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Evaluation of Intussusception Following Pentavalent Rotavirus Vaccine (RotaTeq) Administration in Five Countries in Africa

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Abstract

Background: A low-level risk of intussusception following rotavirus vaccination has been observed in some settings and may vary by vaccine type. We examined the association between RotaTeq vaccination and intussusception in low-income settings in a pooled analysis from five African countries that introduced RotaTeq into their national immunization program.

Methods: Active surveillance was conducted in 20 sentinel sites to identify intussusception cases. A standard case report form was completed for each enrolled child and vaccination status was determined by review of the child's vaccination card or clinic record. The pseudo-likelihood adaptation of self-controlled case-series method was used to assess the association between RotaTeq administration and intussusception in the 1–7, 8–21, and 1–21 day periods after each vaccine dose in infants 28 to 245 days of age.

Results: Data from 318 infants with confirmed rotavirus vaccination status were analyzed. No clustering of cases occurred in any of the risk windows after any of the vaccine doses. Compared to the background risk of naturally occurring intussusception, no increased risk was observed after dose 1 in the 1–7 day (relative incidence=2.71, 95% confidence interval (CI)=0.47–8.03) or the 8–21 day window (relative incidence=0.77, 95%CI=0.0–2.69). Similarly, no increased risk of intussusception was observed in any risk window after dose 2 or dose 3.

Conclusions: RotaTeq vaccination was not associated with an increased risk of intussusception in this pooled analysis from five African countries. This finding mirrors what was reported in similar analyses with other rotavirus vaccines in low-income settings and highlights need for vaccine-specific and setting-specific risk monitoring.

Introduction

Intussusception, which occurs when one segment of the bowel folds into a distal segment causing a blockage, is the most common cause of bowel obstruction in young children. Incidence of intussusception is low in young infants <3 months of age, but peaks during the first year of life at 4–7 months of age.[1] The cause of most cases of intussusception is unknown. In the late 1990s, a live oral rotavirus vaccine (RotaShield) was associated with an increased risk of intussusception in the United States with an estimated 1 excess case of intussusception per 10,000 vaccinated infants.[2–4] This vaccine was subsequently withdrawn from the US market [5] and not introduced in any other country.

Prior to the availability of rotavirus vaccines, rotavirus was the most common cause of severe diarrhea in children <5 years of age globally. In 2006, two new live, oral attenuated rotavirus vaccines (Rotarix (GSK), a monovalent rotavirus vaccine based on an attenuated human rotavirus strain, and RotaTeq (Merck), a pentavalent rotavirus vaccine based on a human-bovine reassortant strain) were licensed for use.[6, 7] In clinical trials in high- and middle-income countries, these vaccines were highly efficacious in preventing severe rotavirus disease and no increased risk of intussusception was detected.[6, 7] In clinical trials in low-income countries, these vaccines were moderately efficacious and their association with intussusception was not evaluated.[8–10]

Following the introduction of rotavirus vaccine into national childhood immunization programs, the burden of rotavirus disease declined substantially in countries across the income spectrum.[11, 12] In post-licensure evaluations of Rotarix and RotaTeq in early-adopting middle- and high-income countries, a small increased risk of approximately 1–6 excess intussusception cases per 100,000 vaccinated infants was observed in some countries.[13–19] This increased risk was primarily reported in the 1–7 days after the first dose of vaccine but a small risk was seen after the second dose in some countries. In contrast, two post-licensure evaluations of Rotarix conducted in Africa, one in South Africa and one in 7 sub-Saharan African countries with pooled data for analysis, found no increased risk of intussusception after either dose of vaccine.[20, 21] Similarly, for another oral, live attenuated rotavirus vaccine (Rotavac, Bharat Biotech) that was pre-qualified by the World Health Organization in 2018, no increased risk of intussusception was observed following Rotavac administration in post-licensure evaluations in India.[22–24]

As rotavirus vaccines are based on different strains and the risk of intussusception may vary by vaccine type and socioeconomic status, generating additional data on rotavirus vaccination and the risk of intussusception for rotavirus vaccines in a variety of settings is important.[25] We report the first assessment of the association between RotaTeq vaccination and intussusception in low-income settings from a pooled analysis of data from five countries in sub-Saharan Africa that introduced RotaTeq into their national immunization program.

Methods

Intussusception surveillance was established in five countries (Burkina Faso, Cote d'Ivoire, The Gambia, Mali, and Rwanda) that introduced RotaTeq into their national immunization program. All countries used a common protocol to ensure comparability of data across countries and to enable pooling of data for analysis. Starting in October 2012, countries began surveillance on a rolling basis depending on when the country introduced RotaTeq vaccine. By February 2021, all five countries in the network had switched to using another rotavirus vaccine in their national immunization program. Thus, each country stopped contributing intussusception cases to this analysis when children who had received RotaTeq were no longer age-eligible to be included in this analysis.

Active surveillance for intussusception was conducted at large pediatric hospitals in the participating countries. Infants <12 months of age with intussusception that met the Brighton Collaboration criteria for level 1 of diagnostic certainty were enrolled. Level 1 of diagnostic certainty requires that the invagination be confirmed during surgery, by specific radiologic findings if reduced by enema, or during autopsy.[26] Demographic and limited clinical data for enrolled infants were collected by interview with the parent or guardian and by review of the medical record. Rotavirus vaccination status and dates of vaccination were obtained from the child's vaccination card, if available, or by review of records at the clinic where the child was vaccinated. For most cases, a photocopy or photograph of the card was retained for future reference and confirmation of vaccination status. RotaTeq was administered through the routine immunization program as a three dose series along with other recommended infant vaccines with doses administered at 6, 10, and 14 weeks, 8, 12, and 18 weeks, or

2, 3, and 4 months of age, depending on the country. If a child experienced an episode of intussusception before completing the vaccine series, the remaining doses of rotavirus vaccine were contraindicated. For infants enrolled before 8 months of age, recontact with the parents or guardians was attempted when the infant reached 8 months of age to determine if additional doses of rotavirus vaccine had been administered, if a second episode of intussusception occurred, and the vital status of the infant at that time.

This evaluation was determined to be public health non-research during the Centers for Disease Control and Prevention human subjects review, and the WHO Research Ethics Review Committee granted an exemption, noting that the procedures involved in the study are part of routine hospital-based surveillance.

Statistical Analysis

The self-controlled case-series method was used to assess the association between RotaTeq administration and intussusception. This method compares the incidence of intussusception in defined risk windows following vaccination (risk period) with the incidence in all other observational periods (unexposed period).[27] To allow for the contraindication of additional doses of rotavirus vaccine after an episode of intussusception, the pseudo-likelihood adaptation of this method was used.[28] Conditional Poisson regression was used to generate age-adjusted relative incidences for the 1–7, 8–21, and 1–21 day periods after each dose of RotaTeq with age adjustment by two week intervals. Bootstrapping with 1000 iterations was used to derive confidence intervals. Based on the timing of rotavirus vaccine administration in these countries, we restricted the analysis to children 28 to 245 days of age at time of onset of intussusception symptoms. Given that some symptoms of intussusception are non-specific and symptom onset date may not accurately reflect date of intussusception onset for some children, we conducted a sensitivity analysis where we used admission date as the date of intussusception onset. The unexposed period was defined as the period from 28 to 245 days but excluding the 1–21 days after each vaccine dose. Children who were not age-eligible to receive rotavirus vaccine (e.g. born prior to vaccine introduction) or who were age-eligible but not vaccinated were also included in the model to provide stability to the underlying age distribution of intussusception cases. Children who received a dose of a rotavirus vaccine other than RotaTeq were excluded.

We estimated that 300 cases of intussusception would provide 80% power to detect a relative risk of 2.5 or more within 1 to 7 days after the first dose of RV1, assuming 90% vaccine coverage and a type 1 alpha level of 0.05. Analyses were performed using Stata software, version 14 (StataCorp) and SAS software, version 9.4 (SAS Institute).

Results

A total of 451 children <12 months of age with intussusception meeting the Brighton Collaboration criteria for level 1 of diagnostic certainty were enrolled from 20 sentinel hospitals in the five participating countries. (Table 1). Of these, 112 (25%) children were excluded because they were <28 days or >245 days at intussusception symptom onset and an additional 21 (5%) of children were excluded due lack of confirmed vaccination status. The majority (n=17; 81%) of children without confirmed vaccination status were from Mali

but were otherwise demographically similar to children with confirmed vaccination status. The remaining 318 (71%) had intussusception symptom onset between 28 and 245 days of age and had their vaccination status confirmed by vaccine card or clinic registry and were included in the analysis. Rwanda was the first country to introduce RotaTeq and began intussusception surveillance in October 2012. Mali and Burkina Faso conducted surveillance for longest period of time (~6 years) and enrolled the greatest number of cases (187 (41%) and 137 (30%), respectively).

The median age of infants included in the analysis was 25 (interquartile range (IQR): 20–29) weeks with only 20 (6%) <15 weeks of age. (Figure 1). A majority (207/318; 65%) were male and only 2% (6/307) had never received any breastmilk. Most (270/316; 85%) were first admitted to another facility and then transferred to the surveillance hospital with a median of 2 (IQR: 1–3) days between admission to the first facility and admission to the surveillance facility. The median time from symptom onset until admission at the surveillance facility was 3 (IQR: 1–5) days. Non-surgical treatment was rare with only 2% (7/314) of intussusception cases reduced by enema. Of the 307 children treated surgically, 130 (42%) required resection. Overall, 16% (50/311) infants died.

Most infants (296/318; 93%) had received at least 1 dose of RotaTeq with 67% (214/318) fully vaccinated with 3 doses, 17% (53/318) receiving 2 doses, and 9% (29/318) having received 1 dose at time of intussusception symptom onset. Only 22 (7%) children were unvaccinated. The median age at dose 1 was 7 (IQR: 6–9) weeks, 13 (IQR: 11–14) weeks at dose 2, and 17 (IQR: 15–19) weeks at dose 3. Despite being contraindicated, 15 children received at least one dose of RotaTeq after intussusception. The families of 84% (225/268) of surviving infants were successfully contacted when the infant reached 8 months of age; 1% (2/152) of these children experienced a second episode of intussusception and 2% (4/197) died after discharge but before 8 months of age.

No clustering of cases occurred in any of the risk windows (1–7 days, 8–21 days, 1–21 days) after any of the doses of vaccine. After dose 1, 4 cases occurred in the 1–7 day window and 3 cases in the 8–21 day window. No cases occurred in the 1–7 day window after dose 2 and 11 cases occurred in the 8–21 day window. After dose 3, 7 cases occurred in the 1–7 day window and 14 in the 8–21 day window. Compared to the background risk, there was no increased risk of intussusception after dose 1 in the 1–7 day window (relative incidence=2.71, 95% confidence interval (CI)=0.47–8.03) or the 8–21 day window (relative incidence=0.77, 95% CI=0.0–2.69). (Table 2). Similarly, no increased risk of intussusception was observed in any of the risk windows after dose 2 or dose 3. Comparable results were obtained in the sensitivity analysis when admission date rather than symptom onset date was used as the date of intussusception onset.

Discussion

RotaTeq vaccination was not associated with an increased risk of intussusception in this pooled analysis of data from five countries in sub-Saharan Africa. This finding of no increased risk of intussusception following RotaTeq administration is similar to what was reported in similar analyses with other rotavirus vaccines, Rotarix and Rotavac, in

low-income settings. No increased risk of intussusception was observed following Rotarix administration in South Africa and in a pooled analysis from 7 sub-Saharan African countries or following Rotavac administration in India.[20–22] The findings are in contrast with analyses from several high- and middle-income countries where a small increased risk of intussusception was observed mainly in the 1–7 days following administration of Rotarix or RotaTeq although a few countries have also observed a small increased risk after dose 2.[13–19]

The reasons for this differential risk between rotavirus vaccination and intussusception by country are likely complex and multifaceted. First, in high burden settings, rotavirus vaccines are often given on an earlier schedule with doses given at 6, 10, and 14 weeks, 8, 10, and 14 weeks, or 2, 3, and 4 months compared to the 2, 4, and 6 month schedule typically used in low burden settings. Natural incidence of intussusception is lower in the first 2 months of life[1] so the intestines of children who receive their first dose of vaccine in this period may be less likely to intussuscept than intestines of children who are vaccinated at an older age. Second, live, oral rotavirus vaccines have been shown to be less efficacious and vaccinated infants shed less vaccine virus, a potential marker of vaccine replication in the gut, in high burden compared with low burden countries.[9, 29] Thus, live, oral rotavirus vaccines may also be less likely to trigger intussusception in children in high burden settings. Third, oral rotavirus vaccines are often co-administered with oral polio vaccines in high burden settings. The first dose of oral polio vaccine is associated with the highest replication of vaccine poliovirus and has been shown to decrease the immunogenicity of the first dose of rotavirus vaccine when co-administered.[30, 31] In an evaluation of intussusception following Rotarix vaccination in Mexico and Brazil, an increased risk of intussusception was seen in the 1–7 days following dose 1 in Mexico, where oral polio vaccine was not co-administered with the first rotavirus vaccine dose; however, no increased risk was observed during the 1–7 days following dose 1 in Brazil, where oral polio vaccine was co-administered with the first rotavirus vaccine dose.[18] Co-administration of oral polio vaccine was hypothesized as a potential reason why no increased risk of intussusception was seen after dose 1 administration in Brazil. The potential impact of the planned global cessation of oral polio vaccine use in favor of inactivated polio vaccine on oral rotavirus vaccine effectiveness in settings where both oral vaccines are given concurrently is unknown. Finally, there may be other differences between low and high burden rotavirus settings such as differences in breastfeeding practices, diet, microbiome, and maternal antibody levels, that may influence the risk of intussusception following rotavirus vaccination.

Although not an objective of this investigation, treatment of intussusception cases, regardless of cause, could be improved in these countries. Almost all cases were treated surgically and mortality was high. Children were delayed in seeking care and capacity to treat the child for intussusception was often not available at the initial facility where the child sought care resulting in further delays while the child was transferred to another facility for treatment. Furthermore, although no increased risk in intussusception was observed following rotavirus vaccination, 15 children received additional doses of rotavirus vaccine after experiencing intussusception. These doses were contraindicated and additional training on the rotavirus vaccine administration guidelines may be warranted in these countries.

This evaluation has several limitations. First, all countries included in this analysis switched from RotaTeq to another rotavirus vaccine. In some countries, it was difficult to determine from the vaccine card which rotavirus vaccine (RotaTeq versus another rotavirus vaccine) was administered to the child. If the vaccine manufacturer was unavailable from the vaccine documentation, we used the date of birth and the date of rotavirus vaccination to determine if the child was vaccinated during a time period when only RotaTeq was available or during a period after which the vaccine switch was initiated. Vaccine type may have been misclassified for some children and thus some children included in this analysis may have received a rotavirus vaccine other than RotaTeq. However, the number of children enrolled around the time of rotavirus vaccine switch is small compared to the overall number of children enrolled. Similarly, we were unable to confirm that vaccination status for a small number of children (6%) enrolled in surveillance due to missing documentation and these children were excluded from the analysis. Second, we used date of symptom onset to determine when the intussusception occurred. Some symptoms of intussusception are non-specific and the onset date may be miscalculated for some children. However, we conducted a sensitivity analysis where we used admission date as the date of intussusception onset and obtained similar results. Finally, given the delays in seeking care and receiving appropriate treatment, some children may have died prior to presenting for care or prior to confirmation of their intussusception diagnosis. If children missed by surveillance were younger than the enrolled children then we may have selectively missed children who were recently vaccinated. However, the age distribution observed in the enrolled children was similar to that seen in other settings with good access to care and treatment and rates of intussusception have been shown to be low during the first few months of life when rotavirus vaccine is administered.[1] Taken together, these observations suggest that the low number of cases enrolled in the first few months of life is likely reflective of the underlying incidence of intussusception by age rather than a systematic exclusion of young infants.

RotaTeq is no longer used in Gavi-eligible countries as the manufacturer withdrew from the Gavi market. All five countries in this analysis have switched to rotavirus vaccines produced by other manufacturers. However, these findings highlight need for vaccine-specific and setting-specific risk monitoring. As countries switch or introduce other rotavirus vaccines, monitoring risk of intussusception in a few representative countries will be important.

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Conflicts of interest:

NA is currently employed by Pfizer and receives travel support from Pfizer to travel to meetings and conferences and has stock/stock options. EL has received consulting fees from the World Health Organization, payment and honoraria from GSK and Novartis for activities unrelated to rotavirus vaccines, and has participated in the Global Influenza Advisory Board for Sanofi Pasteur and Moderna. All other authors report no conflicts of interest.

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Key Points

The risk of intussusception following rotavirus vaccination may vary by vaccine type and socioeconomic status. In a pooled analysis of data from 5 countries in Africa, RotaTeq vaccination was not associated with an increased risk of intussusception.

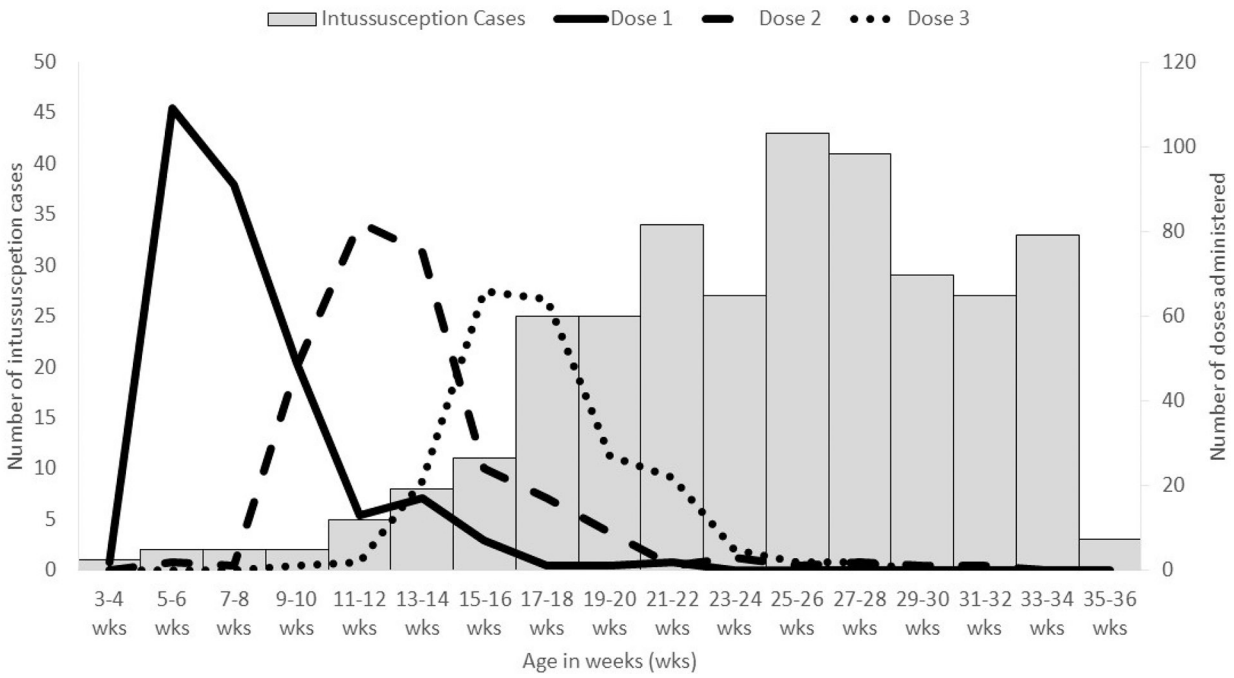

Figure 1.

Age at Intussusception Onset and Age at RotaTeq Vaccination by Dose, October 2012-November 2021

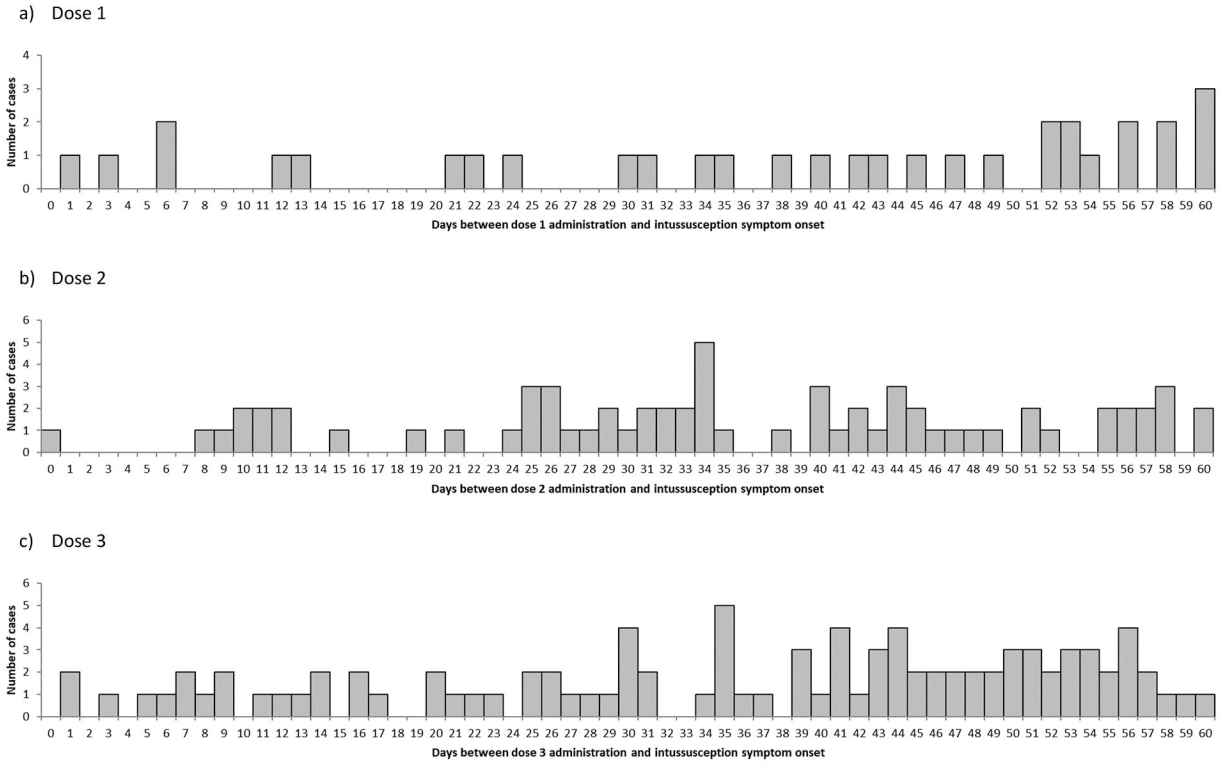

Figure 2.

Number of Intussusception Cases by Day* after Administration of a) Dose 1, b) Dose 2, and c) Dose 3 of RotaTeq, October 2012-November 2021

*Note: An additional 262 cases occurred >60 days after dose 1, an additional 195 cases occurred >60 days after dose 2, and an additional 108 cases occurred >60 days after dose 3

Table 1.

RotaTeq Vaccine Introduction Dates, Enrollment Dates, and Number of Surveillance Sites and Enrolled Children with Intussusception, by Country, October 2012-November 2021

Country	Month and Year of RotaTeq Introduction	Vaccine Schedule	Enrollment Period	Number of Sentinel Sites	Number (%) of children <12 months of age with intussusception	Number (%) of children 28–245 days of age with intussusception and confirmed vaccination status
Burkina Faso[¶]	October 2013	8, 12, and 16 weeks	January 2015 – July 2020	2	137 (30%)	96 (30%)
Cote d'Ivoire[○]	March 2017	6, 10, and 14 weeks	April 2017 – September 2019	7	48 (11%)	36 (11%)
Gambia[†]	August 2013	2, 3, and 4 months	May 2015 – February 2016	1	3 (1%)	2 (1%)
Mali[§]	January 2014	6, 10, and 14 weeks	May 2015 – November 2021	6	187 (41%)	131 (41%)
Rwanda[≠]	May 2012	6, 10, and 14 weeks	October 2012 – December 2017	4	76 (17%)	53 (17%)
Total	--		--	20	451 (100%)	318 (100%)

[¶]Burkina Faso switched to using Rotasiil in 2020. Children born on 1 March 2020 or later were excluded from this analysis if rotavirus vaccine type was unknown.

[○]Cote d'Ivoire switched to using Rotarix in their national immunization program in May 2019 and stopped enrolling intussusception cases for this network.

[†]Gambia switched to using Rotarix in their national immunization program in February 2017 and stopped enrolling intussusception cases for this network.

[§]Mali began switching to Rotasiil in February 2021. Children born on 1 February 2021 or later were excluded from this analysis if rotavirus vaccine type was unknown.

[≠]Rwanda switched to using Rotarix in their national immunization program in April 2017 and only enrolled children with intussusception who had confirmed receipt of RotaTeq after that date.

Table 2.

Relative Incidence of Intussusception in the Risk Periods after Each Dose of RotaTeq, October 2012-November 2021

Dose and Risk Period	Number of Cases	Relative Incidence (95% CI)
Dose 1		
Days 1–7	4	2.71 (0.47, 8.03)
Days 8–21	3	0.77 (0.0, 2.69)
Days 1–21	7	1.16 (0.35, 3.11)
Dose 2		
Days 1–7	0	--
Days 8–21	11	0.83 (0.38, 1.50)
Days 1–21	11	0.56 (0.25, 1.05)
Dose 3		
Days 1–7	7	0.72 (0.25, 1.47)
Days 8–21	14	0.61 (0.31, 1.05)
Days 1–21	21	0.63 (0.37, 1.02)