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Evaluation of Intussusception Following Rotavirus Vaccination in Africa

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Abstract

Background: Post-licensure evaluations have identified an association between rotavirus vaccination and intussusception in several high and middle-income countries. We assessed the association between monovalent human rotavirus vaccine and intussusception in seven lower income African countries.

Methods: Intussusception cases meeting international (Brighton level 1) criteria were enrolled using active surveillance. Rotavirus vaccination status was confirmed by review of the vaccine card or clinic records. The risk of intussusception within 1–7 and 8–21 days of vaccination among children 28–245 days of age was assessed using the self-controlled case-series method.

Results: Data from 717 children with intussusception and confirmed vaccination status were analyzed. One case was observed in the 1–7 days and 6 cases in the 8–21 days post dose 1. Five cases and 16 cases were observed in the 1–7 days and 8–21 days post dose 2. No elevated risk of intussusception was detected in the 1–7 days post dose 1 (relative incidence (RI): 0.25; 95% confidence interval (CI), <0.001–1.03) or in the 1–7 days post-dose 2 (1–7 days: RI: 0.76; 95% CI, 0.17–1.70). Similarly, no elevated risk was detected in the 8–21 or 1–21 days post dose 1 or post dose 2.

Conclusions: An increased risk of intussusception following monovalent human rotavirus vaccine administration was not identified in these seven, lower income, sub-Saharan African countries.

Intussusception is a rare event which occurs when one segment of the bowel telescopes into another resulting in obstruction. A previously licensed rotavirus vaccine (RotaShield, Wyeth-Lederle Laboratories) was associated with intussusception following introduction in the routine immunization program in the United States.[1] An estimated 1 excess case of intussusception per 10,000 infants vaccinated with RotaShield occurred in the United States.[1,2] This vaccine was subsequently withdrawn from use. Based on this finding, the World Health Organization (WHO) recommended that intussusception be carefully monitored during the clinical trials of the newer rotavirus vaccines, the monovalent Rotarix (RV1, GlaxoSmithKline) and pentavalent RotaTeq (RV5, Merck) vaccines. Pre-licensure clinical trials (~60,000–70,000 infants each) of RV1 or RV5 did not find an association with intussusception.[3,4] However, post-marketing surveillance detected an increased intussusception risk of ~1–6 excess cases per 100,000 vaccinated children with both RV1 and RV5 in several high- and middle-income countries including Australia, Mexico, Brazil, United States, Singapore, and United Kingdom.[5–10] The increased risk was seen primarily in the first week following receipt of the first dose of rotavirus vaccine, although an increased risk has been observed following the second dose in some settings.[5,8,10] The WHO's Global Advisory Committee on Vaccine Safety, which continually reviews data from vaccines in current use, has evaluated available data to-date and reaffirmed its recommendation for vaccine use recognizing that the real-world benefits of rotavirus vaccination including documented declines in childhood mortality and hospitalizations related to diarrhea outweigh the short-term smaller risk of intussusception.[11]

By June 2017, 32 countries in Sub-Saharan Africa, where over half of all rotavirus deaths occur, had introduced rotavirus vaccine into their national immunization programs.[12] No large scale safety assessments of rotavirus vaccine have been conducted in low-income countries, including those in Africa, and only sparse data regarding incidence of intussusception exists in the region.[13] Available data indicate diagnosis and treatment of intussusception in Africa is markedly different from that reported in other regions, and the disease is often associated with greater fatality rates likely due to suboptimal access and late presentation to medical care.[14] Furthermore, efficacy and effectiveness of rotavirus vaccines are lower in low-income countries compared to middle- and high-income countries.[15–18] Thus, findings from evaluations of the association between rotavirus vaccine and intussusception that have been performed in middle and high-income countries may not be extrapolated to low-income settings given the differences in diagnosis, treatment, and outcome of intussusception between these settings.

To assess whether there is any association between RV1 and intussusception following introduction of vaccine into the routine childhood immunization schedule in African countries, the African Intussusception Surveillance Network was established in seven low and low-middle income, sub-Saharan African countries that were early adopters of RV1.

Methods

To monitor the safety of rotavirus vaccines in use in national immunization programs, intussusception surveillance was established at sentinel hospitals in seven countries that were early adopters of RV1 in sub-Saharan Africa (Ethiopia, Ghana, Kenya, Malawi,

Tanzania, Zambia, and Zimbabwe). Countries joined the network on a rolling basis following introduction of RV1 into their routine childhood immunization programs. Surveillance began in the first country in February 2012 and ended in all countries in December 2016. Participating countries used a common surveillance protocol to allow for pooling of data across sites and countries. Site investigators conducted active surveillance to identify cases of intussusception at major pediatric hospitals located in large urban areas of the participating countries. Children <12 months of age meeting the Brighton Collaboration criteria for level 1 of diagnostic certainty for intussusception were enrolled, regardless of RV1 vaccination status. Level 1 of diagnostic certainty requires confirmation of intussusception during surgery or by specific radiological findings if reduction occurred by enema or at autopsy.[19] Limited clinical and sociodemographic data were collected from interviews with parents and by review of the child's medical record. Onset of intussusception was defined as the date of first reported symptoms by the parent or guardian. Vaccination status and dates were obtained from vaccination cards brought by the parent or guardian to the hospital or, if the vaccine card was unavailable, by visiting the child's home or clinic where the child was vaccinated. For most cases, a photocopy or photograph of the vaccine card or clinic record was made for future reference and for confirmation of vaccination status. In all participating countries, two doses of RV1 were recommended to be given at the first two Expanded Program on Immunization (EPI) visits at 6 and 10 weeks of age along with the other EPI vaccines including oral polio. Additional doses of rotavirus vaccine were contraindicated if a child experienced an episode of intussusception prior to completion of vaccine series. For intussusception case-patients who were diagnosed prior to 8 months of age, efforts were made to re-contact their families when the child reached 8 months of age to determine if the child had received any additional doses of rotavirus vaccine or had a recurrent episode of intussusception and to assess the vital status of the child.

Risk Analysis

The resource efficient and validated self-controlled case-series (SCCS) method was applied to assess intussusception risk after RV1.[8,10,20] The SCCS methodology relies on identification of intussusception cases and on linking these records with their vaccination status. Since each case acts as its own control for time-invariant confounders in the SCCS method, no external controls or population level vaccination data were required for the assessment of risk. We used an adaptation of the SCCS method (the pseudo-likelihood method) that allowed for contraindication of rotavirus vaccination following an episode of intussusception.[21]

Given findings from previous analyses of RV1 and intussusception, we hypothesized the risk of intussusception would be greatest in the 1 to 7 days following vaccination (day 0) which corresponds to the period when peak intestinal replication of the RV1 vaccine virus is thought to occur.[22] We also examined risk periods of 8 to 21 days and 1 to 21 days after each dose of RV1. Given the timing of rotavirus vaccine administration, we limited the analysis to children 28 to 245 days of age at time of intussusception onset. To account for the varying underlying age distribution of intussusception cases, we controlled for age in the model using 14 day age bands. Children not RV1 age-eligible (e.g. children born several

months before vaccine introduction) and children who were age-eligible but did not receive RV1 were also included in the model to provide stability to the underlying age distribution. Relative incidences and confidence intervals were calculated using conditional Poisson regression comparing the incidence within the risk window with the incidence in all other observation windows for each infant. Confidence intervals were derived by bootstrapping with 1000 iterations.

We estimated that 400 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 70% vaccine coverage and a type 1 alpha level of 0.05. Data were analyzed using Stata version 14 (StataCorp, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC). All authors vouch for the completeness and accuracy of data and analysis presented. This evaluation was determined to be public health non-research during CDC human subjects review and the WHO Ethical Review Committee (ERC) granted exemption noting that the protocol is part of routine hospital-based surveillance.

Results

A total of 1060 children <12 months of age with intussusception were enrolled in surveillance from 29 sentinel hospitals located in 7 countries. (Table 1) Of these, 239 children were excluded from the analysis because they were <28 days or >245 days at time of intussusception symptom onset and an additional 104 children were excluded because their vaccination status could not be confirmed, resulting in 717 children included in the analysis. Ghana, the first country in the network to introduce rotavirus vaccine, contributed the greatest number of cases (258; 36%) to the analysis.

The median age of children included in the analysis was 25 weeks with few cases of intussusception detected in very young infants 4–11 weeks of age (Figure 1); 61% (436/717) were male. Among those for whom information was available, only 2% (10/664) of children had never received any breastmilk prior to intussusception onset, 68% (438/644) lived in a household where at least one person was employed, 73% (455/627) lived in a household that had electricity at least part of the time, and 80% (522/650) live in a household with a mobile phone. The median duration between symptom onset and admission to a surveillance facility was 3 days (interquartile range (IQR): 1–4 days) with 78% (420/537) of children first seeking care at another facility. The majority of the children were treated surgically (87%; 615/704) with 57% (353/615) of these children requiring resection of the bowel; 13% (89/704) were treated by enema. Overall, 12% (80/681) of intussusception cases died.

Vaccination coverage was high and receipt was timely. (Figure 1) Ten percent of the intussusception cases included in the analysis were unvaccinated, 6% received only one dose of RV1, and 84% received two doses of RV1. The median age at dose 1 was 6 weeks (IQR: 6–7 weeks) and at dose 2 was 11 weeks (IQR: 10–12 weeks). Despite the contraindication, 5 children received at least one dose of RV1 following intussusception. Of the 445 (69%) surviving children re-contacted at 8 months of age, 14 (3%) children had experienced a second episode of intussusception and 7 (2%) children died after hospital discharge and before reaching 8 months of age.

No clustering of cases occurred in any of the risk windows (1–7 days, 8–21 days, or 1–21 days) following receipt of either dose of RV1. (Figure 2) One case was observed in the 1–7 days and 6 cases in the 8–21 days post dose 1. Five cases and 16 cases were observed in the 1–7 days and 8–21 days, respectively, post dose 2. (Table 2) No elevated risk of intussusception was detected in the 1–7 days post RV1 dose 1 (relative incidence (RI), 0.25; 95% confidence interval (CI), <0.001–1.16) or in the 1–7 days post RV1 dose 2 (1–7 days: RI, 0.76; 95% CI, 0.17–1.70). Similarly, no elevated risk was detected in the 8–21 or 1–21 days post dose 1 or post dose 2. (Table 2)

Discussion

Unlike previous data from high and upper-middle income countries, we did not find an increased risk of intussusception associated with RV1 in low and low-middle income, sub-Saharan African countries. We hypothesize several possible explanations for this difference in risk by setting. First, although the exact mechanism is not known, intussusception is possibly related to intestinal replication of the orally administered, live vaccine rotavirus strain. Because oral rotavirus vaccines are less efficacious and shedding of vaccine virus, a potential marker of vaccine replication, is less frequently detected in low-income countries compared with high- and middle-income countries[15,17], rotavirus vaccines might also be associated with a lower intussusception risk in low-income countries. Second, rotavirus vaccine is co-administered with oral polio vaccine in low-income countries and the first dose of oral polio vaccine, which is associated with the greatest replication of the vaccine poliovirus, has been shown to decrease the immunogenicity of the first dose of RV1 when co-administered.[23] This phenomenon was hypothesized as a potential reason why no increased risk of intussusception was seen after the first dose of RV1 in Brazil, the other country where no such association was observed post dose 1.[10] However, a low level association between RV1 and intussusception was observed after the second dose in Brazil.[10] Third, the two doses of RV1 were administered at a young age (6 and 10 weeks) in African countries compared with older age schedules (generally 2 and 4 months) in high and middle come countries. Because intussusception is uncommon in the first 2 months of life, RV1 administration at these young ages might not be associated with intussusception in African countries, especially if the causes of intussusception are different in younger infants compared with older infants. Finally, other factors that may play a role in the risk of intussusception in younger infants and that are different in these low-income African countries compared with high- and middle-income countries (e.g. diet, breastfeeding practices, microbiome, or levels of maternal antibodies) might also partially explain the differences in the risk of intussusception following RV1 vaccination via unknown mechanisms.

Given the higher background rate of intussusception in older children, the initial WHO recommendations issued in 2009 specified that the rotavirus vaccine series be initiated by 15 weeks of age to avoid amplifying any potential vaccine-associated risk of intussuception.[24] However, recognizing that many children could be excluded from receiving rotavirus vaccine under these age restrictions, especially in some low-income, high burden countries where delays in vaccination are more common, these age restrictions were reviewed. A modeling study using vaccine efficacy data from clinical trials and the available data on

risk of intussusception following vaccination from post-licensure evaluations in middle- and high-income countries found that removing these age restrictions would avert 154 rotavirus deaths for every intussusception death related to the vaccine in low-income countries.[25] Based on these data, in January 2013, WHO recommended removal of age restrictions for rotavirus vaccines to improve vaccine coverage. The timely administration of RV1 in the early vaccine introducing countries included in this analysis, with 3% of children receiving RV1 after 15 weeks of age, may limit the generalizability to countries with significant delays in vaccine administration. If the dynamics of RV1 replication and immune response are different (e.g. greater) in older children, the risk of intussusception could be different.

Our study had some limitations. First, the lack of suspicion of intussusception and delays in seeking health care could have resulted in some children dying from intussusception prior to reaching a surveillance facility. While this would have reduced the number of cases identified, these delays would likely have been independent of vaccination status and therefore would not likely have biased our results. However, if intussusception cases that did not present for treatment were more likely be vaccinated late, then our results may not be generalizable to those children. The age distribution of our cases was similar to that seen in the United States and other countries with good access to care[14,26] with few cases occurring in the first 12 weeks of life indicating that we were not selectively missing cases in younger children during the period when vaccine doses are given. Exact reasons for lower rates of intussusception in younger children are not well understood but may be related to the decline of maternal antibodies to pathogens associated with intussusception or to age-related milestones in intestinal lymphoid tissue maturation. If we did selectively miss cases among younger children, then we may have underestimated the true risk of intussusception following vaccination. Second, we used date of first reported symptom by the parent as the date of intussusception onset rather than date of hospital admission as has been used in many of the previous analyses. We chose to use the symptom onset date because there was a median of 3 days between symptom onset and admission to the surveillance facility. If admission date was used as the marker for the date that intussusception occurred, we were concerned that some children would be excluded from the 1–7 day risk window. If we used date of hospital admission as the onset date for the analysis or a longer risk window, we also did not see an increased risk of intussusception. Third, children frequently travelled long distances to reach the surveillance facilities and often did not bring their vaccine cards with them. This necessitated great effort by surveillance staff to find ways to confirm the vaccination status of the enrolled children. Overall, we were able to confirm the vaccination status of 87% of age-eligible children and there was no difference in the age distribution of children for whom we confirmed the vaccination status and those for whom we did not. Finally, the presentation and treatment of intussusception in the countries this evaluation differs from that observed in other regions of the world in terms of delays in presentation, surgery rates, and mortality.[14] While better understanding these data are important for better treatment and outcomes for intussusception patients, such analyses were outside the scope of the current evaluation.

The self-controlled case-series approach provided an efficient method that can be applied in resource-limited settings to evaluate the risk of intussusception following rotavirus vaccination. As intussusception is a rare adverse event and a large sample size is required

to assess the risk of intussusception following rotavirus vaccination, such evaluations may not be feasible and practical in all countries introducing rotavirus vaccine. As this vaccine or other rotavirus vaccines in the pipeline are introduced into other regions such as Asia where evaluations of rotavirus vaccine and intussusception have not been performed and given the regional differences in the epidemiology of intussusception, similar evaluations will be important to assess the regional benefits and risks of rotavirus vaccination. In the 29 African countries that had introduced rotavirus vaccine into their national immunization program by the end of 2014, ~135,000 rotavirus hospitalizations and 21,000 rotavirus deaths were estimated to be prevented in 2016.[27] Given these large health benefits, the lack of increased risk of intussusception following RV1 administration in our study is reassuring.

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Appendix:

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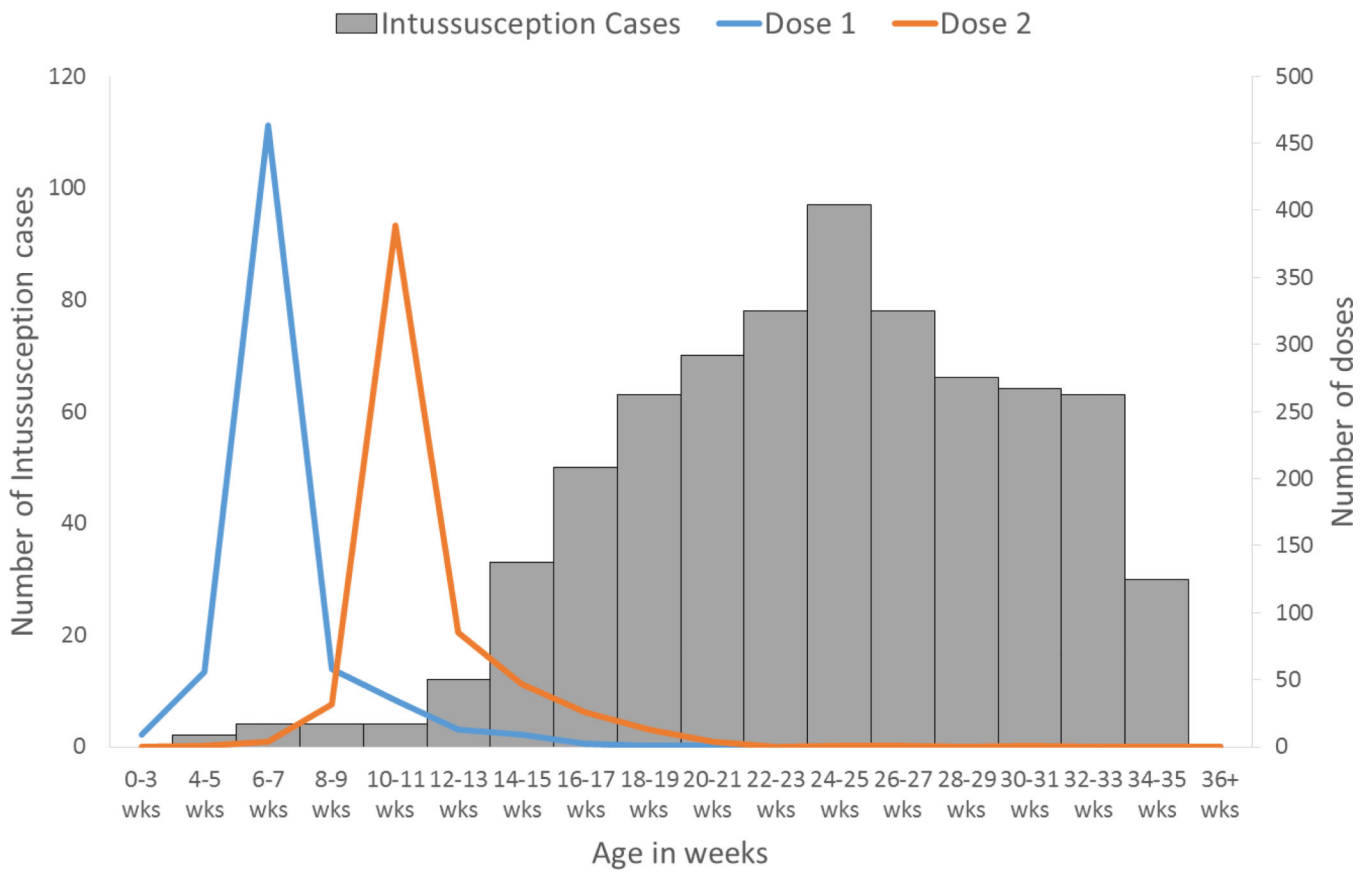

Figure 1.

Number of intussusception cases by age at symptom onset and number of doses of rotavirus vaccine administered by age, African Intussusception Surveillance Network, February 2012-December 2016

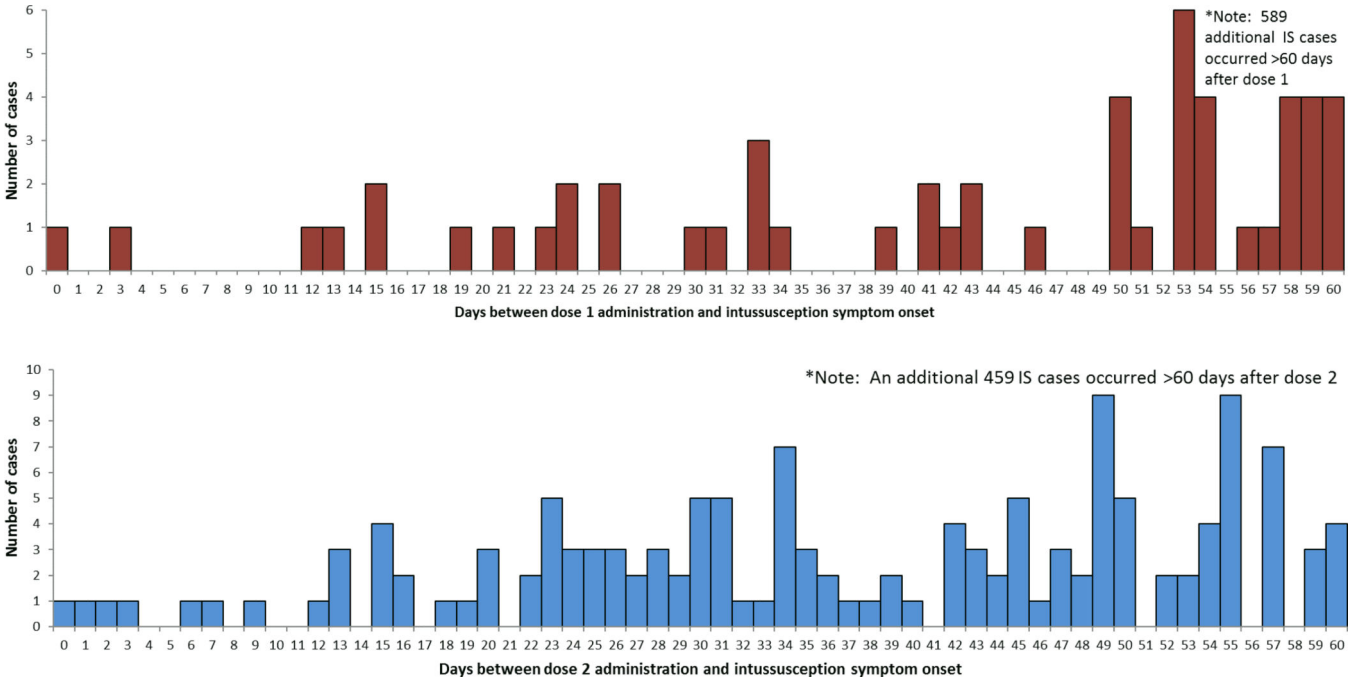

Figure 2.

Distribution of intussusception cases in the 60 days following the first and second doses of monovalent rotavirus vaccine, African Intussusception Surveillance Network, February 2012-December 2016

Table 1.

Rotavirus Vaccine Introduction, Enrollment Periods, and Number of Intussusception Cases Enrolled by Country

Country	Rotavirus vaccine introduction	Enrollment period	Number of sentinel hospitals	Number of IS cases <12 months of age	Number of IS cases 28–245 days with confirmed vaccination status included in analysis
Ethiopia	November 2013	Dec 2013 - Dec 2016	6	164 (16%)	80 (11%)
Ghana	April 2012	Feb 2012 - Dec 2016	2	381 (36%)	258 (36%)
Kenya	July 2014	Oct 2014 – Dec 2016	5	135 (13%)	97 (14%)
Malawi	October 2012	Nov 2013 - Nov 2016	4	28 (3%)	23 (3%)
Tanzania	January 2013	Jan 2013 - Dec 2016	7	201 (19%)	144 (20%)
Zambia	January 2012 *	Aug 2013 - Nov 2016	4	61 (6%)	47 (7%)
Zimbabwe	May 2014	Aug 2014 – Dec 2016	1	90 (9%)	68 (10%)
Total	--	Feb 2012 – Dec2016	29	1060 (100%)	717 (100%)

* Introduced in Lusaka Province as part of a demonstration project in January 2012 and nationwide in November 2013

Table 2.

Relative incidence of intussusception in the risk periods after the first and second dose of monovalent rotavirus vaccine, African Intussusception Surveillance Network, February 2012-December 2016

	Risk period (days)	N cases in risk period	Relative Incidence (95% CI)
Dose 1	1–7	1	0.25 (<0.001, 1.16)
	8–21	6	1.01 (0.27, 2.31)
	1–21	7	0.85 (0.35, 1.73)
Dose 2	1–7	5	0.76 (0.17, 1.70)
	8–21	16	0.74 (0.39, 1.20)
	1–21	21	0.81 (0.49, 1.22)