ORIGINAL ARTICLE

Evaluation of Intussusception after Monovalent Rotavirus Vaccination in Africa

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ABSTRACT

BACKGROUND

Postlicensure 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 lower-income sub-Saharan African countries.

METHODS

Using active surveillance, we enrolled patients from seven countries (Ethiopia, Ghana, Kenya, Malawi, Tanzania, Zambia, and Zimbabwe) who had intussusception that met international (Brighton Collaboration level 1) criteria. Rotavirus vaccination status was confirmed by review of the vaccine card or clinic records. The risk of intussusception within 1 to 7 days and 8 to 21 days after vaccination among infants 28 to 245 days of age was assessed by means of the self-controlled case-series method.

RESULTS

Data on 717 infants who had intussusception and confirmed vaccination status were analyzed. One case occurred in the 1 to 7 days after dose 1, and 6 cases occurred in the 8 to 21 days after dose 1. Five cases and 16 cases occurred in the 1 to 7 days and 8 to 21 days, respectively, after dose 2. The risk of intussusception in the 1 to 7 days after dose 1 was not higher than the background risk of intussusception (relative incidence [i.e., the incidence during the risk window vs. all other times], 0.25; 95% confidence interval [CI], <0.001 to 1.16); findings were similar for the 1 to 7 days after dose 2 (relative incidence, 0.76; 95% CI, 0.16 to 1.87). In addition, the risk of intussusception in the 8 to 21 days or 1 to 21 days after either dose was not found to be higher than the background risk.

CONCLUSIONS

The risk of intussusception after administration of monovalent human rotavirus vaccine was not higher than the background risk of intussusception in seven lower-income sub-Saharan African countries. (Funded by the GAVI Alliance through the CDC Foundation.)

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*A list of additional members of the African Intussusception Surveillance Network is provided in the Supplementary Appendix, available at NEJM.org.

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Intussusception is a rare event that occurs when one segment of the bowel telescopes into another, which results in obstruction. A previously licensed rotavirus vaccine (RotaShield, Wyeth-Lederle Laboratories) was found to be associated with intussusception after its introduction in the routine immunization program in the United States.[1] It has been estimated that 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.

On the basis of 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 vaccine (RV1, GlaxoSmithKline) and pentavalent RotaTeq vaccine (RV5, Merck). Prelicensure clinical trials (involving approximately 60,000 to 70,000 infants each) of RV1 or RV5 did not find an association with intussusception.[3,4] However, postmarketing surveillance detected an increased risk of intussusception, of approximately 1 to 6 excess cases per 100,000 vaccinated children, in association with both RV1 and RV5 in several high- and middle-income countries, including Australia, Mexico, Brazil, the United States, Singapore, and the United Kingdom.[5-10] The risk was seen primarily in the first week after receipt of the first dose of rotavirus vaccine, although an increased risk has been observed after the second dose in some countries.[5,8,10] The WHO Global Advisory Committee on Vaccine Safety, which continually reviews data on vaccines in current use, has evaluated the data available to date and reaffirmed its recommendation for use of the vaccine, 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, a total of 32 countries in sub-Saharan Africa, where more than half of all deaths due to rotavirus occur, had introduced rotavirus vaccine into their national immunization programs.[12] Data from large-scale safety assessments of the rotavirus vaccine conducted in low-income countries, including those in Africa, are lacking, and only sparse data regarding the incidence of intussusception in the region are available.[13] The available data indicate that the diagnosis and treatment of intussusception in Africa is markedly different from that reported in other regions, and the disease is often associated with higher fatality rates in Africa, probably because of less access and late presentation to medical care.[14] Furthermore, the efficacy and effectiveness of rotavirus vaccines are lower in low-income countries than in middle- and high-income countries.[15-18] Thus, it may not be valid to extrapolate the findings from studies of the association between rotavirus vaccine and intussusception that have been performed in middle- and high-income countries 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 vaccination and intussusception after introduction of the 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

Study Design

To monitor the safety of the rotavirus vaccines that are 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 after the 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 that were located in large urban areas of the participating countries. Infants younger than 12 months of age whose condition met 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, by specific radiologic findings (if reduc-

tion occurred as a result of an enema), or at autopsy.[19]

Limited clinical and sociodemographic data were collected in interviews with the parents or guardians and by review of the infant's medical record. The onset of intussusception was defined as the date of the first symptoms reported by the parent or guardian. Vaccination status and dates were obtained from vaccination cards that were brought to the hospital or, if the vaccine card was unavailable, by visiting the infant's home or the clinic where the infant 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 the oral polio vaccine. Additional doses of rotavirus vaccine were contraindicated if an infant had an episode of intussusception before completion of the vaccine series. For case patients whose intussusception was diagnosed before 8 months of age, efforts were made to recontact their families when the infant reached 8 months of age to determine whether the infant had received any additional doses of rotavirus vaccine or had had a recurrent episode of intussusception and to assess the vital status of the infant.

The authors vouch for the completeness and accuracy of the data and analysis presented. This evaluation was determined to be public health nonresearch 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 resource-efficient and validated self-controlled case-series method was applied to assess intussusception risk after RV1 administration.[8,10,20] This method relies on the identification of intussusception cases and on linking each record with the vaccination status of the patient. Since each case acts as its own control for time-invariant confounders in this method, no external controls or population-level vaccination data were required for the assessment of risk. We used an adaptation of the self-controlled case-series method (the pseudo-likelihood method) that allowed for contraindication of rotavirus vaccination after an episode of intussusception.[21]

Given the findings from previous analyses of RV1 and intussusception, we hypothesized that the risk of intussusception would be highest in the 1 to 7 days after vaccination (with vaccination occurring on day 0), which corresponds to the period during which 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 infants who were 28 to 245 days of age at the time of intussusception onset. To account for the varying underlying age distribution of patients with intussusception, we controlled for age in the model using 14-day age bands. Infants who were not age-eligible for RV1 vaccination (e.g., infants who had been born several months before vaccine introduction) and infants who were age-eligible but did not receive RV1 were also included in the model to provide stability to the underlying age distribution. Relative incidence and confidence intervals were calculated with the use of 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 incidence of 2.5 or more within 1 to 7 days after the first dose of RV1, under the assumption of 70% vaccine coverage and a type 1 alpha level of 0.05. Data were analyzed with the use of Stata software, version 14 (StataCorp), and SAS software, version 9.4 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 1060 infants who were younger than 12 months of age and had intussusception were enrolled in surveillance from 29 sentinel hospitals located in seven countries (Table 1). Of these infants, 239 were excluded from the analysis because they were younger than 28 days of age or older than 245 days of age at the time of intussusception symptom onset, and an additional

Table 1. Rotavirus Vaccine Introduction, Enrollment Periods, and Numbers of Patients with Intussusception Enrolled According to Country, February 2012 through December 2016.

Country	Month and Year of Vaccine Introduction	Enrollment Period	Sentinel Hospitals (N=29)	Patients <12 Mo of Age with Intussusception (N=1060)	Patients 28–245 Days of Age with Intussusception and Confirmed Vaccination (N=717)
			no.	*no. of patients (%)*	
Ethiopia	November 2013	December 2013–December 2016	6	164 (15)	80 (11)
Ghana	April 2012	February 2012–December 2016	2	381 (36)	258 (36)
Kenya	July 2014	October 2014–December 2016	5	135 (13)	97 (14)
Malawi	October 2012	November 2013–November 2016	4	28 (3)	23 (3)
Tanzania	January 2013	January 2013–December 2016	7	201 (19)	144 (20)
Zambia	January 2012*	August 2013–November 2016	4	61 (6)	47 (7)
Zimbabwe	May 2014	August 2014–December 2016	1	90 (8)	68 (9)

* The vaccine was introduced in Lusaka Province as part of a demonstration project in January 2012 and was introduced nationwide in November 2013.

104 infants were excluded because their vaccination status could not be confirmed, which resulted in 717 infants being included in the analysis. Ghana, the first country in the network to introduce the rotavirus vaccine, had the largest number of patients in the analysis (258 infants [36%]).

The median age of the infants included in the analysis was 25 weeks, with few cases of intussusception detected in very young infants 4 to 11 weeks of age (Fig. 1); 61% of the infants (436 of 717) were male. Among the infants for whom information was available, only 2% (10 of 664) had never received any breast milk before the onset of intussusception, 68% (438 of 644) lived in a household in which at least one person was employed, 73% (455 of 627) lived in a household that had electricity at least part of the time, and 80% (522 of 650) lived in a household with a mobile telephone.

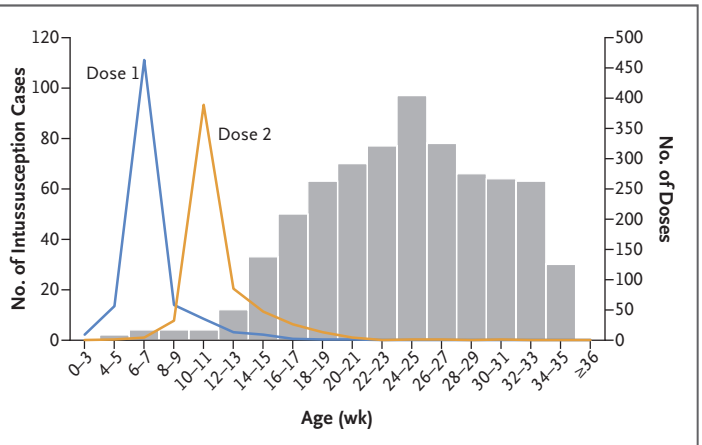

Figure 1. Ages at Immunization and at Onset of Intussusception, February 2012 through December 2016.

Gray bars indicate the numbers of intussusception cases according to age at symptom onset, and the blue and orange lines indicate the numbers of doses of rotavirus vaccine administered according to age at immunization.

CLINICAL FEATURES OF INTUSSUSCEPTION AND VACCINATION COVERAGE

The median duration between symptom onset and admission to a surveillance facility was 3 days (interquartile range, 1 to 4), with 78% of the infants (420 of 537) first seeking care at another facility. The majority of the infants were treated surgically (87% [615 of 704]), with 57% of these infants (353 of 615) undergoing resection of the bowel; 13% (89 of 704) were treated with an enema. Overall, 12% (80 of 681) of the patients with intussusception died.

Vaccination coverage was high, and receipt of the vaccine was timely (Fig. 1). A total of 10% of the patients with intussusception who were in-

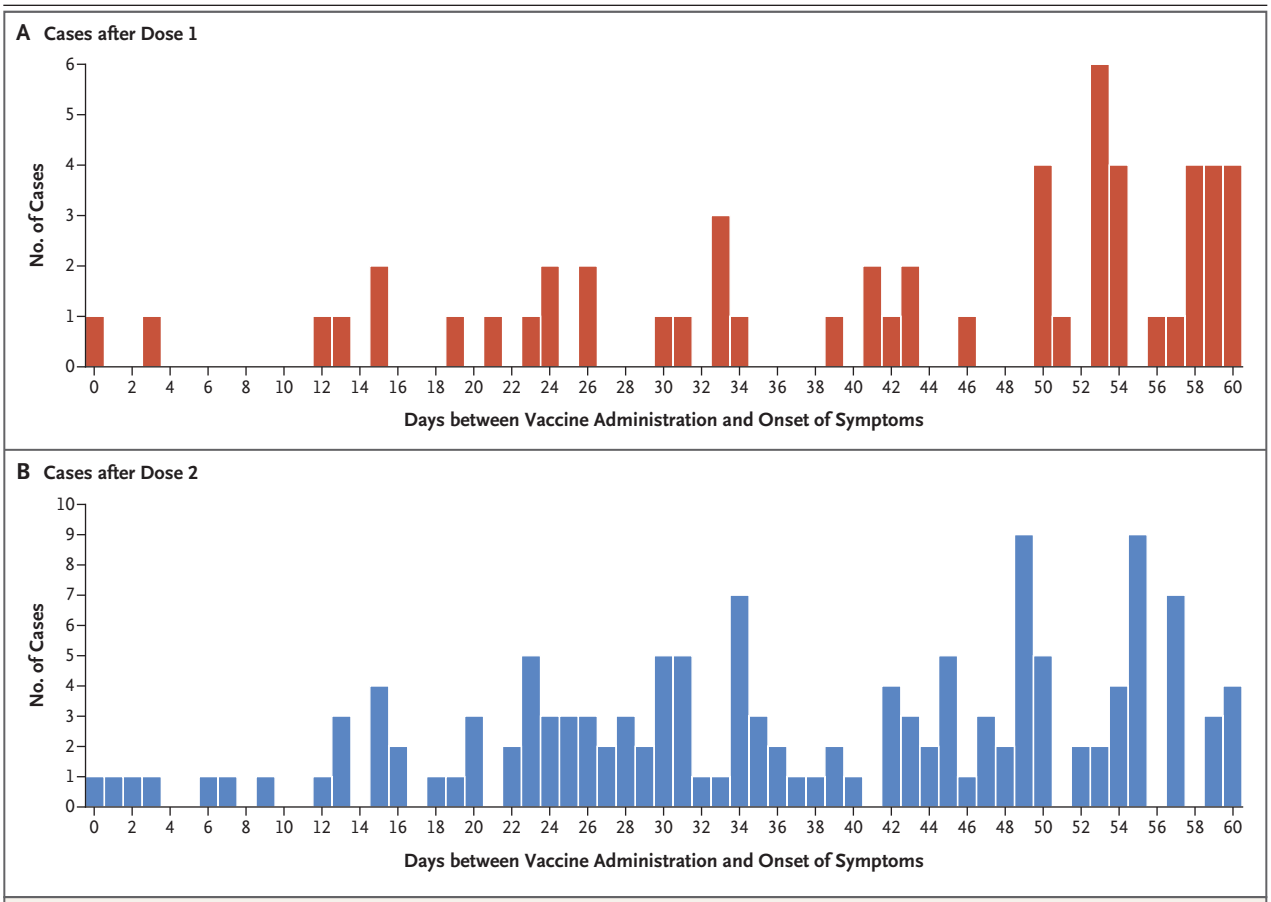

Figure 2. Cases of Intussusception after Dose 1 and Dose 2 of the Rotavirus Vaccine, February 2012 through December 2016.

Shown are the distributions of cases of intussusception during the 60 days after the first and second doses of monovalent rotavirus vaccine. An additional 589 cases occurred more than 60 days after dose 1, and an additional 460 cases occurred more than 60 days after dose 2.

cluded in the analysis were unvaccinated, 6% had received only one dose of RV1, and 84% had received two doses of RV1. The median age at dose 1 was 6 weeks (interquartile range, 6 to 7), and the median age at dose 2 was 11 weeks (interquartile range, 10 to 12). Despite the contraindication, 5 infants received at least one dose of RV1 after intussusception. The families of 445 (70%) of the 637 surviving infants were recontacted when the infants were 8 months of age; 14 infants (3%) had had a second episode of intussusception, and 7 (2%) had died after hospital discharge and before reaching 8 months of age.

EVALUATION OF INTUSSUSCEPTION RISK AFTER VACCINATION

No clustering of cases occurred in any of the risk windows (1 to 7 days, 8 to 21 days, or 1 to 21 days) after receipt of either dose of RV1 (Fig. 2). One case occurred in the 1 to 7 days after dose 1, and 6 cases occurred in the 8 to 21 days after dose 1. Five cases occurred in the 1 to 7 days after dose 2, and 16 occurred in the 8 to 21 days after dose 2 (Table 2). The risk of intussusception in the 1 to 7 days after dose 1 was not higher than the background risk (relative incidence, 0.25; 95% confidence interval [CI], <0.001 to 1.16); findings were similar for the 1 to 7 days after dose 2 (relative incidence, 0.76; 95% CI, 0.16 to 1.87). In addition, the risk of intussusception in the 8 to 21 days or 1 to 21 days after either dose was not higher than the background risk (Table 2).

DISCUSSION

In our study in low- and low-middle-income countries in sub-Saharan Africa, the risk of

Table 2. Relative Incidence of Intussusception in the Risk Periods after the First and Second Doses of Monovalent Rotavirus Vaccine, February 2012 through December 2016.

Dose and Risk Period	No. of Cases	Relative Incidence (95% CI)*
Dose 1		
Days 1–7	1	0.25 (<0.001–1.16)
Days 8–21	6	1.01 (0.26–2.24)
Days 1–21	7	0.85 (0.35–1.73)
Dose 2		
Days 1–7	5	0.76 (0.16–1.87)
Days 8–21	16	0.74 (0.39–1.20)
Days 1–21	21	0.81 (0.49–1.22)

* Relative incidence is a ratio of the incidence within the risk window versus the incidence in all other observation windows for each infant, calculated with the use of conditional Poisson regression.

intussusception in association with RV1 vaccination was not higher than the background risk. This finding contrasts with previous studies in high- and upper-middle-income countries, in which an association with intussusception was found. There are several possible explanations for this difference in risk according to setting. First, although the exact mechanism is not known, intussusception may be 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 than in high- and middle-income countries,[15,17] rotavirus vaccination might also be associated with a lower intussusception risk in low-income countries. Second, rotavirus vaccine is coadministered 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 coadministered.[23] This phenomenon was considered as a potential reason for the absence of an increased risk of intussusception after the first dose of RV1 in Brazil, the other country in which no such association was observed after dose 1.[10] However, in Brazil, a low-level association between RV1 vaccination and intussusception was found after the second dose.[10] Third, the two doses of RV1 were administered at younger ages (6 and 10 weeks) in these low-income African countries than in high- and middle-income countries (generally 2 and 4 months). 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 differ between younger infants and older infants. Finally, other factors that may play a role in the risk of intussusception in younger infants and that differ between these low-income African countries and high- and middle-income countries (e.g., diet, breast-feeding practices, microbiome, or levels of maternal antibodies) might, through unknown mechanisms, also partially account for the differences in the risk of intussusception after RV1 vaccination.

Given the higher background rate of intussusception among older infants, the initial WHO recommendations that were 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 intussusception.[24] However, because of the recognition that many infants 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 in which data on vaccine efficacy from clinical trials and the available data on the risk of intussusception after vaccination from post-licensure evaluations in middle- and high-income countries were analyzed showed that removing these age restrictions would avert 154 deaths from rotavirus infection for every death from vaccine-related intussusception in low-income countries.[25] On the basis of these data, in January 2013, the WHO recommended removal of the age restrictions for rotavirus vaccines in order to improve vaccine coverage. The timely administration of RV1 in these countries that were early adopters of the vaccine, with only 3% of infants receiving RV1 after 15 weeks of age, may mean that the generalizability of our results to countries with substantial delays in vaccine administration is limited. If the dynamics of RV1 replication and immune response differ between older infants and younger infants (e.g., if repli-

cation and immune response are greater in older children), the risk of intussusception may also differ.

Our study had some limitations. First, a lack of suspicion of intussusception and delays in seeking health care could have resulted in some infants dying from intussusception before they reached a surveillance facility. Although this would have reduced the number of cases identified, these delays probably would have been independent of vaccination status and therefore probably would not have biased our results. However, if infants with intussusception who were not brought to a health care facility for treatment were more likely to have been vaccinated late, then our results may not be generalizable to those infants. The age distribution of the patients with intussusception in our study 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, which indicated that we were not selectively missing cases in younger infants during the period when vaccine doses are given. The exact reasons for lower rates of intussusception among younger infants are not well understood, but they may be related to the decline in maternal antibodies to pathogens associated with intussusception or to age-related milestones in the maturation of intestinal lymphoid tissue. If we did selectively miss cases among younger infants, then we may have underestimated the true risk of intussusception after vaccination.

Second, we used the date of the first symptom reported by the parent as the date of intussusception onset, rather than the date of hospital admission, which has been used in many previous analyses. We chose to use the date of symptom onset because there was a median of 3 days between symptom onset and admission to the surveillance facility. We were concerned that if the admission date were used as the marker for the date that intussusception occurred, some infants would be excluded from the 1-to-7-day risk window. When we used the date of hospital admission as the date of onset or a longer risk window for the analysis, we still did not see an increased risk of intussusception.

Third, the infants and their parents or guardians frequently traveled long distances to reach the surveillance facilities, and they often did not have their vaccine cards with them. This necessitated great effort by surveillance staff to find ways to confirm the vaccination status of the enrolled infants. Overall, we were able to confirm the vaccination status of 87% of age-eligible infants, and there was no significant difference in the age distribution between infants for whom we confirmed vaccination status and those for whom we did not.

Finally, the presentation and treatment of intussusception in the countries in this evaluation differ from those observed in other regions of the world in terms of delays in presentation, surgery rates, and mortality.[14] Although a better understanding of these data is important for better treatment and outcomes for patients with intussusception, 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 after rotavirus vaccination. Because intussusception is a rare adverse event and a large sample size is required in order to assess the risk of this condition developing after rotavirus vaccination, such evaluations may not be feasible and practical in all countries in which the rotavirus vaccine is introduced. As this vaccine or other rotavirus vaccines in the pipeline are introduced into other regions, such as Asia, in which 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 for an assessment of the regional benefits and risks associated with rotavirus vaccination. In the 29 African countries that had introduced rotavirus vaccine into their national immunization program by the end of 2014, approximately 135,000 hospitalizations and 21,000 deaths resulting from rotavirus infection were estimated to have been prevented in 2016.[27] Given these large health benefits, the absence of increased risk of intussusception after RV1 administration in our study is reassuring.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC) or the World Health Organization.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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