical exemptions, and a lower rate of increase for non-medical exemptions [22,30]. In addition, states that have more stringent requirements for non-medical exemptions are more likely to have higher rates of medical exemptions [22]. With regards to administrative complexity to obtain a medical exemption, Ontario would be classified as "easy", scoring one out of a possible six criteria proposed by Stadlin et al. [22]. Ontario's requirement for notarization of the parental statement of religious or personal belief objection, which as of July 2013 can be obtained online, would be classified as somewhere in the middle with respect to the administrative complexity to obtain a non-medical exemption [30]. However, many US states have more stringent processes, including healthcare provider documentation that the parent has been counselled regarding the risks and benefits of immunization and of VPDs [31]. Other jurisdictions have adopted more targeted interventions focusing on geographical regions, or

providers associated with high levels of exemptions [23]. Despite the ISPA, two doses measles coverage was 88% among 7-year-olds and 95% among 17-year-olds in the 2012-13 school year [32], underscoring the need to have parallel approaches to both improve coverage and decrease exemptions, particularly among younger students.

Conclusion

This assessment confirms that non-medical exemptions have increased in Ontario over the last 11 school years, consistent with trends reported elsewhere. The general trend towards increasing religious/conscientious exemptions coupled with declining medical exemptions explains why total exemptions have remained stable or decreased, at a provincial level. Despite relatively low levels of non-medical exemptions provincially, there is marked variability by PHU suggesting the potential role for targeted interventions. These should be tailored and sensitive to whether exemptions are on the basis of religious belief, or conscientious objection.

Acknowledgements

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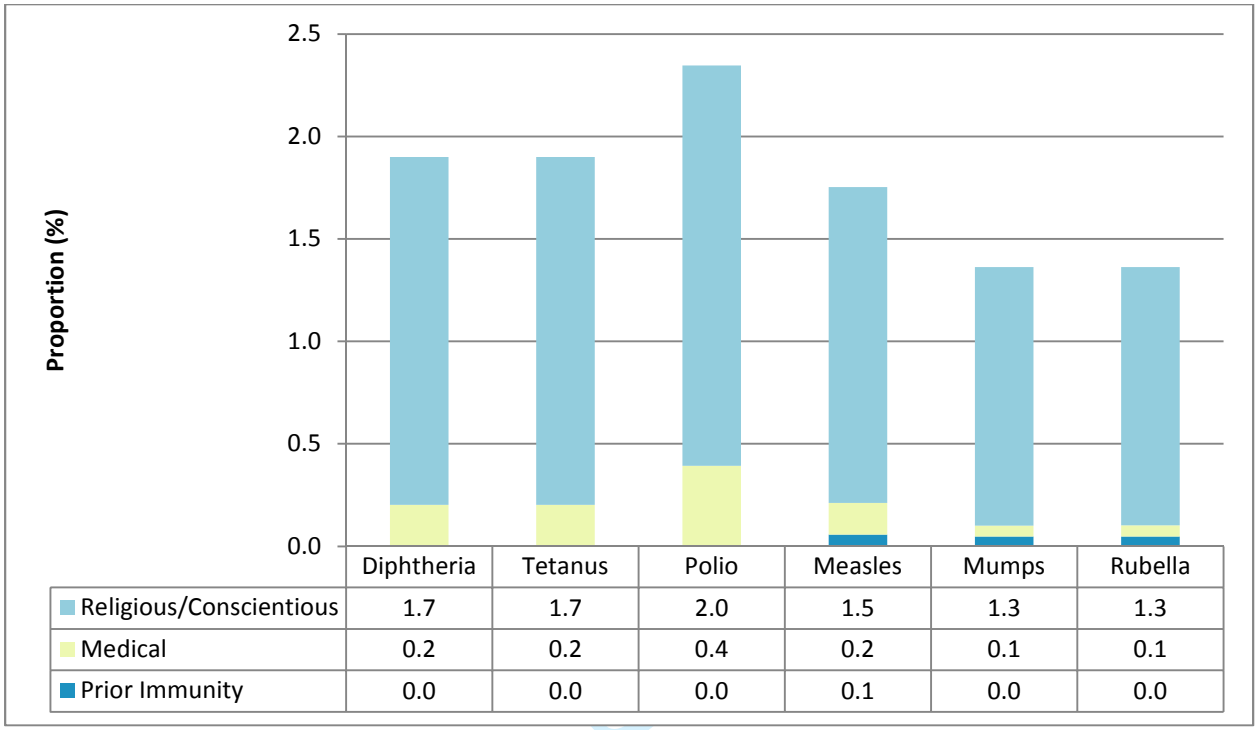
Figure 1: Exemptions by classification among 7-year-old Ontario students: 2012-13 school year



	Diphtheria	Tetanus	Polio	Measles	Mumps	Rubella
Religious/Conscientious	1.7	1.7	2.0	1.5	1.3	1.3
Medical	0.2	0.2	0.4	0.2	0.1	0.1
Prior Immunity	0.0	0.0	0.0	0.1	0.0	0.0

Figure 2A: Proportion of 7-year-old students with an exemption to measles containing vaccine due to religious or conscientious belief, by Ontario Public Health Unit: 2012-13 school year

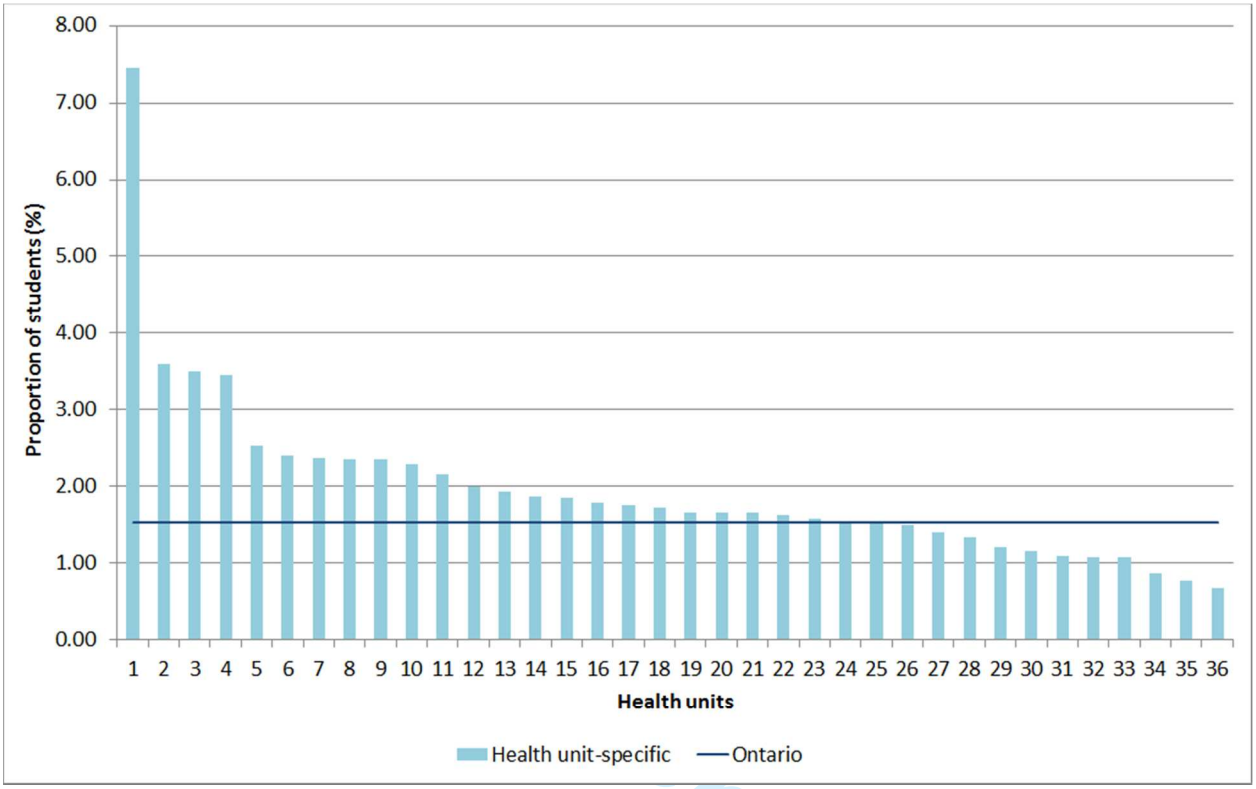


Figure 2B: Proportion of 7-year-old students with a medical exemption to measles containing vaccine, by Ontario Public Health Unit: 2012-13 school year

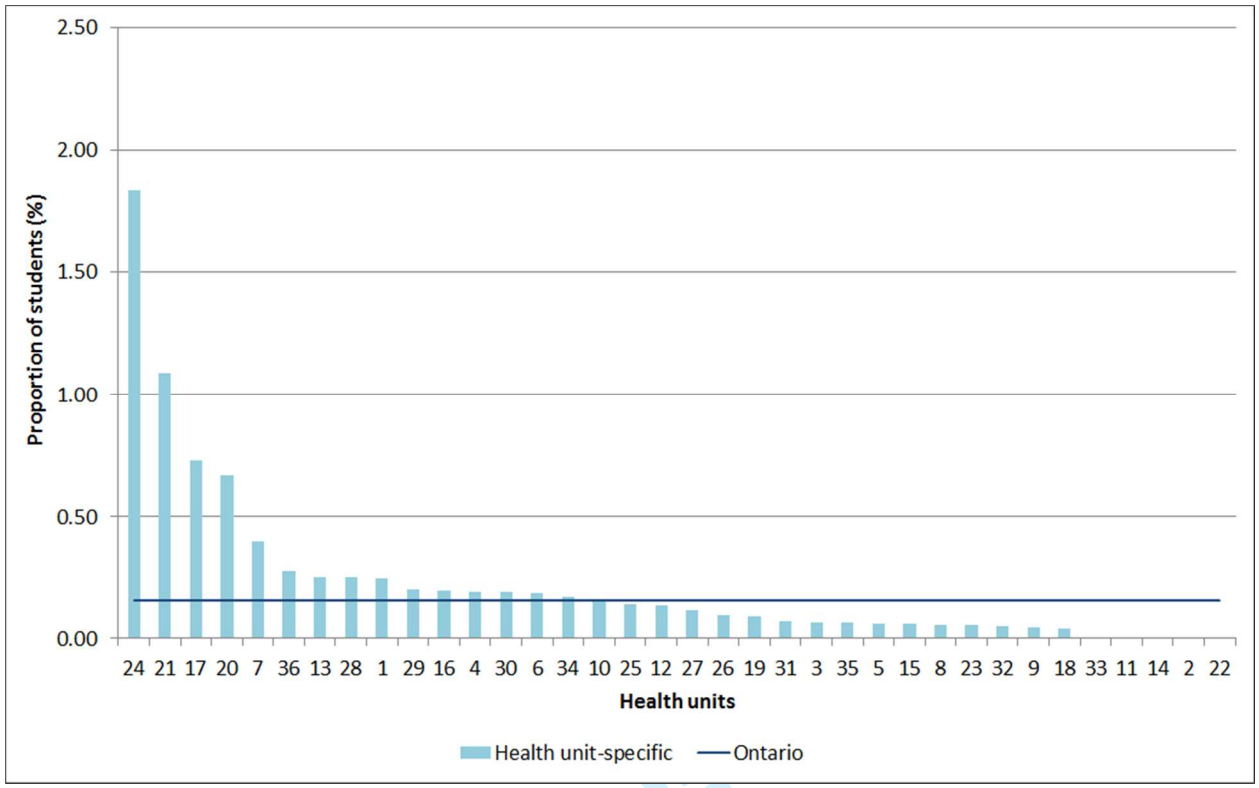


Figure 3A: Temporal trends in immunization exemptions to measles containing vaccine among 17-year-old Ontario students, by exemption classification: 2002-3 to 2012-13 school years

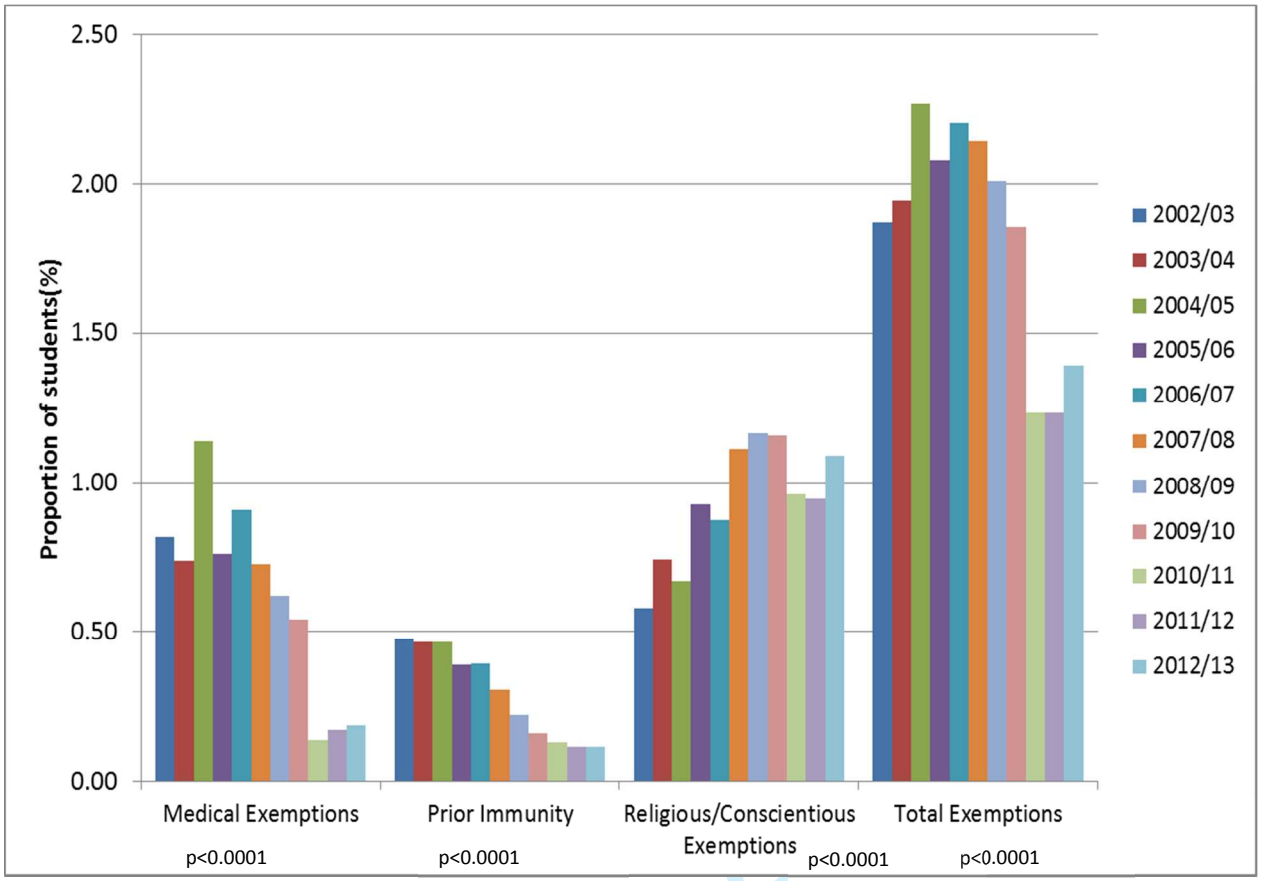


Figure 3B: Temporal trends in immunization exemptions to measles containing vaccine among 7-year-old Ontario students, by exemption classification: 2002-3 to 2012-13 school years

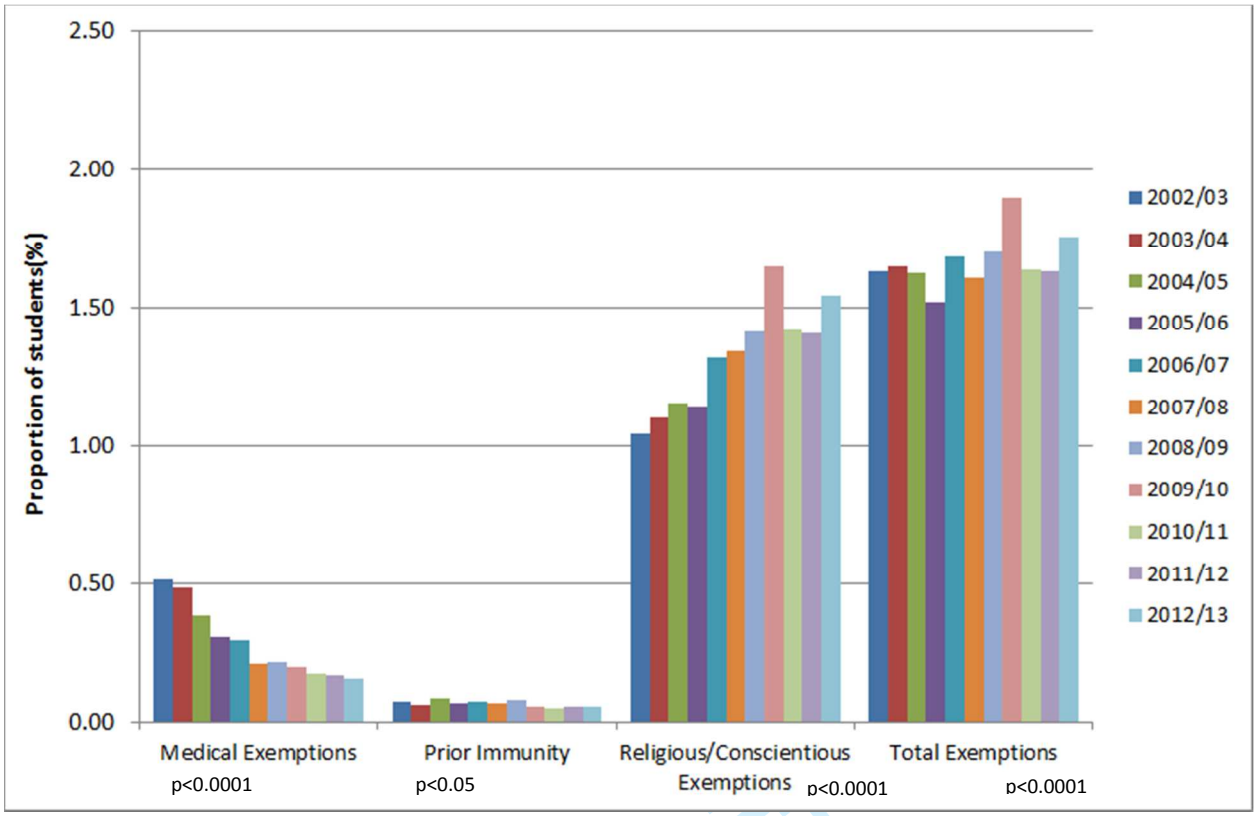


Figure 4A: Temporal trends in immunization exemptions to measles containing vaccine due to religious or conscientious belief among Ontario students by year of birth: 1985-2005

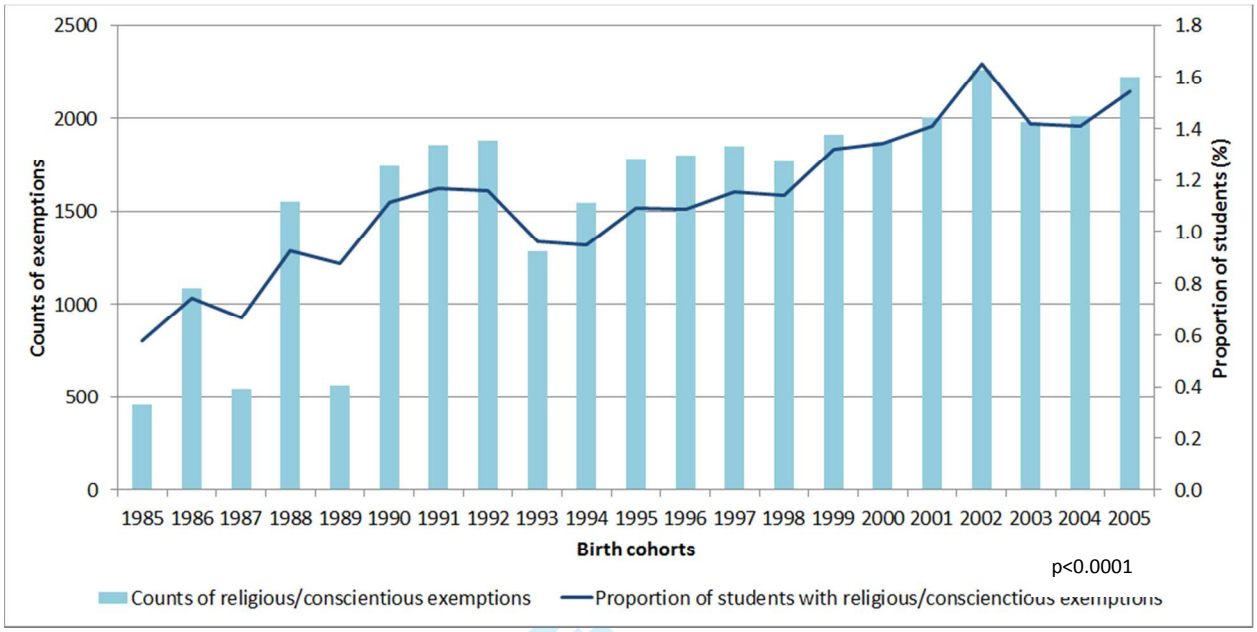
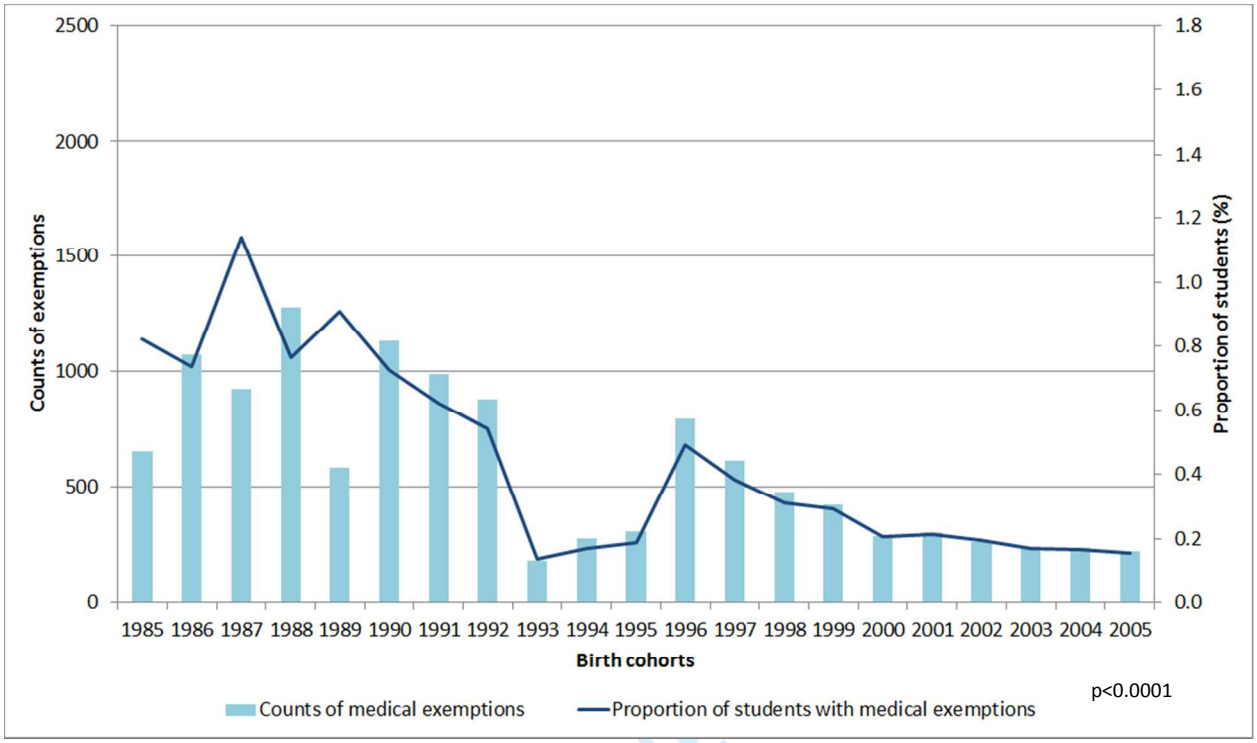


Figure 4B: Temporal trends in medical exemptions to measles containing vaccine among Ontario students by year of birth: 1985-2005



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

First author statement (SW): We feel that our analyses generally conform to the checklist and that the manuscript clearly articulates the data quality issues within our provincial surveillance system which prohibited us from completing additional analyses that would only have been possible with individual-level data (i.e. adjustment for confounders, sub-

group analyses, etc.). The limitations of the data source and its implications for analyses are cited in both the methods and given prominent mention in the discussion section.

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Sarah Wilson, Chi Yon Seo, Gillian Lim, Jill Fediurek, Natasha Crowcroft and Shelley Deeks (the "Authors") have carried out research and prepared a paper entitled

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