The success of publicly funded rotavirus vaccine programs for preventing hospitalized rotavirus disease in Canadian children: an observational study

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Rotavirus is a major cause of pediatric gastroenteritis worldwide with severe manifestations in up to 1%-2% of infected infants. Economic modeling in Canada showed that publicly funded rotavirus vaccination programs would be cost effective if societal costs were considered. (1)Two live attenuated vaccines, monovalent Rotarix ® (Rot-1; GlaxoSmithKline Biologicals, Rixensart, Belgium) and pentavalent RotaTeq ® (Rot-5; Merck & Co., West Point, PA, USA) are available for infants at either 2 and 4 months of age (Rot-1) or 2, 4 and 6 months of age (Rot-5).

In the United States (US) and Australia, studies have shown rotavirus vaccine effectiveness ranges from 78% to 89% and annual rotavirus hospitalization rates decreased by 75% to 80% after the introduction of rotavirus vaccine. (2–4) In England there was a 26% decline in all cause gastroenteritis hospitalizations within one year of program implementation. (5) A prior Canadian study using national discharge rates from 2007 to 2017 determined that for children under 2 years, the rotavirus gastroenteritis hospitalizations had decreased by more than 80% between the pre and post vaccine periods.(6)

The aim of this study was to determine the effects of publicly funded rotavirus immunization programs on the epidemiology of community acquired (CA) and hospital associated (HA) rotavirus disease hospitalizations within the Canadian Immunization Monitoring Program, ACTive (IMPACT), a surveillance network of tertiary care pediatric hospitals (https://cps.ca/en/impact).

Methods

Study Locations

Active, surveillance for hospital admissions and hospital acquired rotavirus infections was conducted by the 12 pediatric IMPACT hospitals since 2005. In Canada, Rot-1 vaccine (Rotarix™) was used primarily until mid-2017 after which Rot-5 (Rotateq™) was used through 2020. The month and year of initiation of publicly funded immunization programs in Canada including provinces and territories without IMPACT sites is shown in Table 1.

Study Subjects

Children 0 to 16 years who had laboratory confirmed rotavirus infections and were hospitalized at the IMPACT hospitals either on an inpatient ward or equivalent (such as a short stay or observation unit) between January 1, 2005 and December 31, 2020 were included. Trained nurse monitors prospectively identified and listed cases from admission lists and microbiology reports on a regular basis. ICD-10 discharge code searches were also conducted annually to identify any missed cases of diarrhea or viral gastroenteritis using the following ICD10 codes: A08 (viral and other intestinal infections), A09 (diarrhea and gastroenteritis of infectious origin), K52.9 (noninfectious gastroenteritis), R11 (nausea and vomiting), and R15 (fecal incontinence) and if found, were screened for rotavirus positivity. The chart abstraction occurred after discharge.

All centers used the same case finding strategies, case definition, and case report form. Identification of rotavirus gastroenteritis was detected using either enzyme linked immunoassay [ELISA] or molecular

diagnostics (polymerase chain reaction) on stool specimens. Individual hospital census data (number of hospital admissions and inpatient hospital days) is reported yearly to IMPACT.

Cases with laboratory confirmation <72 hours after hospital admission were defined as community acquired cases (CA). Rotavirus identified from patients ≥72 hours after admission or readmitted with rotavirus ≤48 hours after the initial discharge were defined as hospital acquired (HA). Cases were included if they had acute gastrointestinal symptoms (diarrhea/vomiting). Cases admitted for unrelated reasons or no acute gastrointestinal symptoms (i.e., incidental cases) were excluded.

The following information was retrieved from review of the medical record: demographic data, pre-existing co-morbid or immune compromising conditions (using pre-defined lists), clinical features (including presence of dehydration, electrolyte abnormalities, seizures), length of stay, number and type of rotavirus vaccine received, and outcome. Prematurity was defined as a child born ≤36 weeks gestation who was still in the first year of life. Children were classified as generally healthy or having a known underlying/immunocompromising condition at the time of admission or during the admission. The determination of dehydration was based on documentation in admission notes. Data for clinical presentations were available from 2008 onwards and was captured only for cases with CA disease.

A vaccine failure was defined as children who had received 2 doses of Rot-1 or 3 doses of Rot-5 vaccine at least 2 weeks prior to admission.

Research Ethics Board or hospital approval was obtained for all sites.

Statistical Analysis

The overall, age-specific and site-specific CA rotavirus hospitalizations rates were reported per 10,000 hospital admissions, based on yearly hospital census data. The rates of HA rotavirus infections were calculated per 1,000 inpatient days. This was stratified by age groups (0-11 months, 12-23 months, 24-59 months, 5-9 years, and 10-16 years).

For each province, the year a rotavirus vaccine program was introduced was designated as year 0 of the program, with the years prior to province specific vaccine programs being designated -15 to -1 and years following introduction designated as +1 to +9. All calculations were done with the year of vaccination program start as “year 0” unless the program started in November or later where the next calendar year was designated as “year 0”. Cases occurring in year “0” at each site were not included in the pre and post vaccine periods as the year “0” was designated a transition year.

Analysis for indirect effect of the vaccine included only individuals within age groups who were previously or currently ineligible for vaccine based on age.(7) Average admission rate in these eligible cohorts was calculated separately for pre and post vaccine periods.

Descriptive statistic comparisons were obtained using Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables, stratified by pre and post vaccine eras. Adjustment for multiple comparisons was not done. Binomial confidence intervals were calculated for proportions.

Analyses were conducted in R (V.4.1.1; The R Project for Statistical Computing, Vienna, Austria) and data cleaning was done in SAS (V.9.4, SAS Institute, Cary, North Carolina, USA).

Results

A total of 5,691 rotavirus hospitalizations were identified at the 12 sites from January 1, 2005, to December 31, 2020 of which 4,323 (76%) were CA and 1,368 (24%) were HA. Overall, the median age for CA cases was 1.5 years (interquartile range (IQR) 0.8 – 2.9 years) whereas the median age for HA cases was 0.8 years (IQR 0.3 to 2 years). The age breakdown was 2,148 (38%) 0-11 months, 1,523 (27%) 12-23 months, 1305 (23%) 24 to 59 months, 479 (8%), 5 to 9 years, and 236 (4%) 10 to 16 years. Of the entire cohort of 5,691 children, 2621 (46%) had underlying co-morbidities and among this group, 790 (14%) were immunosuppressed.

Comparisons Pre and Post vaccine periods

The overall average rate of hospitalization admissions due to CA rotavirus decreased from 60.3 [95% CI 52.0-68.6] per 10,000 hospital admissions in the pre vaccine period to 10.98 [95% CI 6.2-15.82] per 10,000 resulting in a rate reduction of 82% [95% CI 74.4%-89.8%] (Figure 1a). The prevalence of HA rotavirus decreased by 85% [95% CI 27.6%-99.7%]; 0.35 per 1000 patient days during the pre vaccine period to 0.05 per 1000 patient days in the post vaccine period (Figure 1b). Differences in CA and HA over the 2 time periods were statistically significant (p-values <0.001).

The demographics of both CA and HA rotavirus cases by pre and postvaccine periods is seen in Table 2. Among CA cases in the pre vaccine period, 2277/3331 (68.4% [95% CI 66.8-69.0]) were generally healthy whereas in the post vaccine period, 372/656 (53.4% [95% CI 52.9-60.4]) were generally healthy. Among HA cases, in the pre vaccine period, 190/1109 (17.1% [95% CI [15.0-19.5]) were healthy compared to the post vaccine period where 9/162 (5.5% [95% CI 3.0-10.2]) were healthy.

The major presenting signs and symptoms for patients with CA disease in the pre and postvaccine periods are seen in Table 3.

The yearly decrease in rates of CA rotavirus hospitalization and HA rotavirus pre and post vaccine periods by age is illustrated in Figure 2a and 2b showing decreasing trends in hospitalizations in various age groups. The average CA rotavirus hospitalization rates and HA rotavirus rates by age cohorts in pre vaccine and post vaccine periods is seen Table 4. There were decreases in both CA and HA associated hospitalizations for those who were not in the vaccine eligible cohorts, and this was seen for all age groups.

In the post vaccine period, 61 (7.4%) of 818 total cases (53 [86.9%] had CA and 8 [13.1%] had HA disease) had received the recommended number of doses of vaccine at least 2 weeks prior to admission and were designated vaccine failures. The mean age for patients with vaccine failures was 1.9 (SD 1.5) years, median 1.7 years (IQR 0.9-2.4 years). Of these, 27 (44%) of 61, had underlying co-morbidities of which 9 (33.3%) had immunocompromising conditions.

During the entire surveillance period, a total of 40 (0.7%) deaths were reported at the same admission as the rotavirus hospitalizations. Of the 40 deaths, 39 (97.5%) had underlying diseases or prematurity (one was unknown) with 26 (65%) occurring in the time period before vaccine programs (-1 to -15 years), 4 (10%) the year a program was initiated (year 0) and 10 (25%) in the post vaccine program periods (+1 to +9 years). In these cases, it is unknown if the rotavirus infection contributed to the deaths. Of the 40 cases, 13 (32.5%) were CA and 27 (67.5%) were HA. Of the 13 who had CA infections, 3 (23%) were 0-11 months, 2 (15.4%) 12 to 23 months, 5 (38.5%) 24-59 months, 1 (7.7%), 5 to 9 years and

2 (15.4%), 10-16 years of age. Of the 27 who had HA rotavirus infections, 13 (48.1%) were 0- 11 months, 2 (7.4%), 12-23 months, 3 (11.1%),24-59, 6 (22.2%), 5-9 years and 3 (11.1%) 5 -16 years.

Of the 10 deaths which occurred in the post vaccine program periods, 6 were CA (3 cases 0-23 months, 3 cases, 24-59 months) and 4 were HA infections (all 0-11 months). Of these, 7 had no RV vaccines, 2 had had 1 dose and one had received the complete series.

Discussion

This 15-year, real-world, active surveillance for rotavirus hospitalization in children demonstrates a significant and sustained decrease in rotavirus hospitalizations for both CA and HA disease in Canadian IMPACT study sites since oral RV vaccine was introduced into provincial vaccine programs. The average rate reduction between pre and post vaccine program implementation was 82% for CA rotavirus admissions and 85% for HA rotavirus infections.

These data add to the world literature on the success of rotavirus immunization programs in decreasing morbidity in high income countries where prior reports from Finland, England, Austria, United States, New Zealand and Australia have shown decreases of 75%-92% in rotavirus hospitalizations mainly in the first 5-6 years of program implementation. (8–12) Data from a surveillance study in the United States (US) conducted at 6-7 years post vaccine program implementation noted an overall vaccine efficacy (VE) against severe disease of 69% (95% CI 43-84) suggesting reasonable longer term vaccine efficacy. (13) In Leipzig Germany, a 10-year follow-up after introduction of RV1 vaccine program the incidence of hospitalization dropped by 85% despite an average vaccinated portion of children of 47.6%. (14) Our data also show that the reduction in both CA and HA disease is sustained at 9 years at sites that had programs as of 2011. In contrast, a report from Poland where vaccine is not being deployed as a publicly funded program leading to low vaccine coverage of 25%, there was no significant impact on hospitalizations due to rotavirus. (15)

Studies reporting the prevalence of HA diseases, including a Canadian study at IMPACT sites prior to availability of RV vaccines, had shown that between 19% to 27% of hospitalized rotavirus cases were HA and represented a significant burden on hospital costs mainly through increases in length of stay. (16,17) Our study and others showed a significant decline in disease in all HA rates especially in the 0 to 11 month age group very rapidly after program implementation suggesting as well, that CA rotavirus admissions are a likely a major source of transmission to hospitalized patients. (18,19)

Given that RV vaccine is given only to infants (with the last dose given prior to 8 months of age) indirect effects on disease incidence on non-vaccine eligible cohorts can be calculated. (7) Our data show parallel decreases in both CA and HA disease in older age groups. In a German cohort, the herd protection was estimated to be 38%. (19) A study from the US three years after RV vaccine introduction in children <3 years of age also noted substantial indirect protection in the cohort 12-23 months.(20) Other studies have noted the indirect VE as up to 82% four years after vaccine introduction.(21) In Australia and the US, including a study 7 years after the RV programs started, rotavirus hospitalization decreased in all age groups, including adult age groups supporting a substantial herd protection. ((22–25) However, data from Finland 5-6 years post vaccine programs have indicated that rotavirus cases continue to occur in older children and in the elderly. (26)

In a meta-analysis of global vaccine efficacy, a very small proportion (5%) of cases had received a complete vaccine series at least 2 weeks prior to hospitalization with vaccine efficacy estimated at over 90% in settings with low mortality. (27) The vaccine failure rate in this cohort was slightly higher at 7.4%. The cause of vaccine failure may include vaccine cold chain issues, host specific blunted immune responses due to underlying illnesses or emergence of genotypes that escape immunity. (28) Genotype analysis of these strains is ongoing.

The major strength of our study is the active, standardized surveillance at the same sites over the 15-year observation period. This consistency provides accurate estimates of hospital admissions for both CA and HA rotavirus disease. The prolonged observation period accounts for the natural variation in disease incidence and underscores the longer-term benefits of rotavirus vaccines in preventing both CA and HA disease.

Limitations include less representation from sites that do not have IMPACT surveillance programs either within the province or in provinces or territories that are not included in IMPACT network. As rotavirus cases could have been admitted to regional or community hospitals not in the IMPACT network, the effect of vaccine against these cases could have been different from those of IMPACT hospitals which admit patients requiring secondary, and tertiary care. The network, however, accounts for up to 90% of pediatric tertiary care hospital beds in Canada. It is possible that patients were admitted to hospital with acute gastroenteritis or in hospital with new diarrheal illnesses and did not have samples sent for laboratory analysis, underestimating the true burden in both pre and post vaccine periods. Rotavirus infections from children recently admitted to other hospitals could have been HA acquired rather than CA cases, thereby underestimating HA cases or overestimating CA cases.

In conclusion, the publicly funded RV immunization programs in Canada have been associated with an 80% decrease in hospitalizations for rotavirus infection in children 0-16 years over the past 9 years at IMPACT sites located in 8 provinces. HA rotavirus disease has also been drastically reduced leading to a decrease in hospital burden and morbidity for children already hospitalized.

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Table 1 Dates of Introduction for publicly funded rotavirus immunization programs in Canada by province with and without IMPACT sites.

Province or Territory	Month/Year	Designated year 0
With IMPACT sites		
Ontario	August 2011	2011
Québec	November 2011	2012
British Columbia	January 2012	2012
Saskatchewan	November 2012	2013
Manitoba	April 2014	2014
Alberta	June 2015	2015
Newfoundland	September 2015	2015
Nova Scotia	November 2019	2020
Without IMPACT sites		
Prince Edward Island	December 2010	NA
New Brunswick	May 2018	NA
Northwest Territories	Fall 2013	NA
Nunavut	December 2017	NA
Yukon	October 2012	NA

Table 2 Demographics of cases in pre-vaccine versus post-vaccine time periods. *

	Pre-vaccine program period rotavirus disease		**Pre-vaccine program Period Total**	**Post-vaccine program period rotavirus disease**		**Post-vaccine program Period Total**	**Overall Totals***
	Community acquired n= 3331	Hospital acquired n= 1109	4440	Community acquired n=656	Hospital acquired n=162	n= 818	n= 5258
Age mean, median, (IQR)	2.3, 1.5 (0.8-2.7)	2.0, 0.8 (0.3-1.8)	2.2, 1.3 (0.6-2.5)	3.4, 2.4 (1.1-4.9)	2.8, 1.0 (0.2-3.4)	3.0,1.8 (0.8-3.8)	2.4, 1.4 (0.6-2.8)
0-11 months n (%)	1118 (34)	648 (58)	1766 (39.8%)	161 (25)	79 (49)	240 (29.3%)	2006 (38.1%)
12-23 months n (%)	1027 (31)	209 (19)	1236 (27.8%)	129 (20)	26 (16)	155 (19%)	1391 (26.5%)
24-59 months n (%)	833 (25)	133 (12)	966 (21.8%)	207 (32)	27 (17)	234 (28.6%)	1200 (22.8%)
5-9 years n (%)	243 (7)	56 (5)	299 (6.7%)	126 (19)	15 (9)	141 (17.2%)	440 (8.4%)
10-16 years n (%)	110 (3)	63 (6)	173 (3.9%)	33 (5)	15 (9)	48 (5.9%)	221 (4.2%)

* Excludes 433 cases from year of vaccine introduction (year 0) at all sites

Table 3 Comparison of clinical features and outcome for **CA infections** in the pre-vaccine and post-vaccine era*

	Pre-vaccine period -1 to -13* n = 1972 n, %, (95% confidence Interval)	Post-vaccine period +1 to +9 n = 656 n, %, (95% confidence Interval)	P-value
Diarrhea, vomiting and fever	1466 74 (72-76)	408 62 (58-66)	<0.001
Dehydration[&]	1594 81 (79-83)	509 78 (74-81)	0.07
Electrolyte abnormalities	920 47 (44-49)	282 43 (39-47)	0.10
Shock[&]	37 2 (1-3)	20 3 (2-5)	0.07
Seizures[&]	145 7(6-9)	54 8 (6-11)	0.46
IV hydration	1906 97 (96-97)	624 95 (93-97)	0.07
Admitted to ICU admission n, % Median days (IQR)	75, 3.8% 2 (1-4)	38, 5.7% 1 (1-3)	0.023
Length of hospital stay, days (median, IQR)	2 (2-4)	3 (2-5)	<0.001

* Data from for this period available only from 2008 onward and excludes cases for from year of vaccine introduction (year 0) at all sites

[&] As noted in patient charts by admitting physician and criteria of low blood pressure and tachycardia for shock. Both febrile and afebrile seizures included.

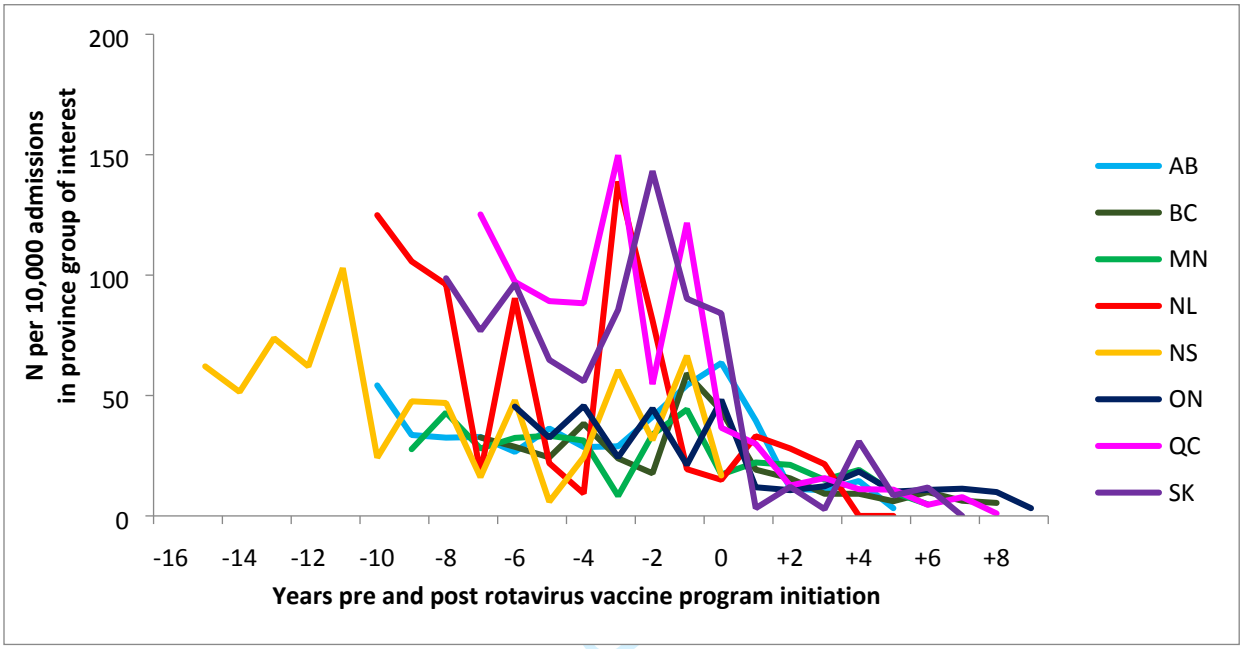
Table 4 Average hospitalization rates for CA and HA disease by age group in the pre-vaccine and post-vaccine time periods.

Age Groups	**Average CA rotavirus admission rates (per 10,000 hospital admissions) by vaccine period**	
	Pre vaccine period	Post vaccine period
0-11 months	18.3	0*
12-23 months	18.2	0*
24-59 months	15.4	1.4
5-9 years	6.1	1.6
10-16 years	2.3	0.5
	Average HA Rotavirus hospitalizations (per 1000 patient days) by vaccine period	
	Pre vaccine period	Post vaccine period
0-11 months	0.19	0*
12-23 months	0.07	0*
24-59 months	0.05	0.003
5-9 years	0.02	0.003
10-16 years	0.01	0.005

*Postvaccine period presents the indirect effect as it excludes patients who were or are in a vaccine eligible cohort.

Figure 1

a) Yearly CA rotavirus admissions per 10,000 hospital admissions from 2005 to 2020 by timing of vaccine program initiation. * The overall average rate of hospitalization due to CA rotavirus decreased from 60.3 [95% CI 52.0-68.6] per 10,000 admissions in the pre vaccine period to 10.98 [95% CI 6.2-15.82] per 10,000 admissions resulting in a rate reduction of 82% [95% CI 74.4%-89.8%]



b) Yearly HA rotavirus admissions per 1,000 patient days from 2005 to 2020 by timing of vaccine program initiation. * The prevalence of HA rotavirus decreased by 85% [95% CI 27.6%-99.7%]; 0.35 per 1000 patient days during the pre vaccine period to 0.05 per 1000 patient days in the post vaccine period.

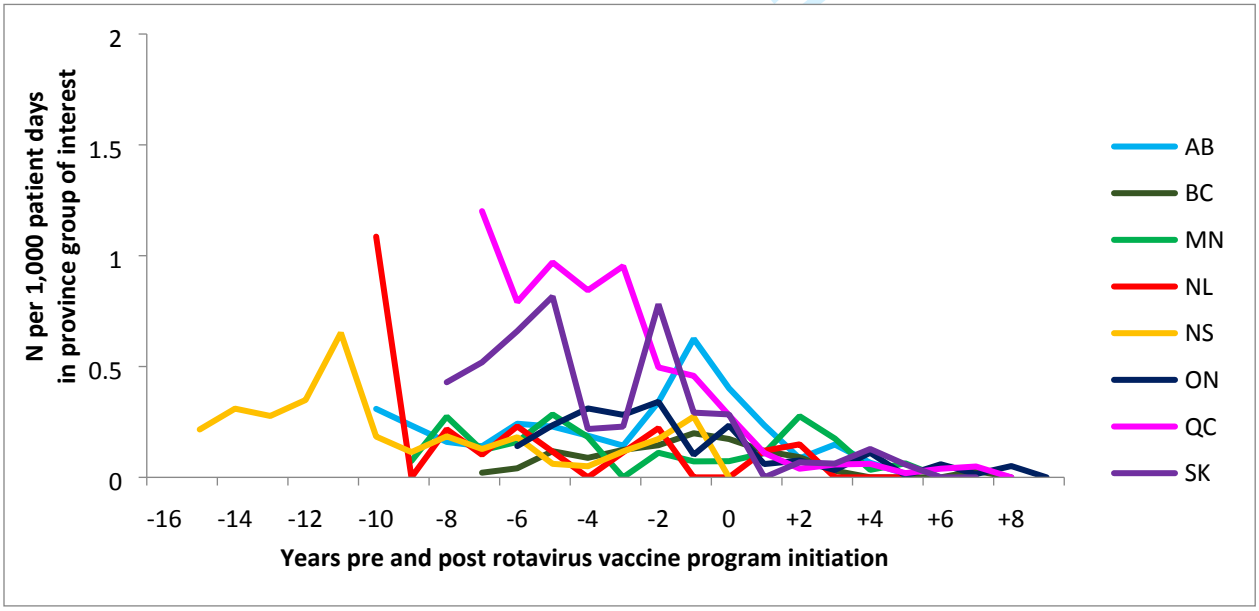
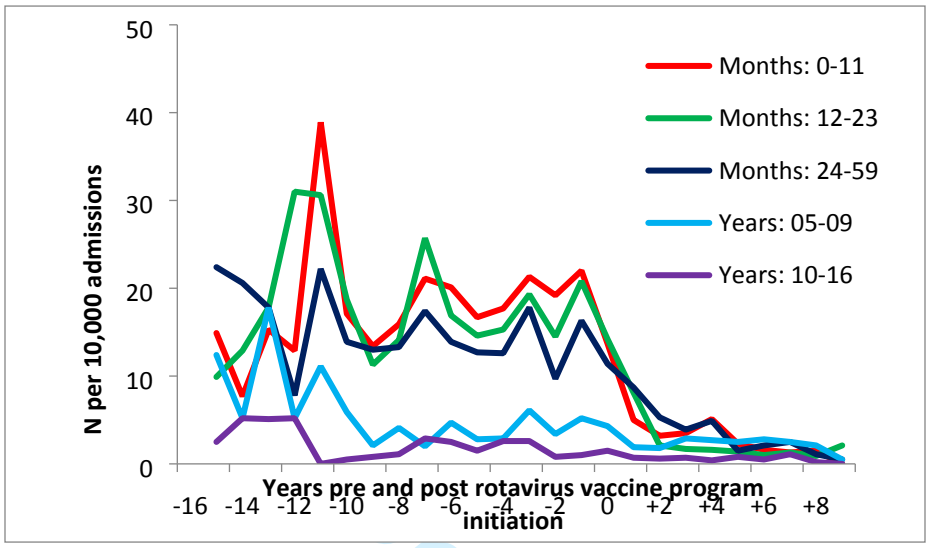
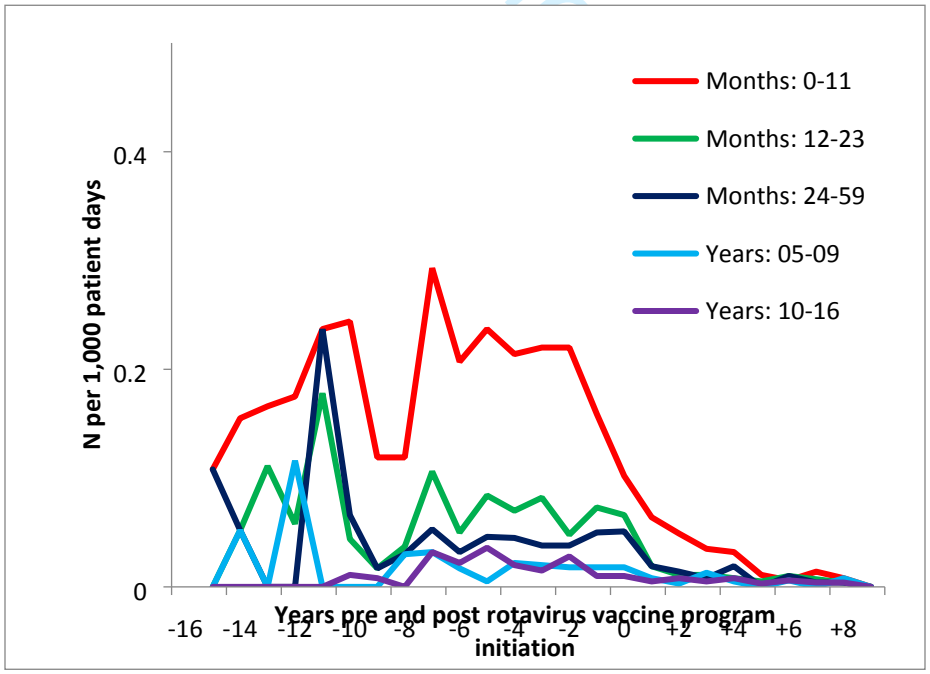


Figure 2

a) The yearly CA rotavirus admissions per 10,000 hospital admissions **by age** pre and post vaccine periods with year 0 as the year of program start in provinces.*



b) The yearly rates of HA rotavirus per 1000 patient days **by age** 2005 to 2020 and pre and post vaccine time periods.



* Years -15 to -1 represent the pre vaccine periods while years 1 to 9 indicate the post vaccine period with year 0 representing the year of program implementation.