HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2024 March 12.

Published in final edited form as:

Vaccine. 2023 November 22; 41(48): 7220–7225. doi:10.1016/j.vaccine.2023.10.042.

Intussusception risk following oral monovalent rotavirus vaccination in 3 Asian countries: a self-control case series evaluation

Eleanor Burnett[1], **Atif Riaz**[2], **Palwasha Anwari**[3], **Theingi Win Myat**[4], **Tyler P. Chavers**[1], **Nabila Talat**[5], **Najibullah Safi**[6], **Nway Nway Thinn Aung**[7], **Margaret M. Cortese**[1], **Shazia Sultana**[2], **Akmal Samsor**[6], **Hlaing Myat Thu**[4], **Nasir Saleem Saddal**[8], **Sohrab Safi**[6], **Htin Lin**[4], **Saqib Hamid Qazi**[2], **Helah Safi**[6], **Asad Ali**[2], **Umesh D. Parashar**[1], **Jacqueline E. Tate**[1]

[1]Division of Viral Diseases, NCIRD, CDC, Atlanta, USA

[2]Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan

[3]London School of Hygiene and Tropical Medicine, London, UK

[4]Department of Medical Research, Ministry of Health and Sports, Yangon, Myanmar

[5]Pediatric Surgery unit, University of Child Health Sciences and Children Hospital, Lahore, Pakistan

[6]JS Consultancy, Kabul, Afghanistan

[7]Yangon Children's Hospital, Ministry of Health and Sports, Myanmar

[8]Deparment of Surgery, National Institute of Child Health, Karachi, Pakistan

Abstract

Rotavirus vaccines have substantially decreased rotavirus hospitalizations in countries where they have been implemented. In some high- and middle-income countries, a low-level of increased risk of intussusception, a type of acute bowel obstruction, has been detected following rotavirus vaccination. However, no increased risk of intussusception was found in India, South Africa, or a network of 7 other African countries. We assessed the association between a 2-dose monovalent rotavirus vaccine (Rotarix) and intussusception in 3 early-adopter low-income Asian countries -- Afghanistan, Myanmar, and Pakistan. Children <12 months of age admitted to a sentinel surveillance hospital with Brighton level 1 intussusception were eligible for enrollment. We collected information about each child's vaccination status and used the self-controlled case series method to calculate the relative incidence of intussusception 1–7 days, 8–21 days, and 1–21 days following each dose of vaccine and derived confidence intervals with bootstrapping. Of the 585 children meeting the analytic criteria, the median age at intussusception symptom onset was 24 weeks (IQR: 19–29). Overall, 494 (84%) children received the first Rotarix dose and 398 (68%)

Correspondence and reprints: Eleanor Burnett, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS 24-5, Atlanta, GA 30329, wwg7@cdc.gov.

Conflicts of interest: The authors indicate that they have no conflicts of interest relevant to this article to disclose.

Disclaimer: The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

received the second dose. There was no increased intussusception risk during any of the risk periods following the first (1–7 days: 1.01 (95%CI: 0.39, 2.60); 8–21 days: 1.37 (95%CI: 0.81, 2.32); 1–21 days: 1.28 (95%CI: 0.78, 2.11)) or second (1–7 days: 0.81 (95%CI: 0.42, 1.54); 8–21 days: 0.77 (95%CI: 0.53, 1.16); 1–21 days: 0.78 (95%CI: 0.53, 1.16)) rotavirus vaccine dose. Our findings are consistent with other data showing no increased intussusception risk with rotavirus vaccination in low-income countries and add to the growing body of evidence demonstrating safety of rotavirus vaccines.

Keywords

intussusception; vaccination; rotavirus vaccine

Introduction

Intussusception, the invagination of a distal bowel segment in a proximal segment, is the most common type of acute bowel obstruction among infants; left untreated, it can be fatal. For reasons that remain unclear, rates of naturally occurring intussusception vary considerably between geographic regions and countries, ranging from 16 per 100,000 infants in Bangladesh to >300 per 100,000 infants in Vietnam (1, 2). The rate of intussusception increases in early infancy and typically peaks around 6 months of age (2). In most cases, the cause of intussusception is unknown. Naturally-occurring intussusception has been associated with some infectious agents, notably adenovirus type C, but not wild-type rotavirus (3). RotaShield, a live, oral rotavirus vaccine first licensed in 1998, was found to cause 1–2 excess cases of intussusception per 10,000 vaccinated infants in the first 1 to 2 weeks after vaccination. Because of this risk, RotaShield was subsequently withdrawn from the market (4). Since then, four live, oral multinational vaccines (Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium), Rotasiil (Serum Institute of India, Pune, India), RotaTeq (Merck, West Point, PA, USA), Rotavac (Bharat Biotech International Ltd., Hyderabad, India)) have been licensed globally for infants. Post-licensure evaluations found an association with intussusception with Rotarix and RotaTeq in 6 high-and middle-income countries (5, 6) of about 1–5 excess cases per 100,000 children vaccinated (7, 8). However, no association was found between Rotarix and intussusception in South Africa nor in in a network of 7 other African countries, and no association between Rotavac and intussusception in India (5, 9, 10).

Globally, rotavirus vaccines have been shown to reduce severe rotavirus disease by around 40%, though they somewhat less effective in low- and middle-income countries than in high-income countries (11, 12, 13). There are several possible explanations for lower rotavirus vaccine performance in low- and middle-income countries, including a higher prevalence of malnutrition and concurrent administration of rotavirus vaccine with oral polio vaccine (OPV) (14, 15, 16, 17, 18). In light of the substantial reductions in rotavirus disease where the vaccines have been introduced and evidence showing any risk of intussusception is low, the World Health Organization (WHO) recommended all countries introduce a rotavirus vaccine into their routine national infant vaccination program in 2009 (19, 20). WHO also recommends countries monitor intussusception after rotavirus vaccine implementation (19).

Though >120 countries have introduced rotavirus vaccines, countries in Asia have been slower to add rotavirus vaccines to their national routine immunization programs than other regions (21). Given the regional differences in intussusception rates and epidemiology, generating post-licensure data from Asia evaluating intussusception is important to provide local decisionmakers additional information while considering rotavirus vaccine introduction. In this analysis, we pooled data from Afghanistan, Myanmar, and Pakistan to assess for any association between a 2-dose, monovalent human rotavirus vaccine (Rotarix) and intussusception.

Methods

Surveillance

Rotarix was introduced nationwide in 2018 in Afghanistan and Pakistan, and 2020 in Myanmar (Table 1). The 2-dose series was recommended for administration at 6 and 10 weeks of age in Afghanistan and Pakistan and 2 and 4 months of age in Myanmar, concurrently with bivalent oral polio vaccine (bOPV) and other routine childhood vaccines. Surveillance periods and the number of sentinel hospitals in each country are presented in Table 1.

Children <12 months of age were eligible to be enrolled in this evaluation if they were admitted to a sentinel surveillance hospital with intussusception that met the Brighton level 1 criteria (22). Briefly, the Brighton level 1 criteria require that the intussusception be confirmed during surgery, by radiologic findings with reduction by enema, or by autopsy. A standardized questionnaire was used to document each child's vaccination status, hospitalization, management, and outcome. Additionally, to ensure methodological assumptions regarding survival were met, children <8 months old at the time of enrollment were recontacted at 8 months of age to determine if the child was living, if they had had any subsequent intussusception episodes, and if any rotavirus vaccine doses administered after the initial intussusception episode. The final analysis was limited to children with written documentation of their rotavirus vaccine status and who were 28–245 days old when their intussusception symptoms began, because almost all of the children who had received rotavirus vaccine were vaccinated in this age range.

Data analysis

For this data analysis, we used the pseudolikelihood self-controlled case series (SCCS) method (23). Using the SCCS method, each child acts as their own control during periods outside of the a priori defined risk windows following an exposure, in this case rotavirus vaccination. The pseudolikelihood method allows for the contraindication of rotavirus vaccine after an episode of intussusception. We calculated the relative incidence of intussusception during three time periods following vaccination (1–7 days, 8–21 days, and 1–21 days) for each of the two Rotarix doses. We also accounted for the changing baseline underlying rate of intussusception with age by calculating risk in 2-week age bands. We estimated 574 cases would be needed to provide 80% power detect a relative incidence of 2.5 during the first 1–7 days following the first dose, at the 0.05 significance level (24).

Confidence intervals were derived by bootstrapping with 1000 iterations. All descriptive statistics are presented as percentages or medians with interquartile range (IQR).

In addition to the overall pooled analysis, we performed a sub analysis of cases from Afghanistan and Pakistan combined after excluding the Myanmar cases as there were several differences between these countries. First, the recommended ages for rotavirus vaccine in Afghanistan and Pakistan are slightly younger than Myanmar (Table 1). Second, Afghanistan and Pakistan are the last two countries in the world that have not eliminated wild polio virus and thus their OPV programs may differ from those of other countries (25). Finally, the cases from Myanmar were collected during only a 10-month period at the beginning of the COVID-19 pandemic, which could introduce bias as the number of enrolled cases was small, there was not adequate time for many in the vaccinated cohort to age to 8 months, and there may have been pandemic-related delays and interruptions to routine vaccination similar to those reported by other countries (26). Enrollment in Afghanistan and Pakistan also continued during the COVID-19 pandemic; however, the full enrollment period started about 2 years earlier in Afghanistan and Pakistan and continued until 2022.

All data analyses were performed using SAS version 9.4 and R version 4.1.2. The SCCS analysis was completed using the SCCS package in R (27). This investigation was reviewed by CDC and conducted consistent with applicable federal law and CDC policy.

Results

In total, 894 children <12 months old were enrolled, of which 585 met the age and vaccination documentation criteria for inclusion in the analysis (Table 1). Of the 585 meeting the analytic criteria, the median age was 24 weeks (IQR: 19–29) at the time of symptom onset (Figure 1) and 351 (60%) were male (Supplementary table 1). Nearly half (n=283, 48%) were transferred from another facility to the surveillance hospital and the interval between the first admission facility and admission to the surveillance hospital was a median 2 days (IQR: 1–3). In all three countries, almost all children (n=574, 98%) had their intussusception managed by surgery, though this ranged from 83% in Myanmar to 100% in Pakistan. Twenty-seven children (5%) died. Characteristics of age eligible children excluded for insufficient vaccination record documentation are in Supplementary Table 1. Of the 445 (76%) children included in this analysis who had documented follow up at 8 months old, 3 (1%) had a second intussusception episode, 12 (3%) had died at some point after discharge from the hospital, and 29 (7%) received ≥1 rotavirus vaccine dose after their intussusception.

Overall, 494 (84%) of children meeting the analysis criteria received the first dose of rotavirus vaccine and 398 (68%) received the second dose before their intussusception (Figure 1). Rotavirus vaccination coverage was similar across all 3 countries. Corresponding with the 2 different recommended vaccination schedules in these 3 countries, age at rotavirus vaccination has an extended right tail for both doses (Figure 1). The median age of administration of the first dose was 7 weeks (IQR: 6–9) in Afghanistan and Pakistan and 10.5 weeks (IQR: 8–14.5) in Myanmar. Across all 3 countries, 21 children (4%) who received the first dose were vaccinated after 15 weeks of age. The median age of administration of the second dose was 13 weeks (IQR: 11–16) in Afghanistan and Pakistan

and 18 weeks (IQR: 16–21) in Myanmar. Across all 3 countries, 17 children (4%) who received the second dose were vaccinated after 24 weeks of age. Concurrent administration of bOPV among rotavirus-vaccinated children was also somewhat higher for both doses in Afghanistan and Pakistan (dose 1: n=452, 97%; dose 2: n=363, 97%) than in Myanmar (dose 1: n=25, 89%; dose 2: n=18, 82%).

No clustering of cases in the 1 or 3 weeks following either dose of rotavirus vaccine was apparent (Figure 2) and the risk following vaccination with either dose was not higher than the background risk. Following the first dose of rotavirus vaccine, intussusception symptoms began for 24 children in the first 1–21 days, a relative incidence of 1.28 (95%CI: 0.78, 2.11) (Table 2). Intussusception symptoms began for 5 children in the first 1–7 days after the first dose, a relative incidence of 1.01 (95%CI: 0.39, 2.60), and symptoms began for 19 children 8–21 after the first dose, a relative incidence of 1.37 (95%CI: 0.81, 2.32). Following the second dose of rotavirus vaccine, intussusception symptoms began for 34 children in the first 1–21 days, a relative incidence of 0.78 (95%CI: 0.53, 1.16). Intussusception symptoms began for 11 children in the first 1–7 days after the second dose, a relative incidence of 0.81 (95%CI: 0.42, 1.54), and symptoms began for 23 children 8–21 after the second dose, a relative incidence of 0.77 (95%CI: 0.49, 1.21).

In the sub-analysis of 550 cases enrolled in Afghanistan and Pakistan, there was no increased of intussusception risk above the baseline during any of the risk periods following the first (1–7 days: 1.08 (0.42, 2.80); 8–21 days: 1.04 (0.57, 1.88); 1–21 days: 0.97 (0.56, 1.69)) or second dose (1–7 days: 0.76 (0.38, 1.51); 8–21 days: 0.64 (0.39, 1.05); 1–21 days: 0.63 (0.42, 0.97)).

Discussion

There was no increased risk of intussusception following rotavirus vaccination with Rotarix in this evaluation using data from 3 Asian countries, Afghanistan, Pakistan, and Myanmar. This is the 4th evaluation of oral rotavirus vaccine and intussusception (the third for Rotarix) in low-income countries which did not show an increase over the baseline risk. Conversely, other reports found an elevated risk of intussusception following rotavirus vaccine in 6 high- and middle-income countries, primarily after the first dose. Of all the post-licensure evaluations of intussusception and rotavirus vaccines, there have been 2 others in Asian countries. An elevated risk 8 times the baseline was found in Singapore after the first dose of Rotarix, the same rotavirus vaccine used in this evaluation (28). No increased risk was found following vaccination with Rotavac vaccine in India (5). Similar to the variation in rotavirus vaccine effectiveness, country income level seems to be more important for differences in intussusception risk following rotavirus vaccination than geographic region or vaccine brand (12, 17). This also suggests lower vaccine performance and lower intussusception risk may be due to the same mechanism that potentially results in decreased replication of the rotavirus vaccine strains in the gastrointestinal tract (5, 10). While we did not assess for other factors attributed to lower rotavirus vaccine performance such as malnutrition, bOPV was administered with rotavirus vaccine in nearly all of the children in this evaluation. These results should be reassuring to ministries of health and local healthcare providers that

rotavirus vaccines are safe while substantially reducing hospitalizations and deaths due to rotavirus disease.

Because underlying rates of intussusception increase with age during the first 6 months of life, it has been hypothesized that rotavirus doses administered at very young ages may be less likely to trigger an intussusception. This rationale guided the initial design of the clinical trials and manufacturer recommended upper age limits of administration (19, 29). However, none of the previously published studies have stratified analyses by age of vaccination to assess the contribution of age at vaccination to risk. For example, there was an increased risk reported from Singapore and nearly all vaccinated cases in their study received the vaccine after 12 weeks of age, following the national schedule (28). In the pooled analysis of 7 African countries and in South Africa, vaccine doses were very timely, and, in both evaluations, there was little overlap between the ages first dose of vaccine and ages of intussusception symptom onset (9, 10). Like the African evaluations, the ages of vaccination with both doses were mostly younger than intussusception symptom onset in Afghanistan and Pakistan, where the recommended ages were 6 and 10 weeks and vaccination was timely. However, the second dose of Rotarix in South Africa is recommended at 14 weeks of age and many doses in the evaluation from India were delayed (5, 9). Similarly, in Myanmar, vaccination was delayed, likely impacted by the COVID-19 pandemic's disruptions to routine vaccination delivery systems (26). The majority of second doses in Myanmar were administered at the ages of peak intussusception symptom onset. Across all three countries, a small percentage of children were vaccinated after the manufacturer's recommended maximum ages of administration of 15 weeks of age for the first dose and 24 weeks of age for the 2-dose series but were still within the countries' recommended ages for vaccination. There was no increased risk of intussusception during any of the risk windows following either dose in the pooled analysis or the combined Afghanistan and Pakistan analysis. The number of cases enrolled in Myanmar was insufficient to assess separately. While the goal of timely vaccination is important to protect children as young as possible from the most serious outcomes of rotavirus disease, our findings reinforce the safety of vaccinating all infants with rotavirus vaccine.

The results presented in this evaluation should be considered alongside a few limitations. The previously published epidemiology of intussusception cases in Myanmar and Pakistan is like that of other countries (2, 30, 31), but the actual rates of intussusception among children <1 year old are unknown in these 3 countries. In other Asian countries, there is a wide range of underlying baseline intussusception rates and the relationship between underlying intussusception rates and vaccine-induced intussusception is unknown. However, even extreme underlying rates should not impact true vaccine-induced intussusception risk (1). Second, because intussusception is rare and case ascertainment is challenging, provider awareness of intussusception and availability of specialized equipment for diagnosis and management is a factor in properly identifying cases. Between and within Afghanistan, Pakistan, and Myanmar, there is considerable variation in healthcare systems and accessibility, as well as the availability of pediatric surgeons and enema reduction, and it is possible not all intussusception cases were identified. Since cases were enrolled independent of their vaccination status, missed cases should not introduce bias. Finally,

this evaluation took place in 3 distinct settings during a unique time period and thus the results may not be generalizable. For example, in addition to the impact of endemic polio in two countries and the COVID-19 pandemic that were considered in our sub analyses, Afghanistan experienced an unexpected political power transition in 2021, disrupting access to the healthcare system. While our results may have limits to their generalizability, they are consistent with findings from other low-income countries showing no increased risk of intussusception associated with rotavirus vaccine.

Findings from this evaluation in Afghanistan, Pakistan, and Myanmar add to the growing body of evidence showing safety of rotavirus vaccines. While this was the 1st such post-introduction assessment of Rotarix in low-income countries in Asia, it is the 4th evaluation with any rotavirus vaccine and the 3rd with Rotarix in low-income countries that found no increased risk of intussusception following rotavirus vaccine. This consistency in the safety of rotavirus vaccination across multiple low- and middle-income countries should be a reassuring consideration for healthcare providers and decisionmakers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Clark AD, Hasso-Agopsowicz M, Kraus MW, Stockdale LK, Sanderson CFB, Parashar UD, et al. Update on the global epidemiology of intussusception: a systematic review of incidence rates, age distributions and case-fatality ratios among children aged <5 years, before the introduction of rotavirus vaccination. Int J Epidemiol. 2019;48(4):1316–26. [PubMed: 30879038]
2. Jiang J, Jiang B, Parashar U, Nguyen T, Bines J, Patel MM. Childhood intussusception: a literature review. PLoS One. 2013;8(7):e68482. [PubMed: 23894308]
3. Burnett E, Parashar UD, Tate JE. Associations of Intussusception With Adenovirus, Rotavirus, and Other Pathogens: A Review of the Literature. Pediatr Infect Dis J. 2020;39(12):1127–30. [PubMed: 33060518]
4. Patel MM, Haber P, Baggs J, Zuber P, Bines JE, Parashar UD. Intussusception and rotavirus vaccination: a review of the available evidence. Expert Rev Vaccines. 2009;8(11):1555–64. [PubMed: 19863248]
5. Reddy SN, Nair NP, Tate JE, Thiyagarajan V, Giri S, Praharaj I, et al. Intussusception after Rotavirus Vaccine Introduction in India. N Engl J Med. 2020;383(20):1932–40. [PubMed: 33176083]
6. Martini Rodrigues CC, Fernandes EG, Dos Santos PP, Eguti RY, Pedroso-de-Lima AC, da Silva GT, et al. Impact of polio vaccines (oral polio vaccine - OPV or inactivated polio vaccine - IPV) on rotavirus vaccine-associated intussusception. Hum Vaccin Immunother. 2022;18(5):2063594. [PubMed: 35439100]
7. Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med. 2011;364(24):2283–92. [PubMed: 21675888]
8. Stowe J, Andrews N, Ladhani S, Miller E. The risk of intussusception following monovalent rotavirus vaccination in England: A self-controlled case-series evaluation Ref. No: JVAC-D-16–01124. Vaccine. 2016;34(50):6115. [PubMed: 27899199]
9. Groome MJ, Tate JE, Arnold M, Chitnis M, Cox S, de Vos C, et al. Evaluation of Intussusception After Oral Monovalent Rotavirus Vaccination in South Africa. Clin Infect Dis. 2020;70(8):1606–12. [PubMed: 31125061]

10. Tate JE, Mwenda JM, Armah G, Jani B, Omore R, Ademe A, et al. Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa. N Engl J Med. 2018;378(16):1521–8. [PubMed: 29669224]
11. Aliabadi N, Antoni S, Mwenda JM, Weldegebriel G, Biey JNM, Cheikh D, et al. Global impact of rotavirus vaccine introduction on rotavirus hospitalisations among children under 5 years of age, 2008–16: findings from the Global Rotavirus Surveillance Network. Lancet Glob Health. 2019;7(7):e893–e903. [PubMed: 31200889]
12. Burnett E, Parashar UD, Tate JE. Real-world effectiveness of rotavirus vaccines, 2006–19: a literature review and meta-analysis. Lancet Glob Health. 2020;8(9):e1195–e202. [PubMed: 32827481]
13. Burnett E, Parashar UD, Tate JE. Global Impact of Rotavirus Vaccination on Diarrhea Hospitalizations and Deaths Among Children <5 Years Old: 2006–2019. J Infect Dis. 2020;222(10):1731–9. [PubMed: 32095831]
14. Patel M, Steele AD, Parashar UD. Influence of oral polio vaccines on performance of the monovalent and pentavalent rotavirus vaccines. Vaccine. 2012;30 Suppl 1:A30–5. [PubMed: 22520134]
15. Velasquez DE, Parashar U, Jiang B. Decreased performance of live attenuated, oral rotavirus vaccines in low-income settings: causes and contributing factors. Expert Rev Vaccines. 2018;17(2):145–61. [PubMed: 29252042]
16. Burnett E, Parashar UD, Tate JE. Rotavirus Infection, Illness, and Vaccine Performance in Malnourished Children: A Review of the Literature. Pediatr Infect Dis J. 2021;40(10):930–6. [PubMed: 34117200]
17. Church JA, Parker EP, Kirkpatrick BD, Grassly NC, Prendergast AJ. Interventions to improve oral vaccine performance: a systematic review and meta-analysis. Lancet Infect Dis. 2019;19(2):203–14. [PubMed: 30712836]
18. Baker JM, Tate JE, Leon J, Haber MJ, Lopman BA. Antirotavirus IgA seroconversion rates in children who receive concomitant oral poliovirus vaccine: A secondary, pooled analysis of Phase II and III trial data from 33 countries. PLoS Med. 2019;16(12):e1003005. [PubMed: 31887139]
19. Rotavirus vaccines: WHO position paper - July 2021. Weekly Epidemiologic Record: World Health Organization; 2021. p. 301 – 219.
20. Clark A, Tate J, Parashar U, Jit M, Hasso-Agopsowicz M, Henschke N, et al. Mortality reduction benefits and intussusception risks of rotavirus vaccination in 135 low-income and middle-income countries: a modelling analysis of current and alternative schedules. Lancet Glob Health. 2019;7(11):e1541–e52. [PubMed: 31607466]
21. Introduction of Rotavirus Vaccine. In: Organization WH, editor. https://immunizationdata.who.int/pages/vaccine-intro-by-antigen/rotavirus.html?ISO_3_CODE=&YEAR=2021.
22. Bines JE, Kohl KS, Forster J, Zanardi LR, Davis RL, Hansen J, et al. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine. 2004;22(5–6):569–74. [PubMed: 14741146]
23. Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. Biostatistics. 2009;10(1):3–16. [PubMed: 18499654]
24. Musonda P, Farrington CP, Whitaker HJ. Sample sizes for self-controlled case series studies. Stat Med. 2006;25(15):2618–31. [PubMed: 16372391]
25. Rachlin A, Patel JC, Burns CC, Jorba J, Tallis G, O'Leary A, et al. Progress Toward Polio Eradication - Worldwide, January 2020-April 2022. MMWR Morb Mortal Wkly Rep. 2022;71(19):650–5. [PubMed: 35552352]
26. Harris RC, Chen Y, Cote P, Ardillon A, Nievera MC, Ong-Lim A, et al. Impact of COVID-19 on routine immunisation in South-East Asia and Western Pacific: Disruptions and solutions. Lancet Reg Health West Pac. 2021;10:100140. [PubMed: 33899040]
27. Farrington P, Whitaker H, Ghebremichael Weldeselassie Y. Self-Controlled Case Series Studies: A modelling guide with R. Boca Raton, FL: CRC Press; 2018.
28. Yung CF, Chan SP, Soh S, Tan A, Thoon KC. Intussusception and Monovalent Rotavirus Vaccination in Singapore: Self-Controlled Case Series and Risk-Benefit Study. J Pediatr. 2015;167(1):163–8 e1. [PubMed: 25882872]

29. Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719–30. [PubMed: 29466164]

30. Myat TW, Thin Aung NN, Thu HM, Aye A, Win NN, Lwin MM, et al. Epidemiology of intussusception among children less than 2 years of age; findings from baseline surveillance before rotavirus vaccine introduction in Myanmar. Heliyon. 2021;7(3):e06601. [PubMed: 33855244]

31. Yousafzai MT, Thobani R, Qazi SH, Saddal N, Yen C, Aliabadi N, et al. Intussusception among children less than 2years of age: Findings from pre-vaccine introduction surveillance in Pakistan. Vaccine. 2018;36(51):7775–9. [PubMed: 28709556]

Highlights:

- In some countries, an increased risk of intussusception was found with rotavirus vaccination.
- We used the self-controlled case series method to assess this association in 3 Asian countries.
- There was no association between intussusception and rotavirus vaccination in these settings.
- Factors that decrease rotavirus vaccine performance may also reduce the intussusception risk.

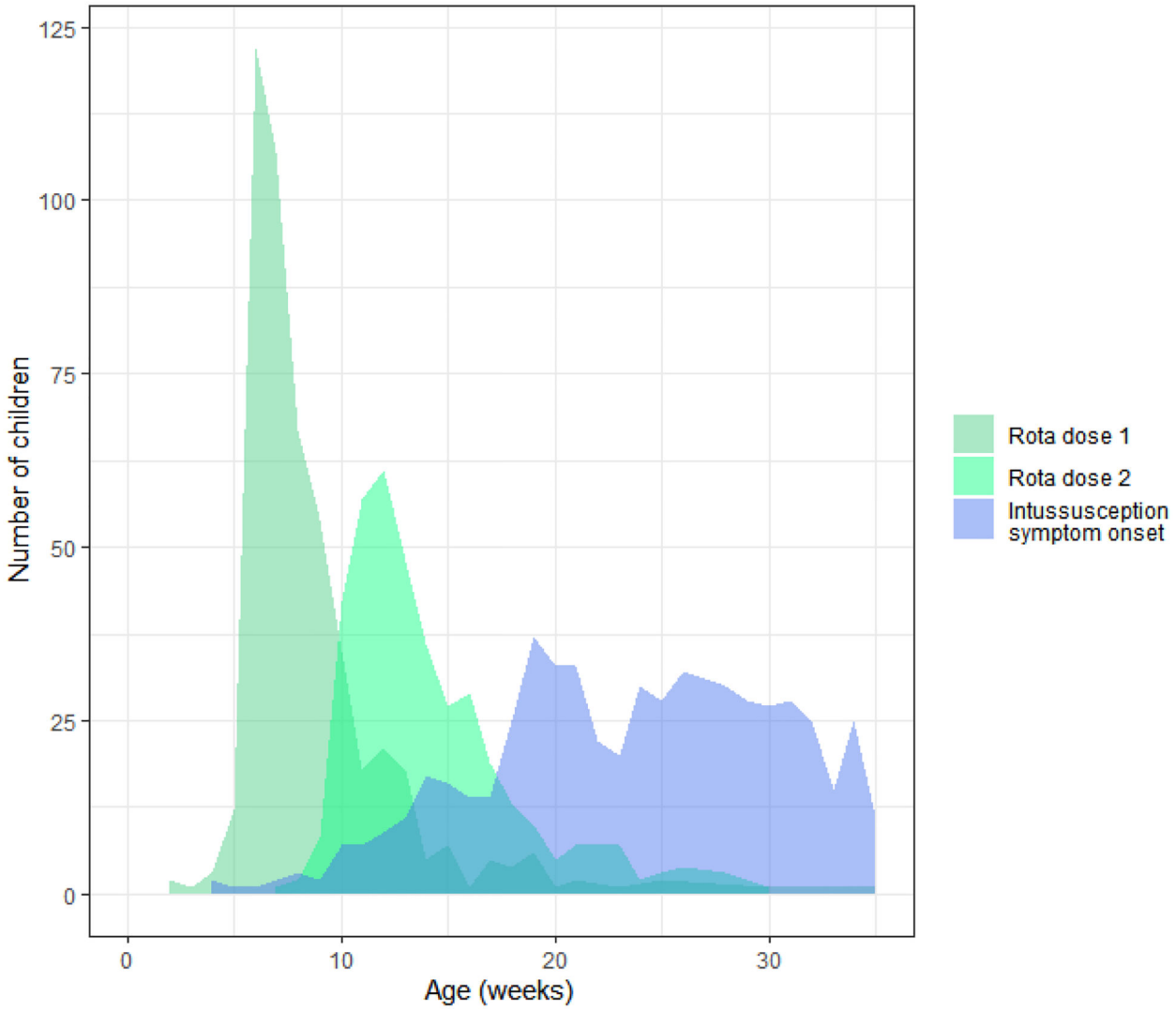

Figure 1.

Age at immunization and intussusception symptom onset among confirmed intussusception cases enrolled at sentinel hospitals in Afghanistan, Myanmar and Pakistan, 2018–2022

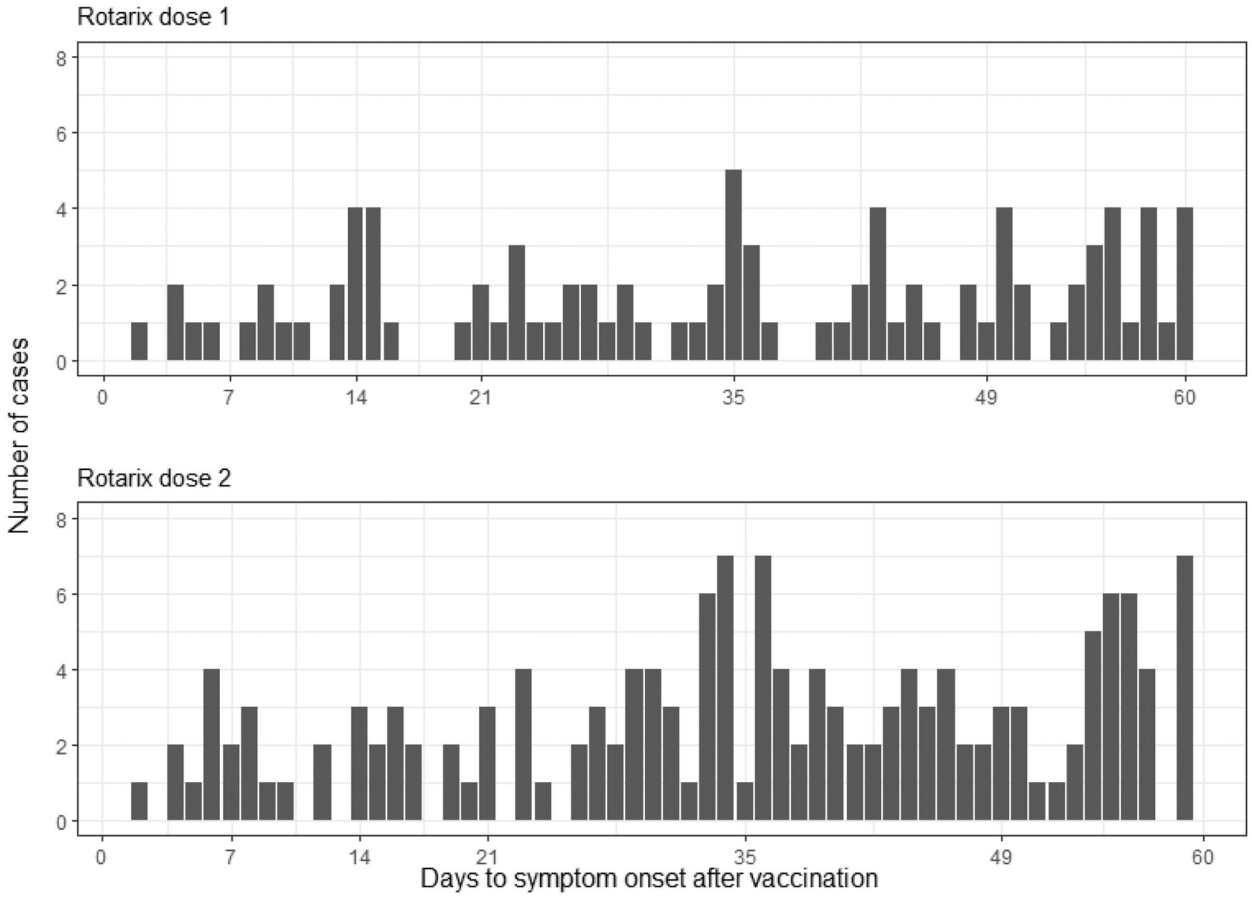

Figure 2.

Number of days confirmed intussusception cases reported intussusception symptom onset after rotavirus vaccine administration at sentinel hospitals in Afghanistan, Myanmar and Pakistan, 2018–2022

Table 1.

Characteristics rotavirus vaccine recommendations, intussusception, and intussusception cases enrolled in Afghanistan, Pakistan, and Myanmar.

Country	Month and year of rotavirus vaccine introduction	Recommended ages of vaccine administration	Enrollment period	Sentinel hospitals	Patients age <12 months with intussusception	Patients 28–245 Days of Age with Intussusception and Confirmed rotavirus Vaccination status
Afghanistan	January 2018	6 and 10 weeks	May 2018-March 2022	4	468	264
Pakistan	January 2018	6 and 10 weeks	May 2018-March 2022	4	385	286
Myanmar	February 2020	2 and 4 months	March 2020-December 2020	3	41	35

Table 2.

Relative incidence of intussusception in the 1–7, 8–21 and 1–21 day risk windows following the first and second doses of rotavirus vaccine in Afghanistan, Myanmar and Pakistan and in Afghanistan and Pakistan.

	All		Afghanistan and Pakistan only	
Dose and risk window	**No. of cases**	**Relative incidence (95%CI)**	**No. of cases**	**Relative incidence (95%CI)**
Dose 1				
1–7 days	5	1.01 (0.39, 2.60)	5	1.08 (0.42, 2.80)
8–21 days	19	1.37 (0.81, 2.32)	14	1.04 (0.57, 1.88)
1–21 days	24	1.28 (0.78, 2.11)	19	0.97 (0.56, 1.69)
Dose 2				
1–7 days	10	0.81 (0.42, 1.54)	9	0.76 (0.38, 1.51)
8–21 days	23	0.77 (0.49, 1.21)	18	0.64 (0.39, 1.05)
1–21 days	33	0.78 (0.53, 1.16)	27	0.63 (0.41, 0.97)