

Updates to the Rotavirus Immunization Program: Product Change Question and Answer Document May 2018

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Program background, rationale and eligibility:

1. Why are we changing the rotavirus vaccine used in BC?

BC participates in a federally coordinated multi-year vaccine purchasing process. This process requires suppliers to respond to a competitive bid; the bid assessment took into account the difference in the number of doses required for series completion for the two available products. For the period beginning April 1 2018 and for up to 3 years, Merck Canada Inc. was the successful bidder.

2. When was RotaTeq® vaccine approved for use in Canada? Is it being used in other countries?

RotaTeq® was approved for use in Canada in August 2006¹. Both RotaTeq® and Rotarix® have been used globally in national immunization programs, with demonstration of comparable effectiveness in post-marketing surveillance. The National Advisory Committee on Immunization recommends either vaccine, without a preferential recommendation for one over the other¹.

3. What is the plan to transition to RotaTeq® vaccine? Will we begin offering it on a certain date provincially to all new babies or based on Health Unit supply?

Because of various amounts of remaining Rotarix® inventory in health units around BC, providers will begin receiving RotaTeq® in May but may receive it later, depending on when their Rotarix® inventory declines.

¹ National Advisory Committee on Immunization. Updated statement on the use of rotavirus vaccines. Canada Communicable Disease Report. 2010; 36(ACS-4): 1-37. Available from <https://www.canada.ca/content/dam/phac-aspc/migration/phac-aspc/publicat/ccdr-rmtc/10pdf/36-ac-4.pdf>

4. Should we save stock of Rotarix® for babies who have started their series with that product? What do we do with remaining stock of vaccine?

Ideally, infants who begin their series with Rotarix® will complete their series with this product. It is important to balance the remaining Rotarix® stock on hand to complete vaccine series in progress if possible, while also minimizing wastage.

5. Will the Panorama forecaster be updated to reflect the new RotaTeq® schedule?

Yes. The Panorama forecaster is being updated to include the RotaTeq® schedule. Panorama is the immunization registry used by several BC health authorities for recording of childhood immunizations.

6. What additional resources will be updated related to the rotavirus vaccine product change?

- The BC Child Health Passport will be updated to include rotavirus vaccine indicated at the 2, 4 and 6 month visits. In the interim, existing health passports can be modified by immunization service providers when a third dose of rotavirus vaccine is indicated.
- There will be separate HealthLinkBC files developed, one for RotaTeq® and one for Rotarix®. During the transition, both health files will be available on-line. Once there is no Rotarix® remaining in the province, the Rotarix® health file will be retired.
- A 'Dear Health Care Provider' letter to notify community vaccine providers of the changes to the rotavirus vaccine product will be available for health authorities to use.

Scheduling and vaccine administration:

7. What is the recommended timing for the administration of RotaTeq® vaccine?

- It is recommended that RotaTeq® be administered at 2, 4 and 6 months together with the other routine infant vaccines given at these ages
- The minimum age for the first dose of RotaTeq® is 6 weeks
- The maximum age for the first dose of RotaTeq® is 20 weeks less 1 day
- The minimum interval between doses of RotaTeq® is 4 weeks
- The maximum age for dose 3 of RotaTeq® is 8 months plus 0 days

8. Why does the BC Immunization Manual, Part 4 - Biological Products, [RotaTeq® page](#), allow for the maximal age for dose 1 to be 20 weeks less 1 day of age?

The recommended schedule for immunization with RotaTeq® vaccine is at 2, 4, and 6 months of age, with an 8 month zero day maximal age for receipt of the 3rd dose. However, children who are delayed for their immunizations (e.g., who enter Canada during early infancy without a record of prior immunization) may receive their first dose as late as 20 weeks less 1 day of age.

When the publicly funded rotavirus vaccine was initially introduced in BC in January 2012, Rotarix® was the product used in the program. The product monograph indicates the following:

Recommended Dose and Dosage Adjustment

The vaccination course consists of two doses. The first dose can be administered from the age of 6 weeks. There should be an interval of at least 4 weeks between doses. ROTARIX® may be given to preterm infants following the same vaccination course. This could be incorporated into the Canadian Immunization Schedule (2 and 4 months). Other immunization schedules have also been evaluated (see CLINICAL TRIALS). The administration of the 2 doses should be completed by the age of 24 weeks.²

It follows that if the maximal age at receipt for dose 2 is 24 weeks and the minimum interval between doses is 4 weeks, the maximal age for receipt of dose 1 was 20 weeks. The product monograph is silent on the maximal age for dose 1 receipt.

The rationale for the Canadian National Advisory Committee on Immunization recommendation for administration of dose 1 before 15 weeks of age is based on the association between vaccine administration and intussusception (see question 15).³ Based on pre-vaccine era US data, rates of intussusception in infants begin to rise at 8 weeks of age and peak at 24-28 weeks of age, then gradually decline.⁴ The basis for recommending dose 1 receipt by 15 weeks of age is to minimize the risk elevation for intussusception by avoiding administration of the vaccine during the weeks of life when baseline rates of this condition are higher.

² GlaxoSmithKline Inc. ROTARIX. Product Monograph. January 26, 2018. Page 11. <http://ca.gsk.com/media/1216129/rotarix.pdf>

³ Canadian Immunization Guide: Part 4 - Active Vaccines. Rotavirus Vaccine. Recommendations for Use. <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-19-rotavirus-vaccine.html>

⁴ Tate JE, Simonsen L, Viboud C, Steiner C, Patel MM, Curns AT, Parashar UD. Trends in intussusception hospitalizations among US infants, 1993-2004: implications for monitoring the safety of the new rotavirus vaccination program. *Pediatrics*. 2008 May;121(5):e1125-32

Data from postmarketing use of rotavirus vaccines indicates administration beyond 15 weeks of age, without clear evidence of a higher risk of intussusception.⁵ Additionally, the low risk of intussusception appears to be comparable for the two vaccines (see question 15).

Furthermore, the World Health Organization has recommended that for children under 24 months of age, rotavirus vaccine be administered in conjunction with DTP-containing vaccines regardless of the age of administration. While it is recognized that the benefit:risk considerations of severe rotavirus infections in low income countries are not the same as in Canada, this recommendation nevertheless supports a loosening of the restriction on vaccine administration.⁶

Quebec has made a similar recommendation to that in BC.

9. What if an infant has received their 1st dose with Rotarix[®] and this product is not available for their 2nd dose?

As there is limited data on the interchangeability of Rotarix[®] and RotaTeq[®], whenever possible complete the vaccine series with the same product.

If the same vaccine product is not available, complete the vaccine series with RotaTeq[®] for a total of 3 doses of rotavirus vaccines.

Here are the possible scenarios that may present:

- a) 1st dose of Rotarix[®] given at 2 months and **Rotarix[®] is available**
 - Provide 2nd dose of Rotarix[®] at 4 months → Series is complete
- b) 1st dose of Rotarix[®] given at 2 months and **Rotarix[®] is not available***
 - Provide 2nd and 3rd doses as RotaTeq[®] at 4 and 6 months, respectively → Series is complete
- c) Infant presents at clinic at 2 months and **Rotarix[®] is not available**
 - Provide 3 doses of RotaTeq[®] at 2, 4, and 6 months → Series is complete
- d) If the 1st dose of rotavirus vaccine product is unknown (e.g., infant arrives from out of province with an immunization record that does not specify which rotavirus vaccine was received)
 - Provide 2 doses of RotaTeq[®] at 4 and 6 months → Series is complete

*If any dose in the series was RotaTeq[®], a total of 3 doses of rotavirus vaccines should be administered.

⁵ Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, Booy R, Bines JE; PAEDS/APSU Study Group. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine*. 2011 Apr 5;29(16):3061-6. See Tables 1-3.

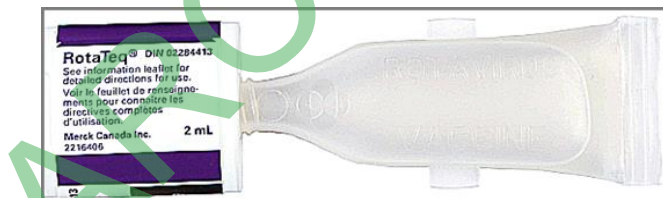
⁶ Rotavirus vaccines. WHO position paper – January 2013. *Wkly Epidemiol Rec*. 2013 Feb 1;88(5):49-64. See page 63.

10. Will we have to obtain additional consent for RotaTeq® if the parent or guardian has already consented to a Rotarix® vaccine series?

No, consent is given for receipt of vaccine for disease protection. Parents and/or guardians of infants who are receiving both vaccine products should be informed of the change in vaccine product and the need for a 3rd dose to complete the series. Contraindications should be reviewed at each visit.

11. How is RotaTeq® supplied?

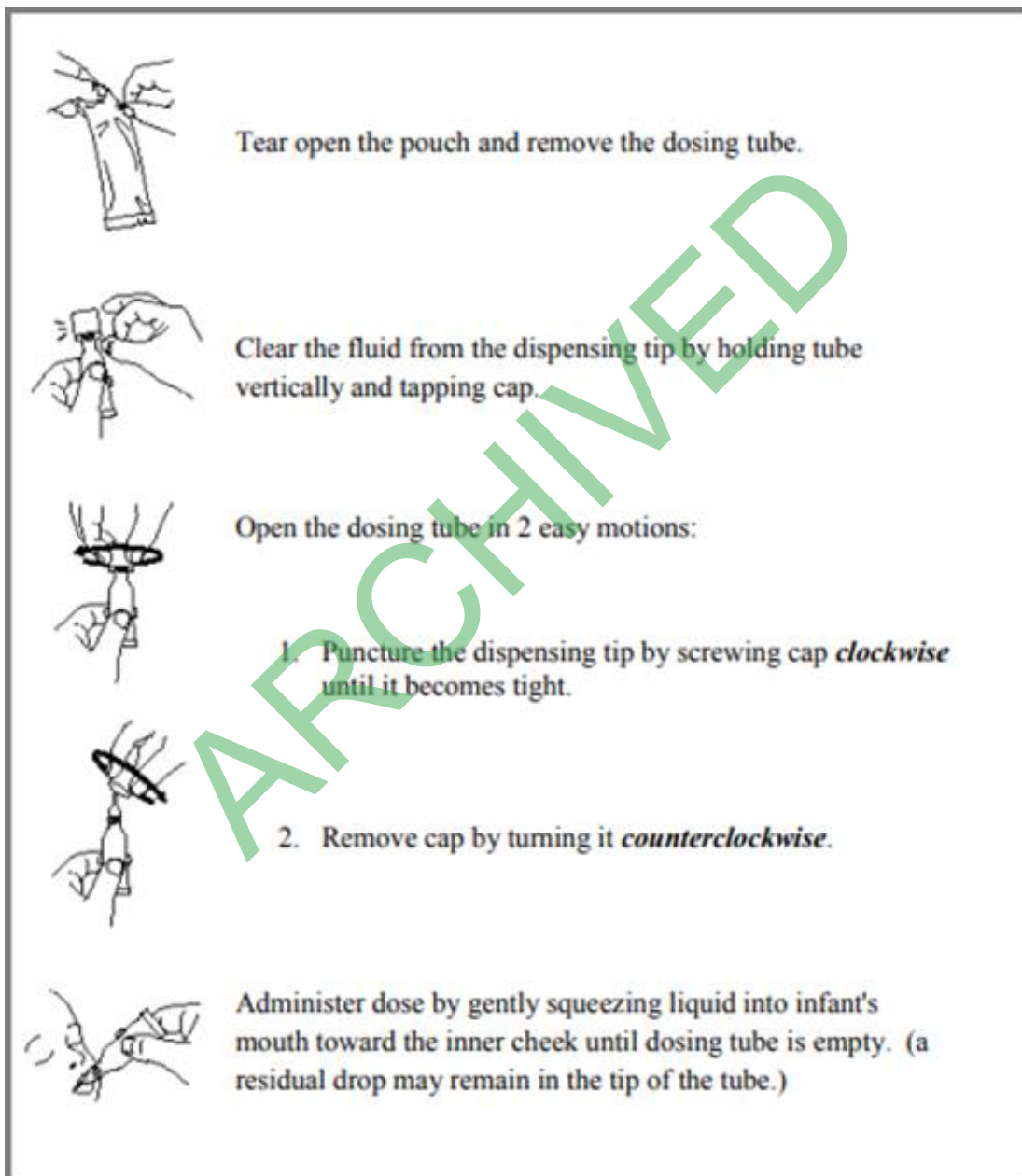
- RotaTeq® is an oral vaccine, supplied in individual dosing tubes allowing for direct oral administration⁷
- Each 2.0 mL dose is supplied in an individual squeezable plastic, latex-free dosing tube with a twist-off cap
- RotaTeq® is a clear liquid with a pale yellow colour and may have a pink tint
- Each individual dosing tube is contained in a pouch and is supplied in single dose boxes or 10 dose boxes. The dimensions of the boxes are as follows:
 - Single dose = 58.7 x 18.5 x 141.3 mm
 - 10 dose pack = 96.3 x 57.2 x 139.7 mm



⁷ MERCK Canada Inc. Product Monograph RotaTeq® [Internet]. Kirkland (QC): 2018. Available from <http://www.merck.ca/en/products/vaccines/>

12. How is RotaTeq® administered?

See graphic from RotaTeq® product monograph below⁷:



13. What if an infant ‘spits out’ or regurgitates a dose of vaccine?

A replacement dose of vaccine is not recommended if an incomplete dose is administered for any reason (e.g., infant spits or regurgitates the vaccine)⁷. Any remaining doses in the series should be completed according to the recommended schedule.

14. Does RotaTeq® have the same effect on injection pain as Rotarix® when given prior to injectable vaccines?

There is one published study which found that administration of Rotarix® prior to injectable vaccines provided a comparable analgesic effect to oral administration of sucrose solution, a known pain reduction method.⁸ Although a similar study with RotaTeq® has not been conducted, RotaTeq® contains sucrose at a concentration that would be expected to provide an analgesic effect. A study using both rotavirus vaccines which did not differentiate effect of one or the other, but did examine use prior to or following receipt of injectable vaccines demonstrated that injection-induced pain in infants was reduced when rotavirus vaccine was provided before, as opposed to after, injectable vaccines.⁹ Based on these findings, it is recommended immunization service providers administer oral rotavirus vaccine prior to injectable vaccines.

Vaccine safety, precautions and efficacy:

15. Does RotaTeq® have a comparable safety profile to Rotarix®?

Yes. Both vaccines were studied in large clinical trials with over 35,000 infants in each of vaccine and placebo groups. Observed adverse events following vaccine receipt in clinical trials were very similar with both vaccines, with the vaccines well tolerated.

In the RotaTeq® trials, fever, vomiting and diarrhea in the 7 days following dose receipt were reported at slightly higher rates in the vaccine group than placebo group. These rates are shown in Table 4 below⁷. Vomiting and diarrhea have not emerged as important adverse events following immunization in post-marketing surveillance of rotavirus vaccines.

⁸ Taddio A, Flanders D, Weinberg E, Lamba S, Vyas C, Illersich AF, Ipp M, McNair C. A randomized trial of rotavirus vaccine versus sucrose solution for vaccine injection pain. *Vaccine*. 2015 Jun 9;33(25):2939-43.

⁹ Yin HC, Shih WM, Lee HL, Yang HJ, Chen YL, Cheng SW, et al. Comparison of iatrogenic pain between rotavirus vaccination before and after vaccine injection in 2-month-old infants. *Human Vaccines and Immunotherapeutics*. 2017; 13(5): 1136-1140.

Table 4 – Adverse experiences (incidence $\geq 1\%$) observed in recipients of RotaTeq[®] at a frequency at least 0.3% greater than the frequency among placebo recipients

Adverse experiences	Vaccine (%)	Placebo (%)
<i>Gastrointestinal disorders:</i>		
Diarrhea	17.6	15.1
Vomiting	10.1	8.2
<i>General disorders and administration-site conditions:</i>		
Pyrexia	20.9	18.7

In these same trials, serious adverse events within 42 days of vaccine receipt occurred at the same or slightly lower rate (bronchiolitis 0.6% RotaTeq[®] vs. 0.7% placebo, gastroenteritis 0.2% RotaTeq[®] vs. 0.3% placebo) in vaccine recipients than in placebo recipients.

The adverse event of most concern with rotavirus vaccines has been intussusception. Intussusception is the most frequent cause of acute intestinal obstruction among young children and occurs without exposure to rotavirus vaccines. Most cases occur in infants with a peak from 4 to 7 months of age. Intussusception was observed at a rate of about 1 in 10,000 among recipients of RotaShield[®], a vaccine approved in the USA in the late 90s. This vaccine was withdrawn from the market, and subsequent clinical trials for Rotarix[®] and RotaTeq[®] were designed to detect a risk of this magnitude, and did not find an association.

Postmarketing studies were subsequently undertaken in several countries in order to detect a risk of lower magnitude. Not all studies have found an association of this event with vaccine receipt. Two recent systematic reviews and metaanalyses of these associations have been published. One, which assessed studies of Rotarix[®] in Mexico, Brazil, Australia and the US, and of RotaTeq[®] in Australia and the US, concluded that the overall relative risk of intussusception within 7 days of receipt of Rotarix[®] was 5.4 post-dose 1 and 1.8 post-dose 2.¹⁰ The overall estimate of relative risk of intussusception during the 7 days after vaccination with RotaTeq[®] was 5.5 post-dose 1 and 1.7 post-dose 2. These findings support a virtually identical risk of intussusception following either vaccine, with the risk largely associated with dose 1, and a lesser risk with dose 2.

The second metaanalysis reviewed a slightly different group of studies; studies from Brazil where OPV is co-administered were excluded.¹¹ Conclusions were similar to the Rosillon study; in addition the intussusception risk following dose 3 of RotaTeq[®] was examined and no increase in risk was found following this dose.¹¹ These authors provided the following advice for counseling parents who may be concerned about a relative risk around 5 for dose 1:

“When advising parents at the vaccination appointment, however, it is important to emphasize the size of the absolute increase in the individual risk of intussusception that is due to the RV vaccination. Without the RV vaccination, one child in 5208 will have an intussusception during

¹⁰ Rosillon D, Buyse H, Friedland LR, Ng SP, Velázquez FR, Breuer T. Risk of Intussusception After Rotavirus Vaccination: Meta-analysis of Postlicensure Studies. *Pediatr Infect Dis J.* 2015 Jul;34(7):763-8

¹¹ Koch J, Harder T, von Kries R, Wichmann O. Risk of Intussusception After Rotavirus Vaccination. *Dtsch Arztebl Int.* 2017 Apr 14;114(15):255-262.

the first 3 months of life, whereas with the RV vaccination the figure is one child in 4785. That is: So long as the vaccination is carried out at the right time, the absolute risk is increased only marginally.”

16. Are there any differences in contraindications to RotaTeq® than there were for Rotarix®?

No, there are no differences in contraindications between the two products. The pre-administration health assessment questions used to identify contraindications to Rotarix® vaccine are still relevant and required prior to the administration of RotaTeq® vaccine.

17. Can infants in NICU receive RotaTeq® vaccine?

Prematurity and/or hospitalization in the NICU are not contraindications to receipt of RotaTeq® vaccine. Refer to the hospital/NICU policies and recommendations with respect to immunization of hospitalized infants.

18. Is RotaTeq® as effective as Rotarix®, and what is the effectiveness of fewer than 3 doses of RotaTeq®?

The data from published studies of the first 10 years of postmarketing rotavirus vaccine effectiveness has recently been summarized.¹² In this systematic review, 48 studies met the inclusion criteria for review from 24 countries in the Americas, Africa, Asia, and Europe. These articles reported 31 RV1 (Rotarix®) vaccine effectiveness (VE) estimates and 27 RV5 (RotaTeq®) VE estimates. Vaccine effectiveness was examined by the following categories: full series for low versus high under 5 mortality countries; by completeness of vaccination series; by age; and by rotavirus disease severity. Relevant results are summarized below:

- VE of RV1 and RV5: RV5 provides very good protection against rotavirus. In studies from low mortality countries (such as Canada), RV1 median VE was 84% (range 19%–97%) from 13 studies; RV5 median VE was 90% (range 63%–100%) from 20 studies.
- VE by completeness of the series: For 15 studies from low through high mortality countries, point estimates of VE in full series recipients against rotavirus hospitalizations was higher than for partial series recipients. However, these differences were not statistically significant in any study. For RV1 in low mortality country studies, the median difference in VE point estimates for 2 doses vs 1 dose was –3%. For RV5 in five studies in such countries, the median difference in VE point estimates was 16% when comparing 3 doses versus 1 dose, and 7% when comparing 3 dose receipt to 2 dose. While the differences in vaccine

¹² Jonesteller CL, Burnett E, Yen C, Tate JE, Parashar UD. Effectiveness of Rotavirus Vaccination: A Systematic Review of the First Decade of Global Postlicensure Data, 2006-2016. Clin Infect Dis. 2017 Sep 1;65(5):840-850.

- effectiveness for partial series completion are small and one or two doses of RV5 provide good protection, completion of a full series is recommended for optimal protection.
- VE by rotavirus disease severity: The two vaccines appear to provide comparable protection against rotavirus disease severe enough to cause hospitalization and emergency room visits. Three of six studies from two low-mortality countries reported VE estimates for each of the two vaccines for these outcomes.
 - RV1 median VE estimate
 - against rotavirus hospitalizations: 88% (range 70%–95%)
 - against emergency department (ED) visits: 80% (range 78%–86%)
 - RV5 median VE estimate
 - against rotavirus hospitalizations: 94% (range 83%–100%)
 - against ED visits: 81% (range 74%–91%)

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