Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants

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ABSTRACT

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Drs. Madhi and Cunliffe contributed equally to this article.


BACKGROUND

Rotavirus is the most common cause of severe gastroenteritis among young children worldwide. Data are needed to assess the efficacy of the rotavirus vaccine in African children.

METHODS

We conducted a randomized, placebo-controlled, multicenter trial in South Africa (3166 infants; 64.1% of the total) and Malawi (1773 infants; 35.9% of the total) to evaluate the efficacy of a live, oral rotavirus vaccine in preventing severe rotavirus gastroenteritis. Healthy infants were randomly assigned in a 1:1:1 ratio to receive two doses of vaccine (in addition to one dose of placebo) or three doses of vaccine — the pooled vaccine group — or three doses of placebo at 6, 10, and 14 weeks of age. Episodes of gastroenteritis caused by wild-type rotavirus during the first year of life were assessed through active follow-up surveillance and were graded with the use of the Vesikari scale.

RESULTS

A total of 4939 infants were enrolled and randomly assigned to one of the three groups; 1647 infants received two doses of the vaccine, 1651 infants received three doses of the vaccine, and 1641 received placebo. Of the 4417 infants included in the per-protocol efficacy analysis, severe rotavirus gastroenteritis occurred in 4.9% of the infants in the placebo group and in 1.9% of those in the pooled vaccine group (vaccine efficacy, 61.2%; 95% confidence interval, 44.0 to 73.2). Vaccine efficacy was lower in Malawi than in South Africa (49.4% vs. 76.9%); however, the number of episodes of severe rotavirus gastroenteritis that were prevented was greater in Malawi than in South Africa (6.7 vs. 4.2 cases prevented per 100 infants vaccinated per year). Efficacy against all-cause severe gastroenteritis was 30.2%. At least one serious adverse event was reported in 9.7% of the infants in the pooled vaccine group and in 11.5% of the infants in the placebo group.

CONCLUSIONS

Human rotavirus vaccine significantly reduced the incidence of severe rotavirus gastroenteritis among African infants during the first year of life. (ClinicalTrials.gov number, NCT00241644.)
Rotavirus is the most important cause of severe gastroenteritis among children worldwide. The World Health Organization (WHO) estimates that globally 527,000 deaths occur each year among children as a result of rotavirus infection; more than 230,000 of the deaths occur in sub-Saharan Africa. Six of the seven countries with the highest mortality due to deaths occur in sub-Saharan Africa. Six of the children against severe rotavirus gastroenteritis. Rotarix, an attenuated human rotavirus vaccine we conducted a clinical trial to determine whether vaccinations in Africa and Asia before the recommend- cacy trials be conducted in representative popula- tions in Africa and Asia before the recommenda- tion is extended. In response to this mandate, we conducted a clinical trial to determine whether Rotarix, an attenuated human rotavirus vaccine containing a G1P[8] strain, could protect African children against severe rotavirus gastroenteritis.

Methods

Study Design and Participants
We conducted a double-blind, randomized, placebo-controlled multicenter study in South Africa and Malawi to assess the efficacy, safety, and immunogenicity of Rotarix. A placebo-controlled design was chosen because the vaccine was not licensed or available in these countries at the time the study was initiated, and data were needed to inform policy decisions in low-resource countries. Children who were infected with human immunodeficiency virus (HIV) and children who had been exposed to HIV were included in the trial on the basis of the absence of serious immunosuppression in infants at the age at which these vaccines are first given (6 weeks), the experience with other live vaccines in HIV-infected children, and the need to inform decisions on the introduction of vaccine in settings with high prevalences of HIV. The study protocol and the informed consent form were approved by the ethics committee at the WHO and by the ethics committees at all study centers. The trial was conducted in accordance with Good Clinical Practice guidelines. The parents or legal representatives of the infants participating in the study provided written informed consent before the initiation of any study-related procedures. All the investigators shared responsibility for the design of the study and the accrual and analysis of the data. All the authors participated in the preparation of the manuscript and made the decision to submit the manuscript for publication.

In South Africa, healthy infants, 5 to 10 weeks of age, were enrolled from October 2005 through January 2006 and from November 2006 through early February 2007, before the anticipated rotavirus seasons of 2006 and 2007, respectively. Since rotavirus is known to circulate year-round in Malawi, infants in Malawi were enrolled from October 2006 through July 2007.

Infants were randomly assigned individually, in a 1:1:1 ratio, into three groups to receive two doses of the rotavirus vaccine at 10 and 14 weeks of age; three doses of the vaccine at 6, 10, and 14 weeks of age; or three doses of placebo. Infants in the two-dose vaccine group received a dose of placebo at 6 weeks of age. Vaccines that are administered routinely according to the guidelines of the Expanded Program on Immunization (EPI) were concomitantly administered with the vaccine or placebo. No restrictions were imposed on the breast-feeding of infants around the time of vaccination.

Testing for HIV
The parents or legal representatives of the infants were given the opportunity to have the infants...
tested for HIV at the time the first dose of vaccine or placebo was administered or 1 month after the last dose, and testing was performed when consent was given. Detailed information regarding the testing and treatment of infants is included in the Supplementary Appendix, available with the full text of this article at NEJM.org.

VACCINE
The study vaccine, the calcium carbonate buffer, and the placebo were developed and manufactured by GlaxoSmithKline Biologicals. The composition of the vaccine was the same as the commercial formulation, and the placebo was the same formulation without the viral antigen.11

ANALYSIS OF STOOL SAMPLES DURING EPISODES OF GASTROENTERITIS
An episode of gastroenteritis was identified by the occurrence of diarrhea, whether or not it was accompanied by vomiting; diarrhea was defined as the passage of three or more stools that were looser than normal within a 24-hour period. Stool samples were collected during each episode of gastroenteritis that occurred between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. Stool samples were tested for rotavirus with the use of an enzyme-linked immunosorbent assay (ELISA) (Rotaclone, Meridian Bioscience). All stool samples that were positive for rotavirus were examined further with the use of a reverse-transcriptase–polymerase-chain-reaction (PCR) assay, followed by a reverse hybridization assay to determine the G and P types.12

ASSESSMENT OF VACCINE EFFICACY
The efficacy of the vaccine was assessed during the period from 2 weeks after the last dose of vaccine or placebo was administered until the child reached 1 year of age. Active surveillance for all gastroenteritis episodes was conducted by members of the study staff through weekly visits to parents or guardians to collect diary cards and through the collection of data from health clinics that served the study populations. The severity of each episode of gastroenteritis was evaluated with the use of the Vesikari scale13 (on which scores range from 1 to 20, with higher scores indicating greater severity) and was categorized as severe if the score was 11 or more.

ASSESSMENT OF SAFETY
All serious adverse events including deaths were recorded for the period between the date the first dose of vaccine or placebo was administered and the date the child reached 1 year of age. The site investigator, who was unaware of the group assignments of the children, determined whether the serious adverse events appeared to have any causal association with vaccination.

ASSESSMENT OF IMMUNOGENICITY
Blood samples were collected from approximately 10% of the infants immediately before the first dose of vaccine or placebo was administered and from all infants 1 month after the last dose to determine the serum concentrations of antirotavirus IgA antibody. The blood samples were analyzed with the use of an ELISA (GlaxoSmithKline Biologicals), with the assay cutoff point set at 20 U per milliliter.14

STATISTICAL ANALYSIS
The primary study analysis compared findings from the pooled vaccine group with those from the placebo group. The secondary end points were the efficacy of each vaccine dose (i.e., the two-dose vaccine and the three-dose vaccine) as compared with placebo. A supplementary analysis was performed to evaluate the efficacy, immunogenicity, and safety of the vaccine according to country.

Infants who had received the complete vaccination course and had entered the efficacy surveillance period, which began 2 weeks after the last dose, were included in the prespecified primary efficacy analysis (per-protocol efficacy cohort). Infants in the pooled vaccine and placebo groups who had at least one episode of severe rotavirus gastroenteritis caused by wild-type rotavirus strains during the period from 2 weeks after the last dose was administered until the infants reached 1 year of age were considered as having achieved the primary outcome. The efficacy analysis was also performed on data from the total cohort, which included infants who received at least one dose of vaccine or placebo. The safety analysis was performed on data from the total cohort. The immunogenicity analysis was performed on data from infants in the per-protocol efficacy cohort for whom immunogenicity data were available. The method used to calculate...
the sample size and specific information about the statistical analysis are shown in the Supplementary Appendix.

**RESULTS**

**STUDY POPULATION**

A total of 4939 infants were enrolled and randomly assigned to one of three groups (Fig. 1); 1647 infants were assigned to the two-dose group, 1651 to the three-dose group (for a total of 3298 in pooled vaccine group), and 1641 to the placebo group. A total of 4417 infants were included in the primary efficacy analysis — 2974 in the pooled vaccine group and 1443 in the placebo group. The reasons for withdrawal from the study are listed in Figure 1. The demographic characteristics of the infants and the proportion of children who were infected with HIV were similar across the study groups. Almost all infants (≥99%) received oral poliovirus vaccine concomitantly with each dose of rotavirus vaccine or placebo (Table 1 in the Supplementary Appendix).

![Figure 1. Study Assignment and Follow-up.](image-url)
Efficacy
Severe gastroenteritis caused by circulating rotavirus was detected in 70 of 1443 infants in the placebo group (4.9%) as compared with 56 of 2974 infants in the pooled vaccine group (1.9%), resulting in a vaccine efficacy against the primary outcome of severe rotavirus gastroenteritis of 61.2% (95% confidence interval [CI], 44.0 to 73.2; P<0.001) (Table 1). Vaccination with the rotavirus vaccine prevented 5.0 episodes of severe rotavirus gastroenteritis per 100 infant-years (Table 2). The vaccine showed efficacy against severe rotavirus gastroenteritis both in infants who received two doses of vaccine (58.7% efficacy; 95% CI, 35.7 to 74.0) and in those who received three doses (63.7% efficacy; 95% CI, 42.4 to 77.8). In South Africa, the efficacy of the vaccine was 76.9% (95% CI, 56.0 to 88.4), and in Malawi the vaccine efficacy was 49.4% (95% CI, 19.2 to 68.3); 4.2 and 6.7 episodes of severe rotavirus gastroenteritis per 100 infant-years were prevented by vaccination in South Africa and Malawi, respectively (Tables 1 and 2). The efficacy of the rotavirus vaccine against rotavirus gastroenteritis of any severity is presented in Table 2 in the Supplementary Appendix.

The distribution of rotavirus G and P types

Table 1: Efficacy of Rotavirus Vaccine with Respect to the Development of Severe Rotavirus Gastroenteritis and Hospitalization for Rotavirus Gastroenteritis.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Infants with at Least One Event</th>
<th>Vaccine Efficacy</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rotavirus Vaccine</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>no./total no.</td>
<td>% (95% CI)</td>
<td>no./total no.</td>
</tr>
<tr>
<td>Severe rotavirus gastroenteritis</td>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled 56/2974  1.9 (1.4–2.4)</td>
<td>70/1443 4.9 (3.8–6.1)</td>
<td>61.2 (44.0–73.2)</td>
</tr>
<tr>
<td></td>
<td>Two-dose 30/1496 2.0 (1.4–2.9)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Three-dose 26/1478 1.8 (1.2–2.6)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Malawi 41/1030 4.0 (2.9–5.4)</td>
<td>38/483 7.9 (5.6–10.6)</td>
<td>49.4 (19.2–68.3)</td>
</tr>
<tr>
<td></td>
<td>Two-dose 21/525 4.0 (2.5–6.0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Three-dose 20/505 4.0 (2.4–6.1)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>South Africa 15/1944 0.8 (0.4–1.3)</td>
<td>32/960 3.3 (2.3–4.7)</td>
<td>76.9 (56.0–88.4)</td>
</tr>
<tr>
<td></td>
<td>Two-dose 9/971 0.9 (0.4–1.8)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Three-dose 6/973 0.6 (0.2–1.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Rotavirus-type–specific severe rotavirus gastroenteritis‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>G1 strain 17/2974 0.6 (0.3–0.9)</td>
<td>23/1443 1.6 (1.0–2.4)</td>
</tr>
<tr>
<td></td>
<td>No-G1 strain 39/2974 1.3 (0.9–1.8)</td>
<td>47/1443 3.3 (2.4–4.3)</td>
<td>59.7 (37.1–74.4)</td>
</tr>
<tr>
<td></td>
<td>Malawi</td>
<td>G1 strain 6/1030 0.6 (0.2–1.3)</td>
<td>5/483 1.0 (0.3–2.4)</td>
</tr>
<tr>
<td></td>
<td>No-G1 strain 35/1030 3.4 (2.4–4.7)</td>
<td>33/483 6.8 (4.7–9.5)</td>
<td>50.3 (17.4–70.0)</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
<td>G1 strain 11/1944 0.6 (0.3–1.0)</td>
<td>18/960 1.9 (1.1–2.9)</td>
</tr>
<tr>
<td></td>
<td>No-G1 strain 4/1944 0.2 (0.1–0.5)</td>
<td>14/960 1.5 (0.8–2.4)</td>
<td>85.9 (55.1–96.6)</td>
</tr>
<tr>
<td></td>
<td>Hospitalization for rotavirus gastroenteritis‡</td>
<td>14/2974 0.5 (0.3–0.8)</td>
<td>16/1443 1.1 (0.6–1.8)</td>
</tr>
</tbody>
</table>

* A total of 4417 infants were included in the efficacy analysis — 2974 in the pooled vaccine group and 1443 in the placebo group.

† P values were calculated with the use of a two-sided Fisher’s exact test. P values of less than 0.05 were considered to indicate a statistically significant difference.

‡ Data in the rotavirus vaccine group are for the pooled vaccine cohort.
differed between South Africa and Malawi (Fig. 1 in the Supplementary Appendix). The G1P[8] strain was detected in 57.0% of the episodes among recipients of the placebo in South Africa and in 12.9% of the episodes among recipients of the placebo in Malawi. The type-specific efficacy against severe rotavirus gastroenteritis and the difference in incidence rates between the vaccine groups and the placebo group are shown in Table 1 and Table 2, respectively.

The incidence rate of severe gastroenteritis from any cause was 8.6% in the pooled vaccine group as compared with 12.3% in the placebo group, corresponding to a reduction in the rate with vaccination of 30.2% (95% CI, 15.0 to 42.6; P<0.001) (Table 3). The reductions in all-cause severe gastroenteritis were statistically significant in both countries. The efficacy of the vaccine in the total vaccinated cohort was similar to that in the per-protocol efficacy cohort (Tables 3 to 6 in the Supplementary Appendix).

**SAFETY**

At least one serious adverse event occurred during the study period in 319 of the 3298 infants in the pooled vaccine group (9.7%; 95% CI, 8.7 to 10.7) and in 189 of the 1641 infants in the placebo group (11.5%; 95% CI, 10.0 to 13.2) (Table 7 in the Supplementary Appendix). During the entire study period, 83 deaths occurred among infants in the pooled vaccine group (2.5%; 95% CI, 2.0 to 3.1) and 43 deaths occurred among those in the placebo group (2.6%; 95% CI, 1.9 to 3.5). A single case of intussusception occurred 11 weeks after the third dose of rotavirus vaccine in a 6-month-old child who was assigned to the three-dose vaccine group. The child underwent bowel resection and recovered fully. Three adverse

**Table 2. Risk of Severe Rotavirus Gastroenteritis in the Pooled Vaccine Group and the Placebo Group, According to Dose, Country, and Rotavirus Strain.**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Rotavirus Vaccine</th>
<th>Placebo</th>
<th>Difference in Rate (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episodes/100 Infants/Yr (95% CI)</td>
<td>Episodes/100 Infants/Yr (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Pooled</td>
<td>2974</td>
<td>1443</td>
<td></td>
</tr>
<tr>
<td>Two-dose</td>
<td>1496</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Three-dose</td>
<td>1478</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Country‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malawi</td>
<td>1030</td>
<td>483</td>
<td>6.7 (2.4–11.9)</td>
</tr>
<tr>
<td>South Africa</td>
<td>1944</td>
<td>960</td>
<td>4.2 (2.4–6.5)</td>
</tr>
<tr>
<td>Rotavirus type‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cohort</td>
<td>2974</td>
<td>1443</td>
<td></td>
</tr>
<tr>
<td>G1 strain</td>
<td>0.9 (0.6–1.5)</td>
<td>2.6 (1.7–3.9)</td>
<td>1.7 (0.6–3.0)</td>
</tr>
<tr>
<td>Non-G1 strain</td>
<td>2.1 (1.5–2.9)</td>
<td>5.3 (4.0–7.1)</td>
<td>3.2 (1.7–5.1)</td>
</tr>
<tr>
<td>Malawi</td>
<td>1030</td>
<td>483</td>
<td></td>
</tr>
<tr>
<td>G1 strain</td>
<td>0.9 (0.4–2.1)</td>
<td>1.7 (0.7–4.0)</td>
<td>0.7 (&lt;0–3.1)</td>
</tr>
<tr>
<td>Non-G1 strain</td>
<td>5.5 (4.0–7.7)</td>
<td>11.3 (8.1–16.0)</td>
<td>5.8 (1.9–10.7)</td>
</tr>
<tr>
<td>South Africa</td>
<td>1944</td>
<td>960</td>
<td></td>
</tr>
<tr>
<td>G1 strain</td>
<td>0.9 (0.5–1.6)</td>
<td>3.0 (1.9–4.8)</td>
<td>2.1 (0.8–3.9)</td>
</tr>
<tr>
<td>Non-G1 strain</td>
<td>0.3 (0.1–0.9)</td>
<td>2.4 (1.4–4.0)</td>
<td>2.0 (0.9–3.7)</td>
</tr>
</tbody>
</table>

* The analyses are based on the efficacy cohort, which comprised 4417 infants — 2974 in the pooled vaccine group and 1443 in the placebo group.
† The difference in rate is calculated as the episodes per 100 infants per year in the placebo group minus the episodes per 100 infants per year in the rotavirus vaccine group.
‡ Data in the rotavirus vaccine group are for the pooled vaccine cohort.
events were judged by the investigators to be related to vaccination — two cases of sepsis and one of otitis media.

**IMMUNOGENICITY**

At 1 month after the last dose of vaccine was administered, the seroconversion rates for antirotavirus IgA in South Africa were 57.1% (95% CI, 44.7 to 68.9) in the two-dose group and 66.7% (95% CI, 54.0 to 77.8) in the three-dose group. The seroconversion rates in Malawi were 47.2% (95% CI, 30.4 to 64.5) in the two-dose group and 57.1% (95% CI, 42.2 to 71.2) in the three-dose group. In the placebo group, the seropositivity rates for antirotavirus IgA at 1 month after the last dose were 16.7% (95% CI, 14.2 to 19.5) in South Africa and 40.4% (95% CI, 34.9 to 46.1) in Malawi.

**DISCUSSION**

This study shows that a live, oral rotavirus vaccine significantly reduces the episodes of severe rotavirus gastroenteritis in African children during the first year of life. The attack rate for severe rotavirus gastroenteritis was higher in these populations than has been reported in other studies of rotavirus vaccines.4,5 Because of this high incidence of severe disease, a vaccine efficacy of 61.2% resulted in a substantial vaccine-attributable reduction in severe rotavirus gastroenteritis (reduction of 5.0 cases per 100 infant-years). In addition, the rotavirus vaccine was associated with a reduction in all-cause severe gastroenteritis of 30.2%. This reduction in the incidence of the disease occurred in a trial that was designed to simulate real-world conditions of use; thus, the rotavirus vaccine is expected to deliver a considerable public health benefit when it is introduced into similar settings.

The overall efficacy of the rotavirus vaccine in preventing episodes of severe rotavirus gastroenteritis (61.2%) was lower than that observed in European studies and Latin American studies (96.4% and 84.8%, respectively), which included some low- to middle-income countries.4-6,15 This finding is consistent with findings from other studies of live oral vaccines, such as the oral poliovirus vaccine,16 the cholera vaccine,17 oral typhoid vaccines,18 and earlier rotavirus vaccines,19 none of which were as immunogenic or effective in populations in developing countries as they were in populations in industrialized countries. Several mechanisms have been proposed to explain why live oral rotavirus vaccines may not be as efficacious in populations of infants from low-income countries.20 Possible reasons include host characteristics, such as poor nutritional status and enteric coinfections; levels of antirotavirus antibodies in breast milk; and interference by maternal antibody or by coadministration of the oral poliovirus vaccine, which may reduce rotavirus antibody levels.21,22 The potential role of these and other factors will be important to elucidate, in order to further improve the performance of these vaccines in populations where they are most needed.

The efficacy of the rotavirus vaccine in Malawian infants in this study was lower than that in their South African counterparts (49.4% vs. 76.9%). In addition to potential differences mentioned above, rotavirus circulation differs in the two countries (a winter–spring peak in South Africa6,9 as compared with year-round circulation in Malawi16), and that difference was reflected in the study enrollment strategies (preceding the
rotavirus season in South Africa as compared with year-round in Malawi). The rotavirus sero-
positive rate among placebo recipients 1 month after the last dose had been given was greater
among Malawian infants than among South African infants (40.4% vs. 16.7%), suggesting that
Malawian infants have high exposure to wild-
type rotavirus infection in the first 5 months of
life. Since infection with wild-type rotavirus con-
fers protection against the development of severe
rotavirus disease later in infancy, the greater
exposure of the infants in the placebo group in
Malawi to rotavirus infection before their entry
into the follow-up period may have lowered the
estimate of vaccine efficacy in Malawi. Despite
the lower point estimate for efficacy, the number
of severe cases of rotavirus gastroenteritis pre-
vented was greater in Malawi than in South Africa
(6.7 vs. 4.2 cases prevented per 100 infant-years),
owing to the higher incidence of severe rotavirus
gastroenteritis in Malawi.

In this study, the diversity of the circulating
strains was striking. In Malawi, only 12.9% of
the rotavirus strains were G1P[8] — the strain
on which this vaccine is based, and the most
commonly occurring strain globally. A sub-
stantial proportion of G2, G8, G9, and G12
strains were isolated during the course of this
study. Rotavirus types G2, G8, and G9 have cir-
culated for several years in both countries, where-
as rotavirus type G12 has been reported more
recently. It is unlikely, however, that these
differences in strains contributed to the lower
vaccine efficacy, since the efficacy against G1
and non-G1 severe rotavirus gastroenteritis was
similar. These data are consistent with an inte-
grated analysis of previous efficacy trials of the
rotavirus vaccine, which indicates that the rota-
virus vaccine provides protection against severe
rotavirus gastroenteritis caused by G1 and non-
G1 strains. The ability of a rotavirus vaccine to
protect against a wide panel of strains is impor-
tant in Africa, where the diversity of rotavirus
strains is substantial.

We did not detect significant differences in
vaccine immunogenicity or efficacy between the
cohort receiving two vaccine doses and the co-
hort receiving three doses, although this study
was not powered to detect such differences. There
was a slight but nonsignificant trend toward
higher seroconversion rates and vaccine efficacy
with the three-dose schedule. It should be noted
that in the two-dose schedule used in this study,
the doses of vaccine were administered at the
second and third childhood vaccine visit, when
the infants were an average of 11 and 16 weeks
of age, respectively. Outside the setting of a clin-
ical trial, a two-dose schedule in which the rota-
virus vaccine is administered at the second and
third childhood vaccination visits is not practi-
cal, since it is recommended that the first dose
of rotavirus vaccine be delivered before the infant
is 12 weeks of age, owing to lingering concerns
stemming from the age-dependent risk of intus-
susception associated with a previous rotavirus
vaccine. Since children in developing countries
frequently present late for vaccination visits, this
age restriction would deny many children the
opportunity to receive the rotavirus vaccine if it
were recommended at a later visit. Although a
two-dose schedule in which the vaccine is admin-
istered at the first and second childhood vaccina-
tion visits is a more practical option, such a
schedule was not tested in this study. Adminis-
tering rotavirus vaccines at younger ages could
lower the immunogenicity of the vaccines, be-
cause of the potential for greater interference of
maternal antibody and enhanced replication of
the oral poliovirus vaccine. It will be impor-
tant to undertake studies to assess the effective-
ness of two doses of rotavirus vaccine adminis-
tered at earlier ages than those at which they
were administered in this study.

The WHO’s Global Advisory Committee on
Vaccine Safety (GACVS) has reviewed the safety of
the currently licensed rotavirus vaccines and
has concluded that in clinical trials of these vac-
cines, no association was seen between receipt of
the vaccines and an increased risk of intussus-
cep tion. Further, postmarketing surveillance data
show that an intussusception risk that is of a
similar magnitude to that which had been asso-
ciated with a previous rotavirus vaccine, Rota-
shield (Wyeth–Lederle), is unlikely. The single
case of intussusception in this trial was not tem-
orally related to rotavirus vaccination, and the
rate of serious adverse events did not differ be-
tween infants who received the vaccine and those
who received the placebo. Continuing surveil-
lance of the safety of the vaccines as they are intro-
duced into more countries will be important.

On the basis of this study and other support-
ing data, SAGE recently recommended that rota-
virus vaccination of infants be included in all na-
tional immunization programs, in conjunction with other proven interventions for diarrheal disease.46 Appropriate financing mechanisms that will allow ministries of health in Africa to bring this potentially lifesaving vaccine to the children in greatest need are urgently needed.

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**REFERENCES**


25. Gentsch JR, Laird AR, Bieffelt B, et al. Serotype diversity and reassortment between human and animal rotavirus strains: implications for rotavirus vaccine pro-
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