ORIGINAL ARTICLE

Intussusception after Rotavirus Vaccine Introduction in India

S.N. Reddy, N.P. Nair, J.E. Tate, V. Thiyagarajan, S. Giri, I. Praharaj, V.R. Mohan, S. Babji, M.D. Gupte, R. Arora, S. Bidari, S. Senthamizh, S. Mekala, K.B. Goru, B. Reddy, P. Pamu, R.P. Gorthi, M. Badur, V. Mohan, S. Sathpathy, H. Mohanty, M. Dash, N.K. Mohakud, R.K. Ray, P. Mohanty, G. Gathwala, S. Chawla, M. Gupta, R. Gupta, S. Goyal, P. Sharma, M.A. Mathew, T.J.K. Jacob, B. Sundaram, G.K.C. Purushothaman, P. Dorairaj, M. Jagannatham, K. Murugiah, H. Boopathy, R. Maniam, R. Gurusamy, S. Kumaravel, A. Shenoy, H. Jain, J.K. Goswami, A. Wakhlu, V. Gupta, G. Vinayagamurthy, U.D. Parashar, and G. Kang

ABSTRACT

BACKGROUND

A three-dose, oral rotavirus vaccine (Rotavac) was introduced in the universal immunization program in India in 2016. A prelicensure trial involving 6799 infants was not large enough to detect a small increased risk of intussusception. Postmarketing surveillance data would be useful in assessing whether the risk of intussusception would be similar to the risk seen with different rotavirus vaccines used in other countries.

METHODS

We conducted a multicenter, hospital-based, active surveillance study at 27 hospitals in India. Infants meeting the Brighton level 1 criteria of radiologic or surgical confirmation of intussusception were enrolled, and rotavirus vaccination was ascertained by means of vaccination records. The relative incidence (incidence during the risk window vs. all other times) of intussusception among infants 28 to 365 days of age within risk windows of 1 to 7 days, 8 to 21 days, and 1 to 21 days after vaccination was evaluated by means of a self-controlled case-series analysis. For a subgroup of patients, a matched case–control analysis was performed, with matching for age, sex, and location.

RESULTS

From April 2016 through June 2019, a total of 970 infants with intussusception were enrolled, and 589 infants who were 28 to 365 days of age were included in the self-controlled case-series analysis. The relative incidence of intussusception after the first dose was 0.83 (95% confidence interval [CI], 0.00 to 3.00) in the 1-to-7-day risk window and 0.35 (95% CI, 0.00 to 1.09) in the 8-to-21-day risk window. Similar results were observed after the second dose (relative incidence, 0.86 [95% CI, 0.20 to 2.15] and 1.23 [95% CI, 0.60 to 2.10] in the respective risk windows) and after the third dose (relative incidence, 1.65 [95% CI, 0.82 to 2.64] and 1.08 [95% CI, 0.69 to 1.73], respectively). No increase in intussusception risk was found in the case–control analysis.

CONCLUSIONS

The rotavirus vaccine produced in India that we evaluated was not associated with intussusception in Indian infants. (Funded by the Bill and Melinda Gates Foundation and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Kang at the Division of Gastrointestinal Sciences, Christian Medical College Vellore, Ida Scudder Rd., Vellore, Tamil Nadu 632004, India, or at gkang@cmcvellore.ac.in.

Drs. S.N. Reddy and Nair contributed equally to this article.

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Postlicensure studies of rotavirus vaccines have shown varying risks of intussusception in different settings worldwide. The association of intussusception with rotavirus vaccination was identified in 1998, when RotaShield (Wyeth–Lederle Vaccines), the first licensed rotavirus vaccine, was withdrawn because of an increased risk of intussusception.[1,2] Subsequent, large, prelicensure trials of the second-generation rotavirus vaccines Rotarix (GlaxoSmithKline Biologicals) and RotaTeq (Merck) did not show an increased risk of intussusception in clinical trials involving 65,000 to 70,000 infants.[3,4] However, postmarketing surveillance of Rotarix in Australia, Brazil, England, Mexico, and the United States showed one to six excess cases of intussusception per 100,000 vaccinated children.[5-10] Postmarketing surveillance of RotaTeq in Australia and the United States showed one to seven excess cases of intussusception per 100,000 vaccinated children.[6,10]

Despite the hypothesis that intussusception might be an adverse event associated with all rotavirus vaccines,[11] the World Health Organization (WHO) recommended the introduction of rotavirus vaccine into childhood vaccination programs because the projected incidences of rotavirus infection and deaths due to diarrhea that were averted were greater than the incidence of additional intussusception, resulting in a favorable risk–benefit ratio.[12] Recently, our understanding of the safety of rotavirus vaccination in specific populations was further informed by the finding that in seven low-income African countries and South Africa, where vaccine efficacy has been lower than that in high-income countries, there was no increased risk of intussusception after Rotarix vaccination.[13,14]

The vaccine we studied, Rotavac (Bharat Biotech International), is an oral monovalent, live, attenuated rotavirus vaccine that contains a naturally occurring bovine–human reassortant 116E strain (G9P[11]).[15,16] The vaccine is administered in a three-dose series at 6, 10, and 14 weeks of age, concurrent with other childhood vaccines. It had an efficacy of 56% against severe rotavirus gastroenteritis in a multicenter, phase 3 clinical trial in India and was licensed in 2014.[17] That trial, in which 6799 infants were randomly assigned in a 2:1 ratio to receive vaccine or placebo, was not large enough to detect a small increased risk of intussusception.[17] This vaccine was introduced into the Universal Immunization Programme of India[18] in 4 states in 2016, in 5 additional states in 2017, in 1 additional state in 2018, and in 10 additional states in 2019.[19] More than 100 million doses of vaccine have been administered to Indian infants.

There are limited background data on intussusception in India. Two studies have shown a general incidence of 18 intussusception cases per 100,000 infants and 20 cases per 100,000 infants.[20,21] The Indian National Technical Advisory Group on Immunization and the WHO recommended the monitoring of vaccine safety after the introduction of the vaccine into the immunization program[22]; in response to this recommendation, we established the Indian Intussusception Surveillance Network.[23] Because the vaccine on which we now report has been prequalified by the WHO, safety data are important for India, for the Gavi Alliance, and for countries considering the introduction of rotavirus vaccines.

METHODS

STUDY SITES

Active surveillance for intussusception was conducted at 27 participating hospitals (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) that could carry out sentinel surveillance (called sentinel hospitals here) in 10 states in India in which half the population of India resides. Surveillance started in 4 states in April 2016 and was expanded concurrently with vaccine introduction. Detailed information about the methods is provided in the protocol, which has been published previously[23] and is available at NEJM.org.

All the infants who were younger than 2 years of age and who met level 1 diagnostic certainty for intussusception according to the Brighton Collaboration criteria were eligible for recruitment as study participants. Level 1 criteria of the Brighton Collaboration require the confirmation of intussusception by radiologic findings (specifically, if the intussusception was reduced by pneumatic or hydrostatic methods or by contrast enema) or during surgery or at autopsy (Table S2).[24] Surveillance staff completed paper case-report forms with information about patients' sociodemographic and clinical characteristics, treatment, and outcomes and obtained copies of ultrasonographic images and reports and treatment notes. Information about rotavirus vaccination status and a copy of the vaccination record

were obtained from the parents or guardians, and the dates of the first, second, and third vaccinations were recorded. For children who were unvaccinated or partially vaccinated, we contacted the child's health subcenter or primary health center to verify vaccination status.

We performed a matched case–control analysis that included a subgroup of patients with intussusception (case patients) and control infants, who were matched for age (date of birth within a window of ±30 days), sex, and location (same state of residence) and who had been admitted with illness unrelated to the gastrointestinal tract within 30 days before or after the admission of the matched case patient. Copies of the vaccination card and vaccination information were obtained for control infants as they were for the case patients. All case-report forms were sent to the central data management team at Christian Medical College Vellore and entered into an audit trail–enabled SQL database, in which data cleaning and query resolution from sites were managed and validated against documents for 10% of all the case-report forms.

STUDY OVERSIGHT

This study was approved by the institutional review board of Christian Medical College Vellore and by the institutional ethics committees of all the participating hospitals. Written informed consent was obtained from the parents or guardians of all enrolled infants and control participants.

Three authors designed the study, two authors led the data acquisition with all the investigators and wrote the first draft of the manuscript, and four authors analyzed the data. The last author, who made the decision to submit the manuscript for publication, vouches for the accuracy of the data and for the fidelity of the study to the protocol.

STATISTICAL ANALYSIS

We calculated that 160 case patients would need to be enrolled[25] for the study to have 80% power to detect a relative incidence of 2, within a 21-day risk window after the administration of any dose of vaccine, at a 5% level of significance; to detect a relative incidence of 2 after the first dose, the sample size was increased to 263 case patients.[25] We used the self-controlled case-series method to assess the risk of intussusception after vaccine administration. We used conditional Poisson regression analysis to calculate the relative incidence by comparing the incidence in the risk windows (i.e., 1 to 7 days, 8 to 21 days, and 1 to 21 days after each dose of vaccine) with the incidence in all other observational periods (non–risk periods) for each case patient, as required for self-controlled case-series analysis.[23,26,27] We used the pseudolikelihood method[27] to allow the contraindication of vaccination after an episode of intussusception, and event ascertainment was independent of vaccination status.

Considering the minimum and maximum ages at which rotavirus vaccine was administered, we restricted the analysis to children who were 28 to 365 days of age at the time of symptom onset. Children with a recurrent episode of intussusception were excluded from the study. Children with a verified vaccination history were included in the self-controlled case-series analysis, and children for whom vaccination history was based only on report from a parent or guardian or who had received a different rotavirus vaccine were excluded. Unvaccinated children were included in the analysis in order to adjust for the background incidence of intussusception according to age. Age was controlled in the model with the use of 14-day windows. The confidence interval estimates were derived by means of bootstrapping with 1000 iterations.

For all the children, we attempted follow-up at approximately 18 months of age. During follow-up, data were obtained regarding the vital status of the child (alive or dead), the incidence of repeat intussusception, and the receipt of additional doses of rotavirus vaccine after the intussusception.

The matched case–control analysis involved a subgroup of infants with intussusception from the self-controlled case-series analysis for whom matched control participants were enrolled. Rotavirus vaccination status with confirmed vaccination was needed for both the case patient and the matched control in order for the pair to be included. We used conditional logistic regression to assess the ratio of the odds that case patients and controls who were matched for age, sex, and location were vaccinated during the same risk window. A reference date was created for controls, which was the date on which the control participant was the same age as the re-

spective case patient at the time of symptom onset. Exposure to the vaccine with the first, second, or third dose in the risk windows of 1 to 7 days, 8 to 21 days, and 1 to 21 days before the reference date was determined. The matched odds ratios are reported as point estimates with 95% confidence intervals.

In sensitivity analyses for both the self-controlled case-series analysis and the matched case–control analysis, we used the date of admission instead of the date of symptom onset. All the statistical analyses were performed with the use of Stata software, version 13.1 (StataCorp).

RESULTS

CHARACTERISTICS AND CLINICAL FEATURES OF THE PATIENTS

A total of 970 children younger than 2 years of age with intussusception meeting the Brighton level 1 case definition were enrolled (Table S1). Of these, 258 children were excluded from the analysis because they were younger than 28 days of age or older than 365 days of age. Of the 712 children who were 28 to 365 days of age, 46 did not have a copy of the vaccination card and 40 had received a vaccine other than the one under study. Rotavirus vaccination status could not be verified by the health subcenter or primary health center for 37 children. Thus, 589 children with intussusception were included in the self-controlled case-series analysis (Fig. S1).

The median age of these 589 patients was 7 months (interquartile range, 5 to 9). Intussusception was more common among male infants than among female infants (ratio, 2:1). Blood in stools and vomiting were the most common symptoms (in 481 patients [82%] and 438 patients [74%], respectively). Other than constipation and blood in stools, there were no significant differences between vaccinated children and unvaccinated children. Ileocolic intussusception, which was seen in 498 children (85%), was the most common type of intussusception; ileoileal intussusception was observed in 33 children (6%). The treatment methods were hydrostatic or pneumatic reduction (in 200 children [34%]), surgical reduction (in 321 [54%]), and intestinal resection (in 68 [12%]). There were six deaths; the case fatality rate was 1%. (Details are provided in Tables S3 and S4.)

VACCINE COVERAGE AND VACCINATION TIMING

Among these 589 children, 289 (49%) had received all three doses of vaccine, 55 (9%) had received two doses, and 33 (6%) had received one dose; 212 children (36%) had not received any dose of vaccine. The median ages of the patients at the administration of the first, second, and third doses were, respectively, 8 weeks (interquartile range, 7 to 9), 13 weeks (interquartile range, 12 to 14), and 18 weeks (interquartile range, 16 to 20). Of the 377 children who had received the first dose of rotavirus vaccine, 330 (88%) had also received oral polio vaccine on the same day. Of the 344 and 289 children who had received the second and third doses of rotavirus vaccine, 300 (87%) and 240 (83%), respectively, had also received the second and third doses of oral polio vaccine on the same day. The third dose of vaccine is scheduled to be administered at 14 weeks of age, but children presented at a median age of 18 weeks, which overlapped with the peak age of intussusception (Fig. 1).

FOLLOW-UP IN THE SELF-CONTROLLED CASE-SERIES ANALYSIS

We were able to recontact 455 of the 589 children at a median age of 16 months (interquartile range, 13 to 22). Of those 455 children, 8 (2%) had a repeat episode of intussusception, and 7 (2%) died after hospital discharge. The deaths occurred between 4 months and 15 months after discharge; none of the deaths were due to intussusception. Although further doses of the vaccine are contraindicated after intussusception by the manufacturer, parents or guardians reported that 22 of 300 children (7%) who had not completed their rotavirus immunization series had received at least one dose of rotavirus vaccine after intussusception (Table S5).

RISK OF INTUSSUSCEPTION AFTER VACCINATION

Self-Controlled Case-Series Analysis

After the first dose of vaccine, 2 cases of intussusception occurred in the risk window of 1 to 7 days after receipt of the vaccine and 2 cases in the risk window of 8 to 21 days. After the second dose of vaccine, 4 cases of intussusception occurred in the risk window of 1 to 7 days and 15 cases in the risk window of 8 to 21 days. After the third dose of vaccine, 15 cases occurred in the risk window of 1 to 7 days and 22

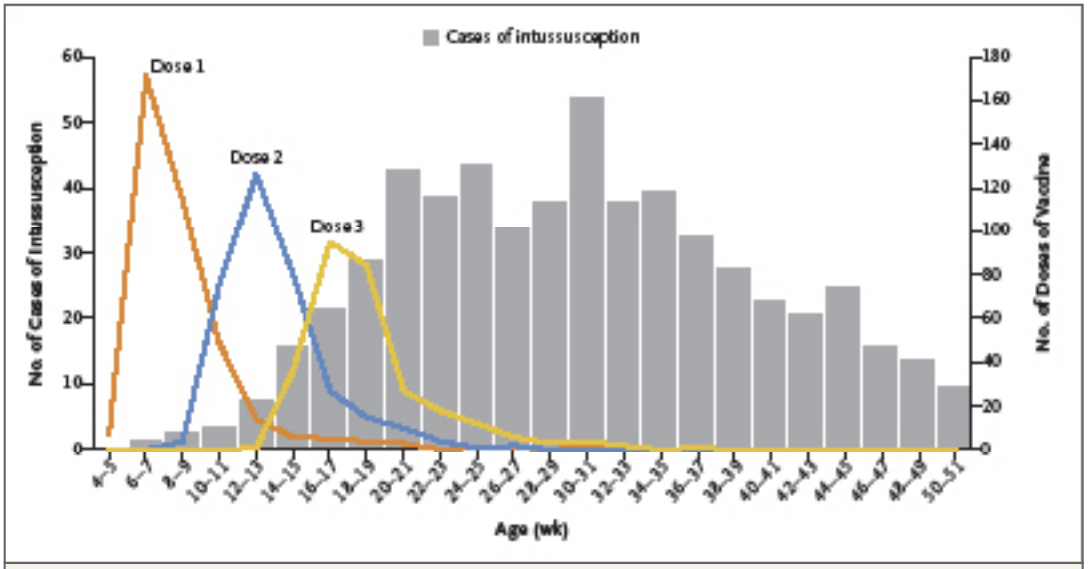

Figure 1. Age at Immunization and at Onset of Intussusception, April 2016 through June 2019.

Gray bars indicate the numbers of intussusception cases according to the age at symptom onset in the infants who were included in the self-controlled case-series analysis. Colored lines indicate the specified doses of rotavirus vaccine administered, according to the infants' age at immunization. Data are from 27 hospitals in 10 states in India.

cases in the risk window of 8 to 21 days (Fig. 2). The risk of intussusception in the 1-to-7-day window (relative incidence, 0.83; 95% confidence interval [CI], 0.00 to 3.00) and in the 8-to-21-day window (relative incidence, 0.35; 95% CI, 0.00 to 1.09) after receipt of the first dose was not higher than the background risk. The risk of intussusception in the 1-to-7-day and 8-to-21-day windows after the second and third doses and the risk in the 1-to-21-day window after any dose were also not higher than the background risk (Table 1).

Matched Case–Control Analysis

The case–control analysis included 162 patients with intussusception who were matched for age, sex, and location with control participants who had a recorded vaccination history (Fig. S2). The odds of intussusception in the 1-to-7-day risk window (matched odds ratio, 1.00; 95% CI, 0.12 to 78.49) and in the 8-to-21-day risk window (matched odds ratio, 0.00; 95% CI, 0.00 to 1.51) after the first dose did not differ significantly among case patients and control participants. Similarly, the odds of intussusception in the 1-to-7-day and the 8-to-21-day windows after the second and third doses, or in the 1-to-21-day window after any dose, did not differ significantly among case patients and control participants (Table 2).

In analyses that used the date of admission instead of the date of symptom onset, the odds ratios did not differ significantly in all the risk windows in both the self-controlled case-series analysis and the matched case-control analysis (Tables S6 and S7). Similar risk estimates were also obtained with the self-controlled case-series analysis that was restricted to include only the 162 infants with intussusception who were included in the matched case–control analysis (Table S8).

DISCUSSION

An increased risk of intussusception was not detected in any risk window after the receipt of any dose of the rotavirus vaccine under study (Rotavac) among children in India in either the self-controlled case-series analysis or the case–control analysis. The results of our postmarketing, active surveillance study provide evidence that there was no adverse safety signal associated with this vaccine in the Indian population.

Our findings differ from those of postlicensure studies of Rotarix or RotaTeq in high-income and middle-income countries that showed a low-

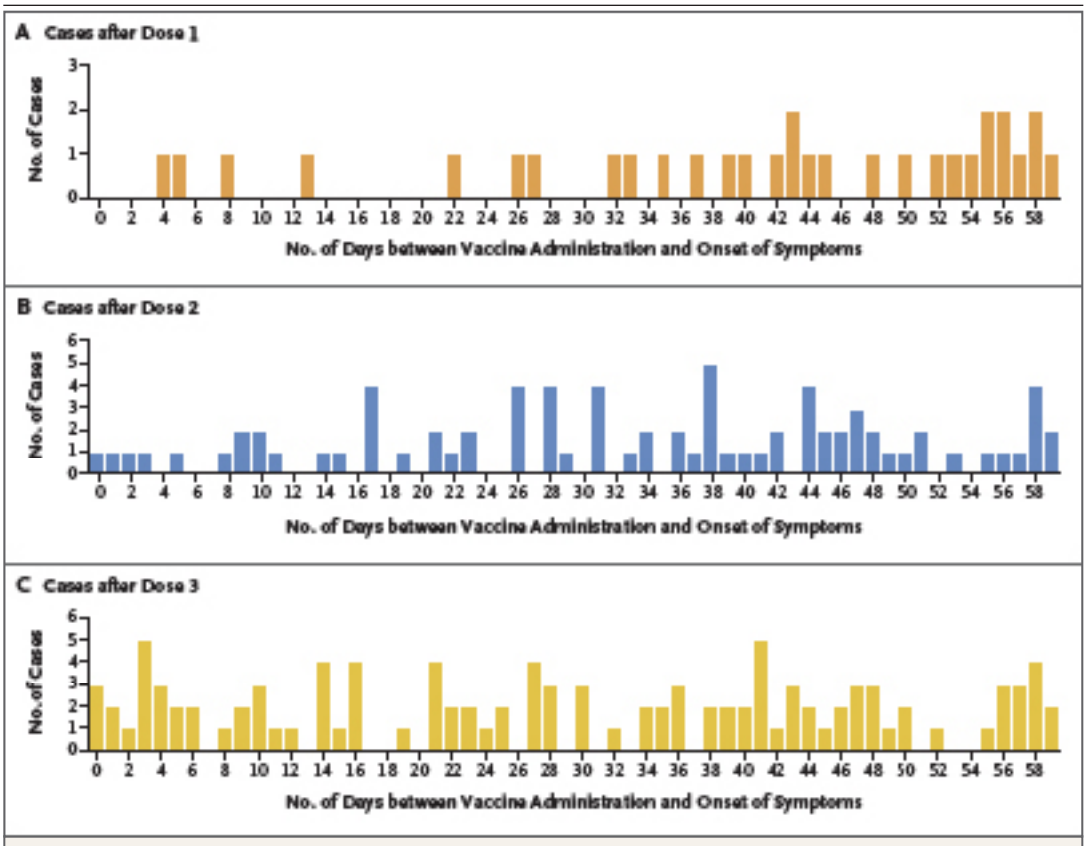

Figure 2. Cases of Intussusception after Rotavirus Vaccine Dose Administration, April 2016 through June 2019.

Shown are the distributions of cases of intussusception during the 59 days after the administration of the first, second, and third doses of rotavirus vaccine. An additional 345 cases occurred more than 59 days after the first dose, an additional 265 cases occurred more than 59 days after the second dose, and an additional 181 cases occurred more than 59 days after the third dose.

level risk of intussusception after rotavirus vaccination. Studies from Australia, England, Mexico, Singapore, and the United States showed an increase in the risk of intussusception by a factor of 2.6 to 8.4 in the 21 days after any dose of Rotarix vaccination.[6-10,28] Studies from Australia and the United States have shown that RotaTeq vaccination was associated with an increase in the risk of intussusception by a factor of 2.6 to 9 in the 21 days after vaccination.[6,10] Conversely, our findings appear to be similar to reports from sub-Saharan Africa and South Africa that did not show an increased risk of intussusception after the administration of a different rotavirus vaccine (Fig. 3).[13,14]

There are no defined criteria on which the risk of intussusception among individual children or in populations can be predicted, although the wide variation in background rates of intussusception indicate that there may be population-based predictors.[29] The earlier ages at which rotavirus vaccines are administered in low-income settings (at 6, 10, and 14 weeks), in contrast to the ages of vaccination in high-income countries (at 2, 4, and 6 months), may be one reason for this lack of association. In addition, the coadministration of rotavirus vaccine with oral poliovirus vaccine may decrease vaccine rotavirus replication in the intestinal epithelium,[30] thus reducing the likelihood of triggering an intussusception. In Brazil, no increased risk of intussusception was found after the administration of the first dose of Rotarix vaccine, a situation in which the rotavirus vaccine was coadministered with oral polio vaccine.[5] In our study, 88%, 87%, and 83% of the infants received the first, second, and third doses, respectively, of rotavirus vaccine and oral polio vaccine on the same day,

Table 1. Relative Incidence of Intussusception in Risk Windows after the First, Second, and Third Doses of Rotavirus Vaccine.*

Dose and Risk Window	No. of Cases	Relative Incidence (95% CI)
Dose 1		
Days 1–7	2	0.83 (0.00–3.00)
Days 8–21	2	0.35 (0.00–1.09)
Days 1–21	4	0.52 (0.08–1.27)
Dose 2		
Days 1–7	4	0.86 (0.20–2.15)
Days 8–21	15	1.23 (0.60–2.10)
Days 1–21	19	1.13 (0.61–1.94)
Dose 3		
Days 1–7	15	1.65 (0.82–2.64)
Days 8–21	22	1.08 (0.69–1.73)
Days 1–21	37	1.24 (0.81–1.82)

* Shown is the relative incidence of intussusception in the risk windows after the first, second, and third doses of Rotavac vaccine in 589 Indian infants who were 28 to 365 days of age and who had a confirmed history of having received or not received rotavirus vaccination. Relative incidence was calculated by the self-controlled case-series method. Of the 589 children included in the analysis, 377 (64%) had been vaccinated with one or more doses, and 212 (36%) had not received any dose of the rotavirus vaccine under study. The date of intussusception was defined as the date of symptom onset.

Table 2. Matched Odds of Intussusception in Risk Windows after Rotavirus Vaccination in Case–Control Pairs of Indian Infants.*

Dose and Risk Window	No. of Cases	No. of Controls	Matched Odds Ratio (95% CI)
Dose 1			
1–7 days	1	1	1.00 (0.12–78.49)
8–21 days	1	5	0.00 (0.00–1.51)
1–21 days	2	6	0.00 (0.00–1.51)
Dose 2			
1–7 days	1	1	1.00 (0.01–78.49)
8–21 days	3	3	1.00 (0.07–13.79)
1–21 days	4	4	1.00 (0.13–7.46)
Dose 3			
1–7 days	6	3	2.50 (0.41–26.25)
8–21 days	7	7	1.00 (0.26–3.74)
1–21 days	13	10	1.40 (0.49–4.42)

* Shown are the matched odds of intussusception in the risk windows after the first, second, and third doses of rotavirus vaccine in 162 case–control pairs of Indian infants. The infants were matched for age, sex, and location and had a confirmed rotavirus vaccination history with the vaccine under study. The date of intussusception onset was defined as the date of symptom onset.

and no increased risk of intussusception was found after any dose.

The safety findings regarding the two different rotavirus vaccines in Africa[13,14] and India (the current study) are interesting in the context of reduced vaccine performance in these geographic settings. The immunogenicity and efficacy of oral vaccines, including rotavirus vaccines, are lower in low-resource communities than in high-income countries.[30,31] Factors, such as inhibition by higher levels of maternal antibodies in serum or breast milk and the coadministration of oral polio vaccine, that lower the effective titers of vaccine virus, thus reducing vaccine virus replication and hence immunogenicity, might also lower the risk of intussusception. Other factors, such as micronutrient deficiencies, malnutrition, environmental enteropathy, and early and constant exposure to other gut pathogens, are also proposed to affect mucosal and systemic responses to vaccination[30-32] and could be responsible for the lower background and vaccine-associated intussusception rates in low-resource settings.

Our large, active surveillance study of intussusception, with high-quality countrywide data on intussusception and its management and consequences, including a case fatality rate, adds safety data to the literature on a relatively new vaccine that has been prequalified by the WHO. Death occurred in 1% of the Indian infants who were hospitalized with intussusception, whereas in a similar study in Africa, 12% of the children with intussusception died.[13]

Our study has certain limitations, which include the exclusion of 12% of eligible infants who had inconclusive evidence of vaccination, an inability of the study to assess an association between intussusception and nutritional status, and a lack of estimates of community-based incidence and case fatality rates. However, background rates of intussusception are not needed for a self-controlled case-series analysis because case patients act as their own control and were identified independent of their vaccination status. Given the large sample size, the study was adequately powered to detect small increases in risk in a 1-week or 3-week window after vaccination and showed none. A limitation of the case–control analysis is the relatively smaller size, because

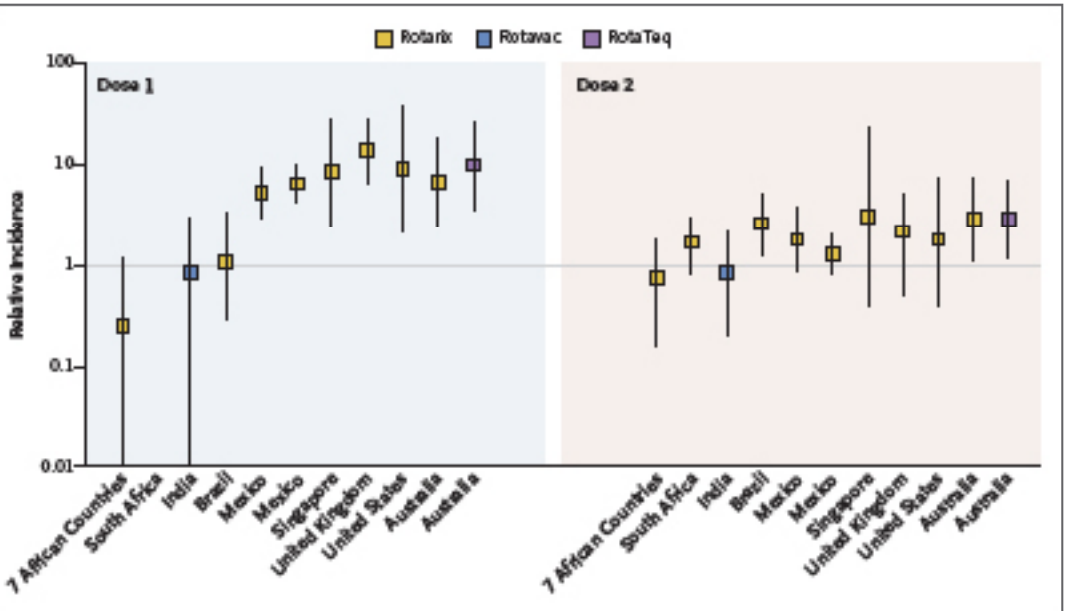

Figure 3. Relative Incidence Estimates of Intussusception after Two Doses of Licensed Rotavirus Vaccine, According to Country.

The relative incidence estimates were calculated by means of self-controlled case-series analyses. Errors bars indicate 95% confidence intervals. Data from studies outside India are from previous studies.[13,14] The seven countries in Africa were Ethiopia, Ghana, Kenya, Malawi, Tanzania, Zambia, and Zimbabwe. In South Africa, there were no cases of intussusception in the 1-to-7-day risk window after the administration of the first dose.

control participants were enrolled for only a subgroup of case patients, and the analysis was adjusted for sex but not for other potential confounders. Nonetheless, the risk estimates from the self-controlled case-series analysis and the case–control analysis were similar except for the wider confidence intervals in the case–control analysis.

In this postmarketing, active surveillance study, we found that Rotavac, an oral rotavirus vaccine produced in India, was not associated with intussusception in the population studied.

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

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No potential conflict of interest relevant to this article was reported.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' full names and academic degrees are as follows: Samarasimha N. Reddy, M.D., Nayana P. Nair, M.Sc., Jacqueline E. Tate, Ph.D., Varunkumar Thiyagarajan, M.Sc., Sidhartha Giri, M.D., Ph.D., Ira Praharaj, M.D., Ph.D., Venkata R. Mohan, M.D., Sudhir Babji, M.D., Mohan D. Gupte, M.D., Rashmi Arora, M.D., Sunita Bidari, D.N.B., Sowmiya Senthamizh, M.P.H., Suhasini Mekala, M.D., Krishna B. Goru, M.D., Bhaskar Reddy, M.Ch., Padmalatha Pamu, M.D., Rajendra P. Gorthi, M.Ch., Manohar Badur, M.D., Vittal Mohan, M.Ch., Saroj Sathpathy, M.D., Hiranya Mohanty, M.Ch., Mrutunjay Dash, M.D., Nirmal K. Mohakud, M.D., Rajib K. Ray, M.D., Prasantajyoti Mohanty, B.D.S., Geeta Gathwala, M.D., Suraj Chawla, M.D., Madhu Gupta, M.D., Ph.D., Rajkumar Gupta, M.D., Suresh Goyal, M.D., Pramod Sharma, M.D., Mannancheril A. Mathew, M.D., Tarun J.K. Jacob, M.Ch., Balasubramanian Sundaram, M.D., Girish K.C. Purushothaman, Ph.D., Priyadarishini Dorairaj, M.D., Muthukumaran Jagannatham, M.Ch., Kulandaivel Murugiah, M.D., Hemanthkumar Boopathy, M.Ch., Raghul Maniam, M.Ch., Rajamani Gurusamy, M.Ch., Sambandan Kumaravel, M.Ch., Ashwitha Shenoy, M.Ch., Hemant Jain, M.D., Jayanta K. Goswami, M.D., Ashish Wakhlu, M.Ch., Vineeta Gupta, M.D., Gopinath Vinayagamurthy, M.Ch., Umesh D. Parashar, M.B., B.S., M.P.H., and Prof. Gagandeep Kang, M.D., Ph.D.

The authors' affiliations are as follows: the Wellcome Trust Research Laboratory, Division of Gastrointestinal Sciences (S.N.R., N.P.N., V.T., S. Giri, I.P., S. Babji, S. Bidari, S. Senthamizh, G.K.), and the Department of Community Health (V.R.M.), Christian Medical College Vellore (T.J.K.J.), and Government Vellore Medical College (G.V.), Vellore, Kanchi Kamakoti Child Trust Hospital (B.S.), the National Institute of Epidemiology (G.K.C.P.), and the Institute of Child Health (P.D., M.J.), Chennai, Government Rajaji Hospital and Madurai Medical College, Madurai (K.M., H.B.), Coimbatore Medical College, Coimbatore (R.M., R. Gurusamy), the Indian Council of Medical Research, New Delhi (S. Giri, I.P., M.D.G.), Translational Health Science and Technology Institute, Faridabad (R.A., G.K.), Kurnool Medical College and Government General Hospital, Kurnool (S.M.), Government General Hospital and Rangaraya Medical College, Kakinada (K.B.G., B.R.), King George Hospital and Andhra Medical College, Visakhapatnam (P.P., R.P.G.), Sri Venkateshwara Medical College, Tirupati (M.B., V.M.), Sardar Valla Bhai Patel Post Graduate Institute of Paediatrics, Cuttack (S. Sathpathy, H.M.), the Institute of Medical Sciences and SUM Hospital, Bhubaneswar (M.D.), Kalinga Institute of Medical Sciences (N.K.M.) and Hi-Tech Hospital (R.K.R., P.M.), Bhubaneswar, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak (G.G.), Shaheed Hasan Khan Mewati Government Medical College, Mewat (S.C.), Post Graduate Institute of Medical Education and Research, Chandigarh (M.G.), Sawai Man Singh Medical College, Jaipur (R. Gupta), Rabindranath Tagore Medical College, Udaipur (S. Goyal), Dr. Sampurnanand Medical College, Jodhpur (P.S.), Malankara Orthodox Syrian Church Medical College Hospital, Kolencherry (M.A.M.), Jawaharlal Nehru Institute of Post-graduate Medical Education and Research, Puducherry (S.K., A.S.), Mahatma Gandhi Memorial Medical College, Indore (H.J.), the Government Medical College, Guwahati, Assam (J.K.G.), King George Medical College, Lucknow (A.W.), and the Institute of Medical Sciences, Banaras Hindu University, Varanasi (V.G.) — all in India; and the Centers for Disease Control and Prevention, Atlanta (J.E.T., U.D.P.).

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