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Article title: The success of publicly funded rotavirus vaccine programs for preventing hospitalized rotavirus disease in Canadian pediatric hospitals: an observational study

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Reviewer 1: Ulrich Desselberger / Department of Medicine, University of Cambridge, Cambridge, UK

A short Abstract should be added.

Done

The first 3 paragraphs should be headed 'Introduction'.

Thank you for this reference since this does give a 15 year follow up. I have added this.

The citation of recent reviews should be considered:

- Burnett E, et al. Trends in Rotavirus Laboratory Detections and Internet Search Volume Before and After Rotavirus Vaccine Introduction and in the Context of the Coronavirus Disease 2019 Pandemic-United States, 2000-2021. J Infect Dis. 2022 Sep 21;226(6):967-974.

- Bergman H, et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2021 Nov 17;11(11):CD008521.

This review summarizes mainly the decreases in incidence of severe rotavirus diarrhea by 90% in low risk countries with a 2 year follow-up. I included this study as ref # 17 (please see other comment).

- Burnett E, et al. Rotavirus Infection, Illness, and Vaccine Performance in Malnourished Children: A Review of the Literature. Pediatr Infect Dis J. 2021 Oct 1;40(10):930-936.

Interesting review but I did not include it as it was not particularly applicable to Canada.

- Soares-Weiser K, Bergman H, Henschke N, Pitan F, Cunliffe N. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2019 Oct 28;2019(10):CD008521.

Agree that the main message was that RV vaccine prevented 80%n of severe diarrhea in countries with low death rates. I used the 2021 update (Bergman is first author now with Soares-Weiser as last author (see above) https://pubmed.ncbi.nlm.nih.gov/34788488/ And this goes up to 2 years so prevented 90% to 97% in children in first year of life and 96% up to year 2

3 Paragraph 3, Table 2. The right most column should be omitted. The subdivision of the heading could be improved.

Thank you and this has been done. The heading is also changed. Made this more specific. Ages of CA and HA RV hospitalizations pre-vaccine versus postvaccine time periods.

Paragraph 5, Table 4. … are seen in Table 4.

4 Last paragraph. Regarding herd immunity consider citation of:

Thank you. This add context. I added this as a reference.
- Pitzer VE, et al.. Demographic variability, vaccination, and the spatiotemporal

dynamics of rotavirus epidemics. Science. 2009 Jul 17;325(5938):290-4.

- Olson DR, et al. Surveillance data confirm multiyear predictions of rotavirus dynamics in New York City. Sci Adv. 2020 Feb 26;6(9):eaax0586.

Modelling shows that various factors such as seasonality and duration of maternal immunity may account for a change in transmission rates.

Added the Olson reference. Did not add the Asare EO, et al. Modeling of rotavirus transmission dynamics and impact of vaccination in Ghana. Vaccine. 2020 Jun 26;38(31):4820-4828
- Asare EO, et al. Modeling of rotavirus transmission dynamics and impact of vaccination in Ghana. Vaccine. 2020 Jun 26;38(31):4820-4828.

- Wierzba TF. Implications and measurement of herd protection (indirect effects) for enteric vaccine development. Vaccine. 2019 Aug 7;37(34):4775-4777.

This reference was already in our list as reference # 7 in the original submission. It is still a reference as #15

- Nymark LS, et al. Inclusion of the value of herd immunity in economic evaluations of vaccines. A systematic review of methods used. Vaccine. 2017 Dec 14;35(49 Pt B):6828-6841.

This study was good but ours did not include an economic analysis.

Reviewer 2: Astrid Guttman / Institute for Clinical Evaluative Sciences

This is a well written paper using Canada's only hospital-based infectious disease clinical surveillance system IMPACT to describe trends in rotovirus hospitalizations pre- and post-implementation of a vaccination program in each province. While IMPACT data are only collected in a select number of hospitals, and thus not population-based, the data are more clinically rich (including lab confirmation) and enabled the authors to both describe hospital acquired disease, which is novel and an important contribution to the literature, as well as clinical details of changes of community acquired disease which are not possible with administrative health records only.

I have only minor comments.

1) Introduction

a. As context, it would be very helpful to have data (ideally by province) on vaccine uptake – this could be mentioned in the Introduction if there is a recent overall proportion for Canada and if provincial data exist added to Table 1or – even if this were a slightly crude measure such as doses/population of eligible

children supplied to the province. If these data are not available, it would be worth mentioning in the discussion, para 2, in part as a data advocacy point!

Really good point. Thank you.

We have included additional data sources for vaccine coverage (4 from provinces that have accessible data and one from the Canadian immunization coverage survey). I have also added the information from US in 2018 that indicates a coverage rate of 73%

2) Methods

a. please state or cite any validation studies of data quality of IMPACT. For this study in particular, how common are admissions with the diagnosis codes for gastroenteritis without a stool sample? Has the proportion changed over the study period?

For our study only lab confirmed rotavirus cases were included, therefore diagnostic codes for gastroenteritis are not relevant. Gastroenteritis was not used as a proxy for rotavirus infections.

b. Please describe how missing data were handled.

Data is verified by a data scrutinizer at the Vaccine center and monitors are asked to recheck charts if data is missing. If unavailable in the hospital chart, data is reported as not available.

c. Please include in an appendix the definitions of co-morbidity and immune compromising conditions used

3) Results

a. Appreciating the low number, it might still be helpful to denominate the mortality numbers on admissions and annualize given that the differential period of observation for pre- and post vaccine eras.

Agree that mortality should be normalized. We calculated the rates per 10,000 admission and have added the range as rates in the two periods.

4) Discussion

a. This was well done and again the HA analyses are– the only limitation that would be worth adding is that there may have been other trends in admission patterns (for instance a shift away from tertiary care hospitals to community hospitals for low complexity cases over time) that could bias especially the community acquired disease results. This has been the case in Toronto and may be in other cities with multiple hospitals that admit children.

Unfortunately, we do not have data for the community care hospitals however, we do know that the severity of disease did not seem to change in the pre vaccine and post vaccine periods. Also in some IMPACT centers, there are no other hospitals that admit children beyond the neonatal period (this is the case in Calgary, Ottawa, Edmonton, Winnipeg, Quebec city,

5) Exhibits

a. Table 4 -- Would be helpful to include the explanation that post vaccine results are measuring indirect effect only OR possibly remove the lines for 1-11 and 12-23 months altogether given that the age specific effects over time are already included in the figures.

Agree this would be helpful.