



Equity and impact: Ontario's infant rotavirus immunization program five years following implementation. A population-based cohort study



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ARTICLE INFO

Article history:

Received 11 September 2018

Received in revised form 18 January 2019

Accepted 29 January 2019

Available online 11 February 2019

Keywords:

Rotavirus

Immunization

Program impact

Equity

Hospitalization

Seasonality

ABSTRACT

Background: Ontario implemented a publicly-funded rotavirus (RV) immunization program in 2011. Our objectives were to evaluate its impact on hospitalizations and emergency department (ED) visits for acute gastroenteritis (AGE) five years after implementation.

Methods: We performed a population-based longitudinal retrospective cohort study to identify hospitalizations and ED visits for RV-AGE and overall AGE in all age groups using ICD-10 codes between August 1, 2005 and March 31, 2016. A negative binomial regression model that included the effect of time was used to calculate rates, rate ratios (RRs) and 95% confidence intervals (CIs) for AGE before and after the program's implementation, after adjusting for age, seasonality and secular trends. We examined the seasonality of RV-AGE hospitalizations among children under five before and after the program and explored its equity impact.

Results: Following program implementation, RV-AGE hospitalizations and ED visits among children under five years declined by 76% (RR 0.24, 95% CI 0.20–0.28) and 68% (RR 0.32, 95% CI 0.21–0.50), respectively. In addition, hospitalizations and ED visits for overall AGE declined by 38% (RR 0.62, 95% CI 0.59–0.65) and 26% (RR 0.74, 95% CI 0.73–0.76), respectively, among children under age five. Significant reductions in both outcomes were also found across a range of age-strata. In the pre-program period, the mean monthly hospitalization rate for RV-AGE among children residing in the most marginalized neighbourhoods was 33% higher than those residing in the least marginalized (RR 1.33, 95% CI 1.17–1.52), this disparity was not evident in the program period (RR 0.95, 95% CI 0.69–1.32). We found no evidence of a seasonal shift in rotavirus pediatric hospitalizations.

Interpretation: The introduction of routine infant rotavirus immunization has had a substantial population impact in Ontario. Our study confirms herd effects and suggests the program may have reduced previous inequities in the burden of pediatric rotavirus hospitalizations.

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1. Introduction

Prior to the introduction of rotavirus immunization programs in Canada, almost all children acquired rotavirus-associated acute

gastroenteritis (AGE) by five years of age with seasonal peaks occurring in the winter and spring [1]. Rotavirus vaccines have been available for use in Canada since 2006 with recommendations issued by the National Advisory Committee on Immunization (NACI) in 2008 and 2010 [2,3]. As of January 2019, 12 of Canada's 13 provinces and territories have implemented routine rotavirus immunization programs [4]. Ontario incorporated rotavirus vaccine into the routine infant immunization schedule, using

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Rotarix[™] (RV1, GlaxoSmithKline Inc.) at two and four months of age, in August 2011. Coverage (series completion) for the first three years of the Ontario program was estimated to be 73.0%, 78.5% and 84.2% [5]. In an analysis exploring factors associated with rotavirus coverage, no association was found between socioeconomic status (assessed using neighbourhood-level income quintiles) and series initiation or series completion [5]. Multiple studies conducted in low, middle and high income countries have assessed the impact of rotavirus immunization programs on burden of disease and/or vaccine effectiveness [6–9], childhood deaths from diarrheal illness [10–12] and seasonality of infections [13,14]. There is also accumulating literature on socioeconomic gradients in pediatric AGE [15–17] and the impact of rotavirus immunization programs on such gradients [16,17]. We previously carried out a preliminary assessment of the impact of Ontario's program on healthcare utilization for AGE which included only one complete rotavirus season following program implementation [18]. Our objectives for this study were to re-evaluate program impact on hospitalizations and ED visits for AGE using a longer observation period (i.e., five years post-implementation) and to assess its impact on both the seasonality of infection, and health equity.

2. Methods

(i) Study population and design

We conducted a population-based longitudinal retrospective cohort study examining healthcare utilization for AGE over the period of August 1, 2005 and March 31, 2016 among all Ontarians with a valid health card for the Ontario Health Insurance Plan (OHIP). OHIP covers almost all of Ontario's approximately 13.5 million residents, except for newcomers who have resided in the province for less than three months and refugees covered under federal health programs.

(ii) Data sources

We linked study datasets as described below using unique encoded identifiers and analyzed them at the Institute for Clinical Evaluative Sciences (ICES). Individual-level hospitalizations and ED visits were identified using the Discharge Abstract Database (DAD) of the Canadian Institutes for Health Information (CIHI) and the National Ambulatory Care Reporting System (NACRS), respectively, using International Classification of Diseases, Tenth Edition (ICD-10) diagnostic codes. The ICD-9 and ICD-10 codes for rotavirus-specific AGE (RV-AGE) have been validated and shown to have a high positive predictive value, but low sensitivity since diagnostic testing for AGE illness is not always performed [19–21]. For this study we assessed two distinct outcomes: (1) events with the diagnostic code specific to RV-AGE (*rotaviral enteritis*, A08.0) and (2) events with either the RV-AGE code or a non-specific code for AGE (hereafter referred to as "overall AGE"). The non-specific codes for AGE included the following: *other viral gastroenteritis* (A08.3), *viral intestinal infection, unspecified* (A08.4), *other specified intestinal infections* (A08.5), *other gastroenteritis and colitis of infectious and unspecified origin* (A09) and *noninfective gastroenteritis and colitis, unspecified* (K52.9). We added the final code (K52.9) after obtaining documentation confirming a change in directive during the study period for the classification of unspecified gastroenteritis within ICD-10, described in detail elsewhere [22,23]. Only the diagnostic code listed as the most responsible for the patient's hospitalization or ED visit (diagnosis type M category) was used for outcome ascertainment. We used the Registered Persons Database (RPDB), a population-based repository of demographic information including health card number under OHIP, to determine OHIP eligibility, age, postal code and

population estimates. We linked postal code to 2006 Statistics Canada postal code information to assign children under five years to a Dissemination Area (DA). DAs are the smallest standard geographic unit for which Canadian Census data are disseminated; DA population sizes vary from 400 to 700 persons [24]. We used the 2006 Ontario Marginalization Index (ON-Marg) to assign DAs to one of five quintiles of material deprivation [25]. The material deprivation dimension of ON-Marg is based on six DA-specific Census measures: proportion of the population aged ≥ 20 years without a high school diploma; proportion of families who are lone parent families; proportion of the population receiving government transfer payments; proportion of the population aged ≥ 15 years who are unemployed; proportion of households living in dwellings that are in need of major repair; and the proportion of the population considered low-income, based on Statistics Canada's low-income cut-off (LICO) [25].

(iii) Statistical analysis

The study was divided into two time periods: pre-program (August 1, 2005–July 31, 2011) and the period following the introduction of the publicly-funded program, hereafter referred to as the "program period" (August 1, 2011–March 31, 2016). To examine program impact on healthcare utilization we calculated unadjusted age-specific average monthly rates of AGE using the two outcome definitions (RV-AGE and overall AGE) separately for hospitalizations and ED visits for the two periods using the following age strata: <5 years, 5–19 years, 20–44 years, 45–64 years and ≥ 65 years. We used a negative binomial regression model to assess the trend in monthly rates of AGE adjusting for age, secular trends and seasonality. We adjusted for age using a categorical variable with the age strata described above, adjusted for secular trends using a linear term (representing month of the year), and adjusted for seasonality using a categorical variable, using groupings of three months with the fall (September–November) set as the reference period. We used a variable indicating the vaccine period to determine the impact of the program, in comparison to the pre-program period on AGE rates. We conducted all regression analyses for the total population and also age stratified. Our primary analysis examined events however, as a sensitivity analysis, we also conducted a person-based analysis. We did this by including only the first healthcare utilization event for all individuals, for hospitalizations and ED visits separately. We repeated our population-based regression models with finer age bands for children under age 5 years by using the following additional age strata: < 12 months, 12–23 months, 24–35 months and 3–4 years.

To explore impact on seasonality, we visually compared figures of unadjusted mean monthly rates and unadjusted mean weekly rates per 10,000 population of RV-AGE hospitalizations among children under five years, in the pre-program and program periods. In addition, we calculated the area under the curve for the figures representing pre- and post-program unadjusted mean monthly rates of RV-AGE hospitalizations among children under five. To assess the potential program impact on equity, we calculated mean annual rates per 10,000 population for RV-AGE hospitalizations among children under five years for the pre- and program periods and compared these across the five material deprivation quintiles using a person-based analysis. We calculated the rate ratio of RV pediatric hospitalizations before and during the program using a negative binomial regression model examining monthly rates of RV-AGE. We treated the marginalization index as a categorical variable and used the most affluent quintile as the reference group. We calculated un-adjusted rate ratios, and rate ratios adjusted for seasonality and secular trends (using a linear term) in the approach previously described.

We conducted all analyses using SAS version 9.4 (SAS Institute, Cary, NC). This study was approved by the Public Health Ontario Ethics Review Board.

3. Results

During our study period which spanned a little over ten years, there were 2779 hospitalizations and 430 ED visits for RV-AGE, and 183,170 hospitalizations and 1,026,811 ED visits for overall AGE in our events-based primary analyses which included all ages. Fig. 1 illustrates that prior to program implementation, hospitalization rates for RV-AGE among children under 5 years were highest among children aged 12–23 months and there was prominent seasonality of rotavirus hospitalizations as well as a biennial pattern (i.e. higher hospitalization rates in odd years as compared to even years). These trends markedly diminished following the program’s introduction in August 2011.

Unadjusted age-specific rates of hospitalizations and ED visits for the outcomes of RV-AGE and overall AGE across the lifespan are presented in Table 1. Prior to program introduction, the highest age-specific rates for both RV-AGE and overall AGE, regardless of setting (hospitalizations or ED) occurred among children 12–23 months. Following the program, the unadjusted mean monthly rate of hospitalizations for children at this age declined by 86% for RV-AGE hospitalizations and by 65% for overall AGE hospitalizations. ED visits for children 12–23 months were reduced by 89% and 37% for RV-AGE and overall AGE, respectively.

We found a significant reduction in both RV-AGE and overall AGE hospitalizations in unadjusted, adjusted and age-stratified analyses, following the program’s implementation (Table 2). At a population level, after adjustment for age, seasonality and secular trends, RV-AGE hospitalizations were reduced by 74% (RR 0.26, 95% CI 0.22–0.30). The reduction in RV-AGE hospitalizations among children under age 5 was similar in magnitude: RR 0.24 (95% CI 0.20–0.28). Significant reductions in RV-AGE hospitalizations were observed across nearly all age strata, with the exception of adults ≥65 years, suggestive of strong direct and indirect effects. Significant reductions in hospitalizations for overall AGE were also observed at both the population level and in age-specific adjusted analyses with attenuated RRs as compared to RV-AGE.

Similar trends were observed for ED visits (Table 2) with an overall reduction for RV-AGE of 71% (RR 0.29, 95% CI 0.20–0.43). ED visits for RV-AGE among children under age five declined by 68% (RR 0.32, 95% CI 0.21–0.50). Significant RRs for the outcome of RV-AGE were also observed across a wide range of ages, with the exception of adults 65 years and older. An adjusted RR could not be calculated for 45–64 year age stratum due to small numbers of events in the pre-program period. Significant RRs for overall AGE ED visits were also noted for all children and adolescents, but with no significant adult findings. The population-level and age-specific findings changed minimally when we repeated the analyses using a person-based, rather than an events-based analysis, with one exception. The age-specific estimate for adults age 45–64 years for overall AGE hospitalization missed statistical significance, RR

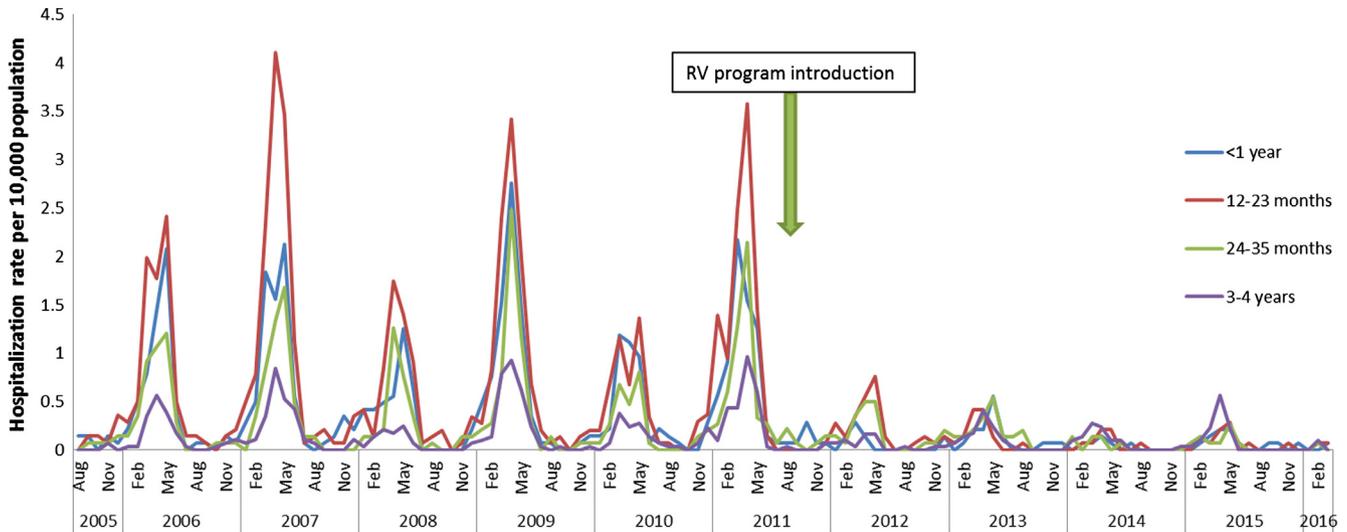


Fig. 1. Hospitalization rates for RV-AGE among children <5 years of age per 10,000 population, by month and year, August 1, 2005–March 31, 2016: Ontario, Canada.

Table 1
Unadjusted average monthly rate (per 10,000 population) hospitalizations and ED visits for RV-AGE and overall AGE before and after RV immunization program implementation, August 1, 2005 to March 31, 2016: Ontario, Canada.

	Hospitalizations				ED Visits			
	RV AGE		Overall AGE		RV AGE		Overall AGE	
	Pre-program	Public program	Pre-program	Public program	Pre-program	Public program	Pre-program	Public program
<1 year	0.509	0.073	4.466	2.495	0.018	0.054	0.077	0.033
12–23 months	0.748	0.099	5.810	2.026	0.025	0.035	0.094	0.015
24–35 months	0.358	0.098	3.506	1.487	0.012	0.023	0.054	0.017
3–4 years	0.172	0.074	1.889	1.089	0.001	0.007	0.014	0.008
5–19 years	0.014	0.009	0.451	0.384	0.001	0.003	0.003	0.001
20–44 years	0.000	0.000	0.707	0.652	0.000	0.000	0.001	0.000
45–64 years	0.000	0.000	1.059	0.953	0.001	0.001	0.000	0.000
≥65 years	0.001	0.001	2.346	1.966	0.006	0.005	0.001	0.000

Table 2

Rate ratios (unadjusted and adjusted) for changes in RV AGE and overall AGE hospitalizations and ED visits following the publicly funded RV immunization program, assessed using events-based analysis: Ontario, Canada.

	Hospitalizations		ED Visits	
	RV AGE RR (95% CI)	Overall AGE RR (95% CI)	RV AGE RR (95% CI)	Overall AGE RR (95% CI)
Unadjusted	0.25 (0.23–0.28)	0.84 (0.83–0.84)	0.32 (0.25–0.40)	0.93 (0.92–0.93)
Adjusted*	0.26 (0.22–0.30)	0.92 (0.90–0.93)	0.29 (0.20–0.43)	0.91 (0.91–0.92)
Age stratified**				
<5 years	0.24 (0.20–0.28)	0.62 (0.59–0.65)	0.32 (0.21–0.50)	0.74 (0.73–0.76)
5–19 years	0.27 (0.18–0.41)	0.85 (0.80–0.91)	0.24 (0.09–0.64)	0.90 (0.89–0.92)
20–44 years	0.01 (0.00–0.40)	1.01 (0.98–1.05)	0.09 (0.02–0.47)	1.00 (0.99–1.02)
45–64 years	0.03 (0.00–0.32)	0.95 (0.92–0.98)	0 (0–.)***	1.01 (0.99–1.03)
≥65 years	1.00 (0.23–4.38)	0.98 (0.94–1.01)	0.79 (0.06–10.34)	0.98 (0.96–1.00)

* Adjusted for age, seasonality, secular trends.

** Adjusted for seasonality and secular trends.

*** Due to small numbers of events in the pre-program period, a rate ratio could not be calculated for this age group.

0.96 (95% CI 0.93–1.00) in the person-based analysis (Supplemental Table S1). Rate ratios (unadjusted and adjusted) for both outcomes and locations of care and including finer pediatric age bands are presented in Supplemental Table S1.

The seasonality of RV-AGE hospitalizations among children under age five in the pre-and program periods is illustrated in Fig. 2. As compared to the pre-program period, the curve representing monthly trends in pediatric RV hospitalizations during the program period has a more gradual rise, a lower magnitude and a smaller area under the curve (0.86, versus 4.52). The peak month for the mean monthly RV-AGE hospitalization rate among children under five years was April for both the pre- and program periods at 1.34 and 0.29 per 10,000 population, respectively. When assessed using weekly rates, the peak mean weekly rate occurred in week 18 in the pre-program period (0.33 per 10,000 population),

as compared to week 15 in the program period (0.10 per 10,000 population).

Prior to the implementation of the vaccine program, the mean monthly hospitalization rate for RV-AGE among children residing in the most disadvantaged neighbourhoods was 34% higher than among children residing in the most affluent communities (RR for quintile 5 as compared to quintile 1: 1.34, 95% CI 1.17–1.53) (Table 3). In the program period, a difference in RV-AGE pediatric hospitalizations across quintiles of material deprivation was no longer found (RR 0.96, 95%CI 0.70–1.33 for quintile 5 as compared to quintile 1). These findings remained after adjustment for season and secular trends (post-program adjusted RR 0.95, 95%CI 0.69–1.32, for quintile 5 as compared to quintile 1). Fig. 3 depicts the mean annual RV-AGE hospitalization rate among children under 5 years in the pre- and program periods by quintile of material

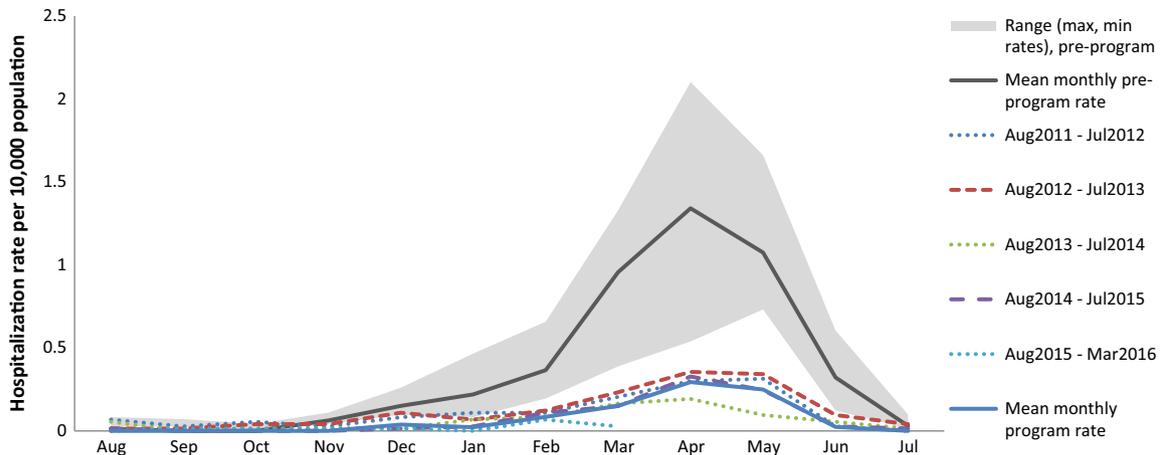


Fig. 2. RV AGE hospitalization rate among children <5 years of age per 10,000 population, pre-program (August 1, 2005 to July 31, 2011), and post-program (August 1, 2011 to March 31, 2016): Ontario, Canada.

Table 3

Rate ratios (unadjusted and adjusted) for changes in RV AGE hospitalizations among children < 5 years of age following the publicly funded RV immunization program, by quintile of marginalization: Ontario, Canada.

	Unadjusted		Adjusted for season, linear term	
	Pre-program	Post program	Pre-program	Post program
1 (least deprived)	Ref	Ref	Ref	Ref
2	1.04 (0.90–1.21)	0.83 (0.58–1.18)	1.04 (0.90–1.20)	0.83 (0.58–1.18)
3	1.18 (1.02–1.36)	0.98 (0.70–1.38)	1.17 (1.01–1.35)	0.98 (0.70–1.38)
4	1.14 (0.99–1.32)	0.86 (0.60–1.22)	1.14 (0.98–1.31)	0.85 (0.60–1.21)
5 (most deprived)	1.34 (1.17–1.53)	0.96 (0.70–1.33)	1.33 (1.17–1.52)	0.95 (0.69–1.32)

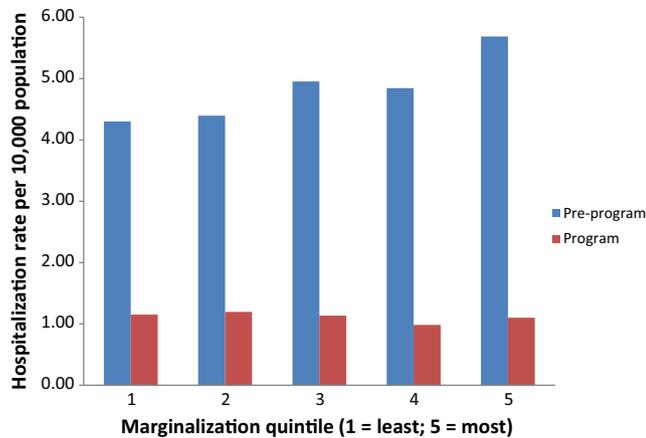


Fig. 3. Mean annual RV AGE hospitalization rate among children <5 years of age per 10,000 population, pre-program (August 1, 2005 to July 31, 2011), and post-program (August 1, 2011 to March 31, 2016), by quintile of marginalization: Ontario, Canada.

deprivation. Prior to the introduction of the rotavirus immunization program, similar inequities in pediatric hospitalizations for overall AGE were also found (Table 4). These were attenuated following the program's introduction but inequity remained for several quintiles, including the most deprived. For example, in the post-program period, the mean monthly hospitalization rate for overall AGE among children living in the most deprived quintile was 18% higher than children living in the most affluent neighbourhood (RR 1.18, 95% CI 1.09–1.27). In the pre-program period, the RR was 1.35 (95% CI 1.29–1.41), with no change following adjustment.

4. Discussion

Our previous analyses of rotavirus program impact in Ontario were limited by the inclusion of only one complete rotavirus season following implementation, and one that was likely to have lower hospitalization rates given the pre-program biennial pattern of rotavirus hospitalizations [18]. These updated analyses with a longer time horizon provide evidence of a sustained reduction in RV-AGE and overall AGE healthcare utilization in Ontario following program implementation, similar in magnitude to our earlier findings, and within the range of other post-licensure observational studies from high income settings [17,26–30]. Recent Ontario data indicating a decrease in the number and percent positivity of stool specimens for rotavirus provide additional support for the program's impact [31]. Our findings of program benefits for older children, adolescent and some adult age groups not eligible for the program are consistent with other studies demonstrating indirect (herd) effects of rotavirus programs [32,33]. In addition, we found that the mean monthly hospitalization rate for RV-AGE among children residing in the most marginalized neighbourhoods was

one-third higher than among children residing in the least marginalized, a finding that disappeared in the program period. A similar direction of effect was observed for pediatric hospitalizations for the outcome of overall AGE, although important differences between the most affluent and most disadvantaged quintiles remained. Taken together, these findings suggest an important health equity impact of the program that merits further study.

Our findings on the potential equity impact of Ontario's RV program add to a small but growing body of literature examining the burden of RV and the benefits of RV vaccination, by neighbourhood-level measures of SES and deprivation. We found a notable difference in pediatric RV hospitalizations prior to program implementation, similar in magnitude to United Kingdom (UK) investigators who found comparable pre-program gradients [15,17] and post-program equity effects [17] when examining all-cause AGE using a UK-specific deprivation index [15,17]. In contrast, our findings differ from those recently reported from the Eastern Townships in Quebec, Canada [16]. Gosselin et al. examined all-cause AGE hospitalizations in children under 5 years after assigning neighbourhoods to tertiles based on the proportion of families below the Statistics Canada low-income cut-off. They found a non-significant SES gradient in hospitalizations prior to program implementation which increased and became significant in the program period [16]. Coverage was approximately 80% and similar across the tertiles. Both UK [15,17] and Quebec investigators [16] used a similar definition of all cause AGE which was broader than that used in our study, and included known bacterial and parasitic causes of AGE that would not be vaccine-preventable. There are other methodological differences that deserve note. Gosselin et al. categorized neighbourhoods into tertiles based on the proportion of families with incomes below the LICO. The ON-Marg index incorporates the LICO in a similar approach, but also incorporates other information (i.e. education, employment, housing quality), making it more similar to the UK deprivation index, although the UK index incorporates a larger number of indicators [34]. These methodologic considerations may help to explain the difference between our findings on the equity impact of the RV program and those reported by colleagues in the province of Quebec.

Our study also assessed the seasonality of pediatric RV-AGE hospitalizations, and we hypothesized that we would see a delay in the peak similar to other assessments of seasonality following program introduction [13,26,35]. However, we found no evidence that a delay or shift in the peak of the 'rotavirus season', as assessed via healthcare utilization data, has occurred. This is consistent with a recent paper from Ontario that examined percent positivity for rotavirus, in addition to genotype distribution before and after program implementation, and reached similar conclusions [31].

Our study has some limitations. First, we assessed program impact using administrative data to quantify healthcare utilization for RV and overall AGE, rather than relying on laboratory confirmation. Therefore, there is the risk of misclassification

Table 4
Rate ratios (unadjusted and adjusted) for changes in overall AGE hospitalizations among children < 5 years of age following the publicly funded RV immunization program, overall and by quintile of marginalization: Ontario, Canada.

	Unadjusted		Adjusted for season, linear term	
	Pre-program	Post program	Pre-program	Post program
1 (least deprived)	Ref	Ref	Ref	Ref
2	1.09 (1.04–1.15)	0.98 (0.9–1.07)	1.09 (1.04–1.15)	0.98 (0.90–1.07)
3	1.17 (1.11–1.23)	1.09 (1.01–1.19)	1.17 (1.12–1.23)	1.09 (1.01–1.19)
4	1.18 (1.12–1.24)	1.01 (0.93–1.09)	1.18 (1.13–1.24)	1.01 (0.92–1.09)
5 (most deprived)	1.35 (1.29–1.41)	1.18 (1.09–1.27)	1.36 (1.30–1.42)	1.18 (1.09–1.27)

and the possibility of incomplete capture of events. This final limitation is also likely to apply to impact assessments using laboratory data as the clinical management of AGE is syndromic and typically does not rely on laboratory confirmation. To mitigate this risk, we also included overall AGE as an outcome measure, similar to other investigators [36,37]. A further potential limitation is the uncertainty in the extent to which vaccine program implementation might influence the coding of events. To our knowledge, only one study has examined the positive predictive value (PPV) of the ICD-10 code for RV-AGE in both pre- and post-vaccine program periods; it provides some reassurance as the PPV did not significantly change following program implementation [21]. Our analyses of pediatric rotavirus hospitalizations by area-level deprivation are limited by use of 2006 Canadian Census data to derive the marginalization index [25]. This assumes that DAs have remained in their respective deprivation quintiles over the past decade, which may not be the case. Also, the absence of individual-level immunization data poses challenges in the interpretation of our equity findings. If immunization coverage was equal across the quintiles, it suggests that the program has been successful in reducing inequities in the burden of rotavirus hospitalizations. If coverage is inversely associated with affluence, the trends observed may be a reflection of affluent vaccine hesitant parents refusing rotavirus vaccines for their children. However, our recent Ontario study examining rotavirus vaccine coverage found no association between neighbourhood income quintile and vaccine coverage [5]. This suggests that the equity impact observed in this study is unlikely to be mediated by differences in coverage, but further confirmation is required in a population-based study with information on both immunization status and outcome.

5. Conclusions

This study reaffirms the impressive population-level impact of the routine infant rotavirus immunization program in Ontario and that its impact has been sustained over the close to five years since program implementation. Our analyses also suggest that the program's implementation has resulted in a reduction in previous inequity in pediatric RV hospitalizations within Ontario. Monitoring equity in the uptake of immunization programs and in the distribution of benefits across the population are essential dimensions of immunization program evaluations.

Funding source

This project was funded by Public Health Ontario.

Acknowledgements

This study was supported by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI.

Data access statement

The dataset from this study is held securely in coded form at the Institute for Clinical Evaluative Sciences (ICES). While data sharing agreements prohibit ICES from making the dataset publicly

available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.01.061>.

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