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Post-Marketing Surveillance of Intussusception after Rotarix Administration in Afghanistan, 2018–2022

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Abstract

Background: In January 2018, Afghanistan introduced the monovalent oral rotavirus vaccine (Rotarix) nationwide, administered as a 2-dose series at six and ten weeks of age. We describe characteristics of intussusception cases and assess potential intussusception risk associated with Rotarix vaccination in Afghan infants.

Methods: Multi-center prospective active hospital-based surveillance for intussusception was conducted from May 2018 to March 2022 in four sentinel sites in Afghanistan. We applied the Brighton Level 1 criteria for intussusception and verified vaccination status by reviewing vaccine cards. We used the self-controlled case series (SCCS) methodology to compare intussusception incidence in the 1 to 21 days after each dose of Rotarix vaccination against non-risk periods.

Results: A total of 468 intussusception cases were identified in infants under 12 months, with 264 cases aged between 28 and 245 days having confirmed vaccination status contributing to the SCCS analysis. Most case-patients (98%) required surgery for treatment, and over half (59%) of those who underwent surgery required intestinal resection. Nineteen (7%) case-patients died. Eighty-six percent of case-patients received the first dose of Rotarix, and 69% received the second dose before intussusception symptom onset. There was no increased risk of intussusception in the 1–7 days (relative incidence: 0.9, 95% CI: 0.1, 7.5), 8–21 days (1.3, 95% CI: 0.4, 4.2), or 1–21 days (1.1, 95% CI: 0.4, 3.4) following receipt of the first dose or in the 1–7 days (0.2, 95% CI: 0.3, 1.8), 8–21 days (0.7, 95% CI: 0.3, 1.5), or 1–21 days (0.6, 95% CI: 0.3, 1.2) following the second dose.

Conclusion: Rotarix vaccination was not associated with an increased intussusception risk, supporting its continued use in Afghanistan's immunization program. However, there was a high level of death and resection due to intussusception among Afghan infants.

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

Keywords

intussusception; rotavirus vaccine; vaccine safety; infant; self-controlled case-series; Afghanistan

Introduction

In 2009, the World Health Organization (WHO) recommended that all countries introduce rotavirus vaccines, and to date, they have been introduced in over 115 countries nationally or sub-nationally, resulting in a substantial reduction in morbidity and mortality from rotavirus acute gastroenteritis among children under 5 years. [1, 2] This achievement, however, was not without challenges. RotaShield, a first-generation rotavirus vaccine based on a rhesus tetravalent rotavirus strain, was licensed for use in the United States in 1998 but was swiftly recalled in 1999 due to an increased risk of intussusception (>30 times above the baseline rate during the 3–7 days after the first dose). [3–5] Intussusception, characterized by the infolding of a bowel segment, is the leading cause of blockage of the intestine in infants and young children. While rare, it is treatable but requires urgent medical intervention, typically through surgical intervention or enema reduction. [6] Left untreated, it can be fatal. [1, 6, 7]

The second generation of live-attenuated oral rotavirus vaccines, including Rotarix™, RotaTeq™, RotaVac™, and RotaSiil™, have been pre-qualified by the WHO for global use. [7–9] WHO recommends monitoring of intussusception risk when introducing rotavirus vaccines into new populations. Numerous post-licensure evaluations of Rotarix in seven sub-Saharan African countries, RotaTeq in South Africa and five other African countries, and RotaVac in India have shown no significant increased risk of intussusception following rotavirus vaccination. [10–13] However, the risk of intussusception associated with the rotavirus vaccine varies by setting as a small risk has been identified in some high- and middle-income countries. [14–17] A systematic review and meta-analysis of 25 randomized clinical trials have reported a relative incidence of intussusception between 0.3 to 5.0, while observational studies reported a short-term increased risk of intussusception of 1.1 to 4.3 excess cases per 100,000 vaccinated infants observed within 1–7 days following the first rotavirus vaccine dose. [18, 19]

An added layer of complexity stems from the natural increase in the incidence of intussusception in infants that occurs around the same age as the vaccine's administration, 2–6 months of age. [20] This overlap underscores the importance of a robust safety monitoring system. Passive vaccine safety reports, while invaluable, have their limitations and determining any excess risk following rotavirus vaccination requires a comprehensive reporting system. A pre- and post-vaccine introduction comparison is not recommended because intussusception is rare and susceptible to changes in quality and diligence of surveillance. [21]

In January 2018, the Afghanistan Ministry of Public Health (MoPH) introduced the monovalent oral rotavirus vaccine (Rotarix) nationally, as a 2-dose series administered at six and ten weeks of age. Afghanistan was a member of the Asian Intussusception Surveillance Network from May 2018 through March 2022. The details on the network are published elsewhere [22]. The pooled analysis of the network reported no increased risk

of intussusception with rotavirus vaccine doses in three South Asian countries including Afghanistan. [22]

In this study, we aim to have a more in-depth look at the data from Afghanistan, assess the potential risk of intussusception associated with the first and second doses of Rotarix vaccine in Afghan infants, and provide a comprehensive view of its safety profile in the country's unique context.

Methods

Study setting

We conducted multi-centric prospective active hospital-based surveillance for intussusception from May 2018 to March 2022 in four sentinel sites. Indira Gandhi Children Hospital (IGCH) and Ataturk Children Hospital (ATCH) are specialty children's hospitals in Kabul province, with a catchment population of over 5 million. Nangarhar Hospital (NRH) and Herat Hospital (HRH) are regional hospitals with a catchment population of over three million. Together, the surveillance sites' catchment populations represent around 25% of the total population of Afghanistan. [23] The study adopted the WHO generic protocol for monitoring intussusception risk after rotavirus vaccination. [21] We applied predefined inclusion criteria across all four sites. Cases were included if they were <12 months old (i.e. admitted before the child's first birthday) and met the Level 1 Brighton Collaboration criteria for intussusception. Level 1 represents a high level of diagnostic certainty, requiring confirmation during surgical or radiological enema reduction, or autopsy verification of the intussusception. [24, 25] Children admitted to the surveillance sites who were older than 12 months or did not meet Level 1 Brighton criteria were excluded from our surveillance. Besides verifying vaccination status by reviewing immunization cards, we collected demographic and clinical features and disease outcomes through a standardized questionnaire. To comply with the assumptions of the self-controlled case series (SCCS) methodology, children who were <8 months of age at the time of hospital admission were followed-up at 8 months of age to determine vital status of the child, whether additional doses of rotavirus vaccine had been administered, and if intussusception had reoccurred. Cases were enrolled on a continuous basis and independent of their vaccination status. Informed consent was obtained from the child's caregiver/guardian. The study obtained ethics approval from the Afghanistan Institutional Review Board (IRB) (ID 444509-April 2018) which categorized it as routine disease surveillance activity and non-research activity. This investigation was also reviewed by the US CDC's Human Research Protection Office and conducted consistent with applicable federal law and CDC policy.

Study design

We used the SCCS methodology, an epidemiological study design in which case-patients serve as their own controls to calculate the risk of intussusception in different fixed time intervals. [26] This involved comparing the intussusception incidence of individual infant cases during the risk period against the incidence during non-risk periods, defined as the period before and >21 days after each dose of Rotarix. Case-patients aged 1–8 months whose vaccination status was verified were included in the SCCS analysis. A sample of

224 cases would provide an 80% power to detect a 2.5 relative incidence of intussusception within 7 days receiving any the two doses of Rotarix at a 5% level of significance during observation period of 28–245 days.

Statistical analysis

We described the overall enrolled population by hospital site and described the population that met the inclusion criteria for the SCCS analysis. We used numbers and proportions to describe categorical variables and medians with interquartile range (IQR) to describe continuous variables.

We employed the pseudolikelihood method of SCCS analysis to account for the multiple doses of vaccine included in the primary series. [27, 28] Using information from published studies to identify the period of peak replication of the vaccine virus in the child's gut, we calculated the relative incidence of intussusception in three periods following each Rotarix dose administration: 1–7 days, 8–21 days and 1–21 days, considering the vaccination day as day zero. [28] The observation period was between day 28 and day 245 (1–8 months) of life. In our evaluation, we included both vaccinated and unvaccinated individuals to capture a comprehensive picture of intussusception occurrences within the population. By doing so, we were able to account for the natural occurrence (background rate) of intussusception, irrespective of vaccination as intussusception incidence varies based on age. To accurately understand this variation, age was controlled for using two-week intervals. It allowed us to better understand when and at what age intussusception cases were most likely to occur.

We computed dose-specific relative incidence (RI) values for intussusception using conditional Poisson regression. The confidence intervals were calculated by bootstrapping with 1000 iterations. Data analyses were conducted using SAS^{R} 9.4 (SAS institute Inc.) and SCCS package in R 3.5.1 (R Foundation for Statistical Computing). [26]

Results

We identified 468 intussusception cases in infants aged <12 months admitted to the four surveillance sites from May 2018 to March 2022, and of whom, 264 were included in the SCCS analysis (Figure 1).

A description of the complete population is shown in Table 1. When comparing between sites, Ataturk Children's Hospital in Kabul was noticeably different than the other three sites; it had a higher proportion of children transferred from another facility (89%), a higher proportion of children with card confirmation of their vaccination status (91%), a higher proportion of children living in a household with at least 1 employed person (99%), and lower mortality than 2 of the other 3 sites (6%). Herat Regional Hospital had the highest proportion of children who died during their hospitalization (15%). Other factors, including male sex (64%), median transfer time to the facility (1 day; IQR 1–2), and household having a mobile phone (96%), were similar among all sites.

Table 2 outlines the characteristics of children included in the SCCS analysis and offers a comparison between age-eligible children with and without verified vaccination status. All

children with unverified vaccination status (n=77) underwent surgical treatment, with an intussusception fatality rate of 22%. In terms of socioeconomic status, age-eligible children with unverified vaccination status exhibited lower levels of parental employment and were less likely to live in a household with access to television.

Median age of SCCS eligible cases at time of admission was 5 months (IQR: 4–6). Almost all cases (n=259; 98%) were managed surgically, and intestinal resection was performed in over half of the cases requiring surgery (n=154; 59%). Half of the cases (n=133) were transferred from another health facility to one of the sentinel hospitals with a median transfer time of a day (IQR: 1–2 and range: 0–13). The hospital stay duration had a median of five days (IQR: 4–7). The intussusception case fatality rate was 7% (n=19). (Table 2)

In total, before the onset of intussusception symptoms, 211 (80%) case patients received the first dose of Rotarix and 171 (65%) received the second dose. The median time between birth and receipt of rotavirus dose 1 and 2 was 52 days (IQR:45, 64) and 94 days (IQR: 81, 112), respectively. The median number of days between rotavirus vaccination and onset of intussusception symptoms was 121 days (IQR: 88, 153) for dose 1 and 84 days (IQR: 51, 116) for dose 2. (Fig. 2 and 3)

Within the initial 1 to 7 days after the first dose, only one child began experiencing intussusception symptoms, with a relative incidence of 0.94 (95%CI: 0.1, 7.5). In the 8 to 21 days post the first dose, symptoms arose in 4 additional children, resulting in a relative incidence of 1.3 (95%CI: 0.4, 4.2). In the first three weeks following the first dose, the relative incidence of intussusception was 1.1 (95%CI: 0.4, 3.4). (Table 3)

In the initial 1 to 7 days after the second dose, only one child had onset of intussusception symptoms, with a relative incidence of 0.2 (95%CI: 0.3, 1.8). Eight children began to experience symptoms in the 8 to 21 days following the second dose, with a relative incidence of 0.7 (95%CI: 0.3, 1.5). Within the first 21 days post the second dose, 9 children exhibited intussusception symptoms resulting in a relative incidence of 0.6 (95%CI: 0.3, 1.2). (Table 3)

Discussion

This evaluation did not detect any significant association between intussusception and receipt of the first and second doses of monovalent rotavirus vaccine in Afghan infants. Only one case of intussusception was identified during the first 7 days after first dose of vaccine and another 4 cases identified during the 8 to 21 days after the first dose. Similarly, 1 and 8 cases occurred in the first 7 days and 8 to 21 days following the second dose, respectively. The risk of intussusception in the 1 to 7 days and 8 to 21 days after each dose of vaccine was similar to the risk of intussusception in all other risk periods after controlling for age. The Afghanistan post-marketing intussusception surveillance was part of a regional intussusception network and contributed to the pooled results of all countries participating countries in the network. Our evaluation results reflect the pooled results of Asian Intussusception Surveillance Network which showed that Rotarix did not increase the risk of intussusception in the 1 to 7 days following dose 1 with an incidence risk of

1.0 (95%CI: 0.4, 2.6). Our findings also agree with the results that found no association between intussusception and Rotarix reported in a pooled analysis in seven sub–Saharan Africa countries and an analysis in South Africa.

The surveillance of intussusception among Afghan infants also highlighted significant variations in the outcomes of treatment, vaccine card verification, and socioeconomic status both within and among provinces. Ataturk Children Hospital, located in the eastern part of Kabul city, reported a higher number of referred cases with a lower fatality rate compared to other sites. The socioeconomic indicators, including access to job employment, home electricity, and smaller family size at this hospital, were markedly different compared to other sites within Kabul and elsewhere. This underscores the broader issue of inequality in access to essential services, which is crucial to address for improving overall health outcomes. A notable contrast emerged between children who received vaccinations and those who had unverified vaccination status, revealing disparities in both health outcomes and socioeconomic status. Notably, children with unverified vaccination status had much higher mortality and reported reduced access to parental job opportunities and had limited access to television, which is a medium for disseminating health information to families. These findings underscore the potential impact of routine health services, emphasizing the importance of vaccination services in fostering improved health and well-being among children.

The strength of this evaluation is that it was multicentric and was conducted for four years following vaccine introduction. Throughout the study, several quality control measures were implemented. Quality control officers conducted frequent, monthly visits to the study sites and cross-checked the enrolled cases with the hospital registry to ensure that case-patients were not missed. Similarly, cases-patient forms were routinely checked for completeness and vaccination cards were consulted for inconsistent vaccination dates. The evaluation happened during the COVID-19 pandemic and political change in the country in mid-August 2021 which subsequently impacted health service delivery. Because intussusception requires immediate surgical attention, there was no interruption in surveillance. The study sites represent three of five regions in the country and one-fourth of total population of the country. Furthermore, we evaluated three distinct lengths of the risk windows following each vaccine dose, 1–7 days, 8–21 days and 1–21 days, enhancing the robustness of our findings.

Our evaluation is subject to certain limitations. We focused on only government-run hospitals. Pediatric surgery accessibility across the entire country is constrained, requiring parents to undertake long journeys to reach specialized pediatric centers. It is conceivable that some cases of intussusception were not captured due to the child being treated in a private health facility or to fatalities occurring before reaching the hospital. It is important to note the coincidental timing of our surveillance with the COVID-19 pandemic. A potential association of SARS-CoV-2 and bowel inflammation with a subsequent intussusception[29] has been reported; we lacked information on SARS-CoV-2 positivity among cases. We do not think either would have introduced systematic bias using the SCCS method.

This evaluation provides further evidence in support of rotavirus vaccine safety in a high burden child mortality setting. Our findings provide robust evidence in favor of continuing

the administration of the Rotarix vaccine to children. Moreover, our results are consistent with observations from other studies in various low-income countries, suggesting a broader consensus on the vaccine's safety in these settings.

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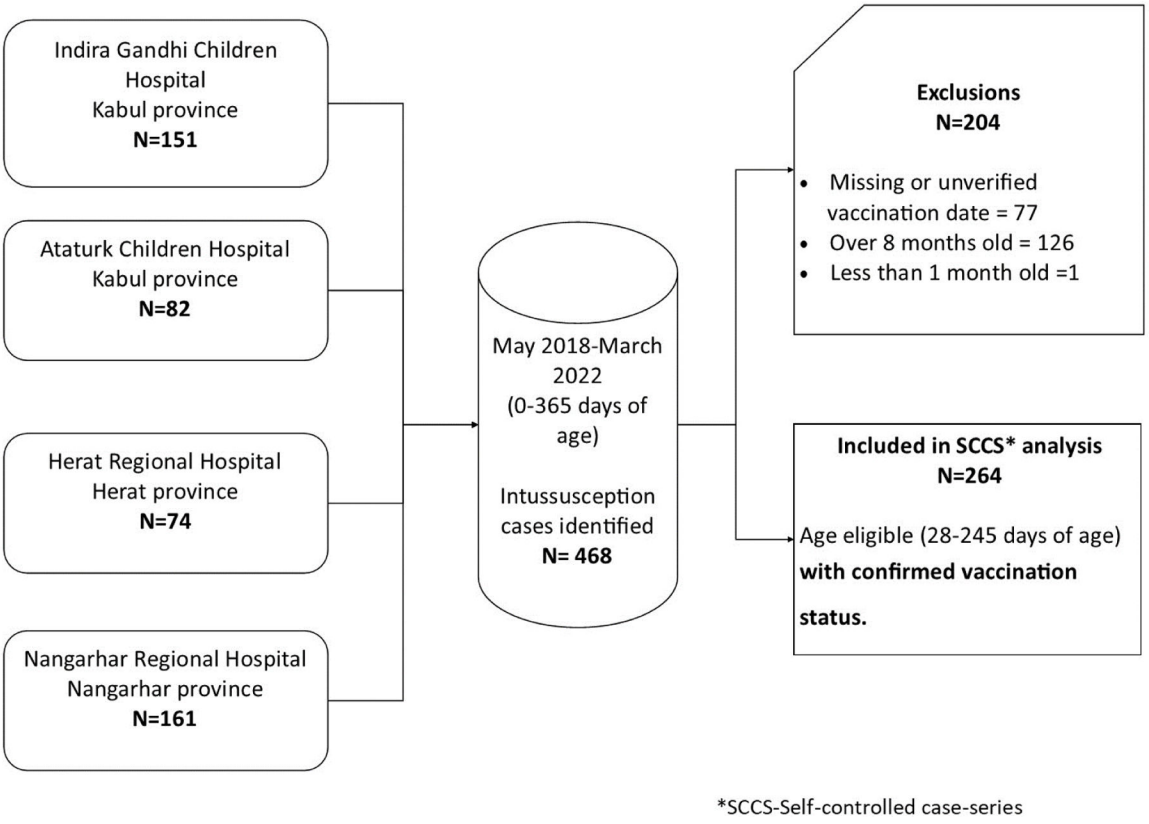

Figure 1.
Self-controlled case-series (SCCS) study recruitment flow diagram, May 2018-March 2022, Afghanistan

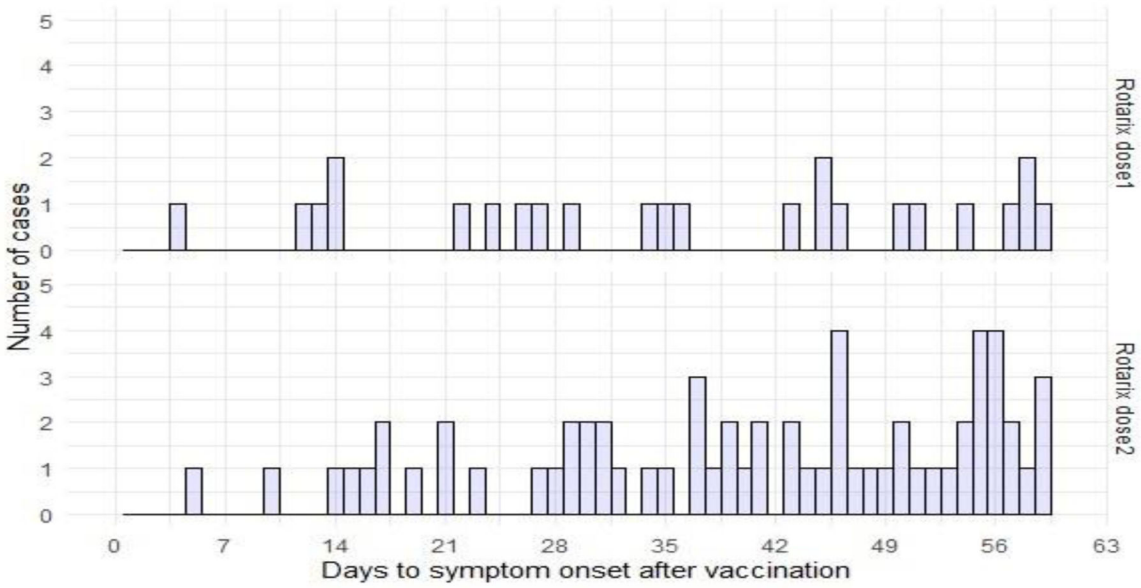

Figure 2.

Onset of intussusception after Rotarix dose 1 and 2, May 2018-March 2022, Afghanistan

Cases of intussusception after dose 1 and dose 2 of Rotarix, May 2018 through March 2022. Shown are the distribution of cases of intussusception cased during the 60 days after the second doses of Rotarix. An additional 192 cases occurred more than 60 days after dose 1 and an additional 116 cases occurred more than 60 days after dose 2.

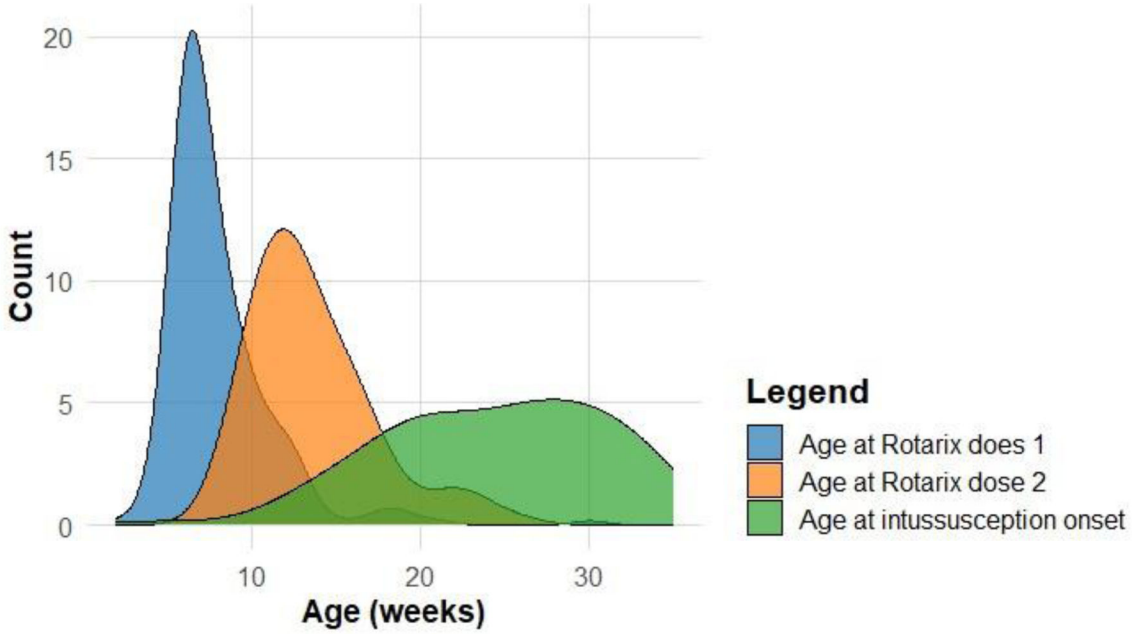

Figure 3.

Age in weeks of administration of the first and second doses of rotavirus vaccine and the age of intussusception symptom onset among intussusception cases enrolled in the self-controlled case series analysis, May 2018-March 2022, Afghanistan

Age at rotavirus immunization and intussusception symptom onset among infants aged 28–245 days with verified vaccination status, May 2018 through March2022.

Table 1:

Characteristics of multisite prospective intussusception surveillance, May 2018- Mar 2022, Afghanistan

Variables	**All sites n=468 (100%)**	**Ataturk Children Hospital n=82 (17.5%)**	**Herat Regional Hospital n=74 (15.8%)**	**Indira Gandhi Children Hospital n=151 (32.3%)**	**Nangarhar Regional Hospital n=161 (34.4%)**
City, Province		Kabul, Kabul	Herat, Herat	Kabul, Kabul	Jalalabad, Nangarhar
Sex (Male)	299 (63.9)	55 (67.1)	43 (58.1)	90 (59.6)	111 (68.9)
Case age in week (Median, IQR)	29 (21, 38)	32 (24, 39)	27 (20, 32)	29 (21, 37)	30 (21, 38)
Child transferred from another health facility	211 (43.4)	73 (89.0)	23 (31.1)	56 (37.1)	59 (36.6)
Transfer time (Median, IQR)	1 (1, 2)	1 (1,2)	1 (1, 3)	1 (0, 2)	1 (0,2)
Outcome (Died)	39 (8.3)	5 (6.1)	11 (14.9)	14 (9.3)	9 (6.0)
Confirmed source of vaccination	385 (82.3)	75 (91.5)	54 (73.0)	119 (78.8)	137 (85.1)
Socioeconomic					
No. of People the household	8 (6, 13)	6 (5, 9)	7 (6,10)	8 (6,11)	12 (8,18)
Employment	190 (40.6)	81 (98.8)	9 (12.2)	49 (32.5)	51 (31.7)
Electricity	133 (28.4)	51 (62.2)	39 (52.7)	24 (15.9)	19 (11.8)
Mobile phone	450 (96.1)	79 (96.3)	66 (89.2)	147 (97.3)	158 (98.1)

Table 2.

Characteristics of intussusception cases included in the self-controlled case-series analysis, May 2018-March 2022, Afghanistan

		Age eligible for SCCS	
Variables	**Characteristics**	**With verified vaccination status included in SCCS analysis**	**With unverified vaccination status Excluded from SCCS analysis**
		N= 264	**N=77**
Sex	Male	158 (59.9)	52 (67.5)
Age	Age in months (Median, IQR)	5 (4, 6)	6 (4, 8)
Intussusception management			
	Surgery	259 (98.1)	77 (100)
	Enema air or liquid contrast	5 (1.9)	0
	Intestinal resection among those treated with surgery	154 (59.5)	43 (55.8)
Outcome/Disposition	Discharged home	236 (89.4)	59 (76.6)
	Transferred	3 (1.1)	1 (1.3)
	Died	19 (7.2)	17 (22.1)
	Abandoned	6 (2.3)	0 (0)
Referred from another facility		133 (50.4)	29 (37.7)
Transfer interval	Days (median, IQR)	1 (1, 2)	1 (0, 2)
	Days (range)	0–13	0–6
Length of stay in the hospital	Days (Median, IQR)	5 (4, 7)	5 (3, 7)
Vaccination history before onset IS symptoms			
Rotarix	Dose 1	211 (79.9)	NA *
	Dose 2	171 (64.8)	NA
Oral polio vaccine	Birth dose	206 (78.0)	NA
	Dose 1	230 (87.1)	NA
	Dose 2	194 (73.5)	NA
	Dose 3	126 (47.7)	NA
Intervals	**(Median, IQR) in days**		
Date of birth to vaccination	RV dose 1	52 (45, 64)	NA
	RV dose 2	94 (81, 112)	NA
With the precedent dose	RV dose 2 and dose 1	37 (32, 51)	NA
Vaccine doses to IS symptom onset	RV dose 1	121 (88.5, 153.5)	NA
	RV dose2	84 (51,116)	NA
Socioeconomic			
No. of people in the household	Median (IQR)	4 (3, 6)	4 (3, 5)

		Age eligible for SCCS	
Variables	**Characteristics**	**With verified vaccination status included in SCCS analysis**	**With unverified vaccination status Excluded from SCCS analysis**
		N= 264	**N=77**
Employment	At least one parent was employed	123 (46.6)	11 (14.3)
Electricity	Yes, but usually just for some hours of the day	143 (54.2)	40 (51.9)
Mobile phone	Number (%)	258 (97.7)	68 (88.3)
Radio	Number (%)	123 (46.6)	32 (41.6)
Television	Number (%)	141 (53.4)	18 (23.4)

* Not available (NA): vaccination history was not available for children with unverified vaccination status.

Table 3

Relative incidence of intussusception in the 1–7, 8–21 and 1–21 days following the first and second doses of Rotarix in Afghanistan, May 2018 through March 2022

Dose and risk window	No. of cases	Relative incidence (95%CI) (28–245 days observation period)
Dose 1		
1–7 days	1	0.9 (0.1, 7.5)
8–21 days	4	1.3 (0.4, 4.2)
1–21 days	5	1.1 (0.4, 3.4)
Dose 2		
1–7 days	1	0.2 (0.3, 1.8)
8–21 days	8	0.7 (0.3, 1.5)
1–21 days	9	0.6 (0.3, 1.2)