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Safety and Efficacy of a Recombinant Hepatitis E Vaccine

Mrigendra Prasad Shrestha, M.B., B.S., Robert McNair Scott, M.D., Durga Man Joshi, M.D., Mammen P. Mammen, Jr., M.D., Gyan Bahadur Thapa, M.B., B.S., Narbada Thapa, Ph.D., Khin Saw Aye Myint, M.B., B.S., Marc Fourneau, B.S., Robert A. Kuschner, M.D., Sanjaya Kumar Shrestha, M.D., Marie Pierre David, M.S., Jitvimol Seriwatana, M.S., David W. Vaughn, M.D., Assad Safary, M.D., Timothy P. Endy, M.D., and Bruce L. Innis, M.D.

ABSTRACT

BACKGROUND

Hepatitis E virus (HEV) is an important cause of viral hepatitis. We evaluated the safety and efficacy of an HEV recombinant protein (rHEV) vaccine in a phase 2, randomized, double-blind, placebo-controlled trial.

METHODS

In Nepal, we studied 2000 healthy adults susceptible to HEV infection who were randomly assigned to receive three doses of either the rHEV vaccine or placebo at months 0, 1, and 6. Active (including hospital) surveillance was used to identify acute hepatitis and adverse events. The primary end point was the development of hepatitis E after three vaccine doses.

RESULTS

A total of 1794 subjects (898 in the vaccine group and 896 in the placebo group) received three vaccine doses; the total vaccinated cohort was followed for a median of 804 days. After three vaccine doses, hepatitis E developed in 69 subjects, of whom 66 were in the placebo group. The vaccine efficacy was 95.5% (95% confidence interval [CI], 85.6 to 98.6). In an intention-to-treat analysis that included all 87 subjects in whom hepatitis E developed after the first vaccine dose, 9 subjects were in the vaccine group, with a vaccine efficacy of 88.5% (95% CI, 77.1 to 94.2). Among subjects in a subgroup randomly selected for analysis of injection-site findings and general symptoms (reactogenicity subgroup) during the 8-day period after the administration of any dose, the proportion of subjects with adverse events was similar in the two study groups, except that injection-site pain was increased in the vaccine group ($P=0.03$).

CONCLUSIONS

In a high-risk population, the rHEV vaccine was effective in the prevention of hepatitis E. (ClinicalTrials.gov number, NCT00287469.)

From the Walter Reed–Armed Forces Research Institute of Medical Sciences Research Unit Nepal (M.P.S., R.M.S., S.K.S.) and the Nepalese Army (D.M.J., G.B.T., N.T.) — both in Kathmandu, Nepal; the Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand (M.P.M., K.S.A.M., T.P.E.); GlaxoSmithKline Biologicals, Rixensart, Belgium (M.F., M.P.D., A.S.) and King of Prussia, PA (B.L.I.); and the Walter Reed Army Institute of Research, Silver Spring (R.A.K., J.S., D.W.V., T.P.E.), and the Military Infectious Diseases Research Program, Army Medical Research and Materiel Command, Fort Detrick (D.W.V.) — both in Maryland. Address reprint requests to Dr. Innis at GlaxoSmithKline, 2301 Renaissance Blvd., King of Prussia, PA 19406-2772, or at bruce.2.innis@gsk.com.

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Hepatitis E virus (HEV) infection is a major public health problem in many developing countries.[1] Hepatitis E occurs sporadically and in epidemics, causing substantial rates of death and complications, especially in pregnant women.[2] On the basis of seroprevalence, an estimated one third of the world's population has been infected with HEV.[3] In India, the lifetime infection risk is more than 60%, which translates to hundreds of thousands of illnesses annually.[4] Hepatitis E is usually self-limited and typically occurs in locations where laboratory diagnosis is unavailable.[5] Consequently, the true burden of hepatitis E is unknown.

Hepatitis E is clinically indistinguishable from other types of acute viral hepatitis.[5] In outbreaks of infection, the average incubation period is approximately 40 days; the highest attack rates are among persons between the ages of 15 and 40 years.[6] The severity of illness increases with age; the overall case fatality ratio is estimated to be 1 to 3%.[7,8] Pregnant women have the highest risk of associated acute hepatic failure. Among these women, the case fatality ratio is 5 to 25%, and survivors have high rates of spontaneous abortion and stillbirth.[5]

HEV, a nonenveloped, single-strand, positive-sense RNA virus of the genus hepevirus, has a genome comprising three overlapping open reading frames (ORFs); ORF-2 encodes the principal capsid protein.[9] There are four HEV genotypes: genotype 1 causes most human disease, genotype 2 is rare, and genotypes 3 and 4 (although prevalent in domestic animals such as swine) may have reduced pathogenicity for humans.[6] Nevertheless, all HEVs can be considered to belong to one serotype.[4] Therefore, a vaccine that is shown to be efficacious in one country should provide protection against hepatitis E elsewhere.

A genotype 1 HEV recombinant protein (rHEV) vaccine, which provided protection in nonhuman primates,[10] was found to be immunogenic in humans.[11] These results prompted a clinical trial of the vaccine's efficacy in volunteers from the Nepalese Army, a population at high risk for hepatitis E.[12,13]

METHODS

STUDY DESIGN

We conducted the study in accordance with good clinical practice guidelines, the provisions of the Declaration of Helsinki, and regulations of both the United States and Nepal. The institutional review boards of the Nepal Health Research Council and the U.S. Army approved the study protocol. The U.S. Army Medical Materiel Development Activity office monitored the conduct of the trial and the veracity of the data. An independent data and safety monitoring board monitored adverse events and confirmed end points before investigators were made aware of study-group assignments. Each subject provided written informed consent before participation.

ROLE OF THE SPONSORS

The study was designed by the U.S. Army with GlaxoSmithKline. Investigators in Nepal and Thailand collected the data; statisticians at GlaxoSmithKline analyzed the data according to a prespecified sponsor-approved plan. All the authors had complete and unfettered access to the data, wrote the manuscript, and vouch for the accuracy and completeness of the article.

STUDY SUBJECTS

A total of 5323 healthy men and nonpregnant women were recruited from 61 Nepalese Army units in Kathmandu. Serologic assessment was performed to assess eligibility.[14] Of these subjects, 66.3% had levels of anti-rHEV immunoglobulin of less than 20 Walter Reed antibody units (WR U) per milliliter. Of these subjects, 1885 who had anti-rHEV immunoglobulin levels of less than 10 WR U per milliliter were initially randomly assigned to study groups; subsequently, 115 who had anti-rHEV immunoglobulin levels of 10 or more WR U per milliliter but less than 20 WR U per milliliter were randomly assigned to study groups, so the entire cohort included 2000 subjects from 45 Nepalese Army units.

GlaxoSmithKline Biologicals prepared a permuted-block, 1:1 randomization list (with 20 subjects to a block) with the use of an algorithm of pseudorandom numbers provided by RS/1 data-analysis software (Bolt Beranek and Newman). Randomization of all subjects was performed at one site without stratification. During the double-blind trial, all investigators and subjects were unaware of study-group assignments.

VACCINE AND PLACEBO

The vaccine was a purified polypeptide produced in *Spodoptera frugiperda* cells infected with a recom-

binant baculovirus containing a truncated HEV genomic sequence encoding the capsid antigen.[15] Vaccine doses contained 20 μg of rHEV antigen in 0.5 ml of buffered saline adsorbed to 0.5 mg of aluminum hydroxide. Placebo doses, which looked identical to the vaccine doses, contained 0.5 mg of aluminum hydroxide in 0.5 ml of saline. Three doses of vaccine or placebo were administered intramuscularly, at months 0, 1, and 6. In addition, all subjects in both study groups were offered hepatitis B vaccine (Engerix-B), beginning 3 months after study entry. A total of 84% of the subjects received all three doses of hepatitis B vaccine.

CASE DEFINITION AND EVALUATION OF EFFICACY

Subjects with hepatitis E were identified through active surveillance every other week at military units and through daily hospital surveillance. Definite hepatitis E was defined as jaundice or illness that lasted for at least 3 days, with at least three of the following symptoms: fatigue, loss of appetite, abdominal discomfort, abdominal pain in the right upper quadrant, nausea, or vomiting.[16] Liver injury had to be confirmed by a serum alanine aminotransferase level of more than 2.5 times the upper limit of the normal range or a serum total bilirubin level of more than 2 mg per deciliter (34 μmol per liter). The presence of HEV RNA had to be detected in serum or stool by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay.[17] HEV infection had to be confirmed by detection of either anti-rHEV IgM of at least 100 WR U per milliliter[18] or anti-rHEV immunoglobulin of at least 2500 WR U per milliliter. The immune response at months 0, 2, 6, 7, and 24 was determined by anti-rHEV immunoglobulin immunoassay with the use of the vaccine antigen.[14]

ADVERSE EVENTS

Investigators asked subjects about any adverse events at all study visits. In addition, investigators reviewed all clinic and hospital admission records daily to identify trial subjects. Subjects in a randomly selected subgroup were interviewed on days 1, 3, 5, and 7 after each vaccination to record injection-site findings and general symptoms (reactogenicity subgroup). Serious adverse events (which were defined as medically significant events, including those resulting in hospitalization, disability, or death) were recorded throughout the study. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*.[19] To analyze safety for this report, adverse events that were coded as HEV infection or hepatitis E were censored.

STUDY END POINTS

The primary efficacy end point was the prevention of definite hepatitis E occurring at least 14 days after the administration of the third dose of vaccine. A secondary efficacy end point was the prevention of definite hepatitis E occurring at least 14 days after the administration of the second dose but before the administration of the third dose.

STATISTICAL ANALYSIS

We estimated that the incidence rate of hepatitis E would be 1.6% during a 1-year period.[12,13] Assuming a vaccine efficacy of 80%, a two-group continuity-corrected chi-square test with a one-sided significance level of 0.05 would have a power of 80% to detect a difference in the incidence of hepatitis E with 866 subjects per group, as calculated by nQuery Advisor, version 5.0 (Statistical Solutions). To compensate for dropouts, 1000 subjects per group were needed.

The vaccine-efficacy cohort included all subjects who received three doses for the primary analysis and all subjects who received two doses for a secondary analysis. A two-sided Fisher's exact test was used to compare the percentages of subjects with hepatitis E in the two study groups. A two-sided 95% confidence interval (CI) for vaccine efficacy (1 minus the relative risk) was computed with the use of the Mantel–Haenszel confidence interval for relative risk.

For robustness, efficacy also was computed in the total vaccinated cohort (all subjects who received at least one vaccine dose) on the basis of the relative risk and by the Cox regression model. The cumulative incidence, expressed as hazard-ratio curves, including the group effect as regressor, was generated to analyze time to occurrence of hepatitis E. The log-rank test was used to compare the groups.

Among the 200 subjects in the reactogenicity subgroup, the proportions of subjects who reported symptoms when questioned by investigators during the 8-day period after vaccination were compared between groups. Among the 1800 subjects in the total vaccinated cohort minus the reactogenicity group and in the reactogenicity subgroup, the proportions of subjects who spontaneously reported adverse events at a follow-up

visit during the 31-day period after receiving any dose were compared between groups. In the total vaccinated cohort, the occurrence of severe adverse events was compared between groups. All comparisons used a two-sided Fisher's exact test.

In a randomly selected immunogenicity subgroup of subjects who complied with all protocol requirements regarding vaccination and blood sampling (including 80 subjects in the vaccine group and 160 subjects in the placebo group), the proportion of subjects with anti-rHEV immunoglobulin levels of at least 20 WR U per milliliter and the geometric mean concentrations of anti-rHEV immunoglobulin were analyzed. Data analysis was performed with the use of SAS software (version 8.2) and ProcStatXact 5 with Windows NT 4.0. All reported P values are two-sided.

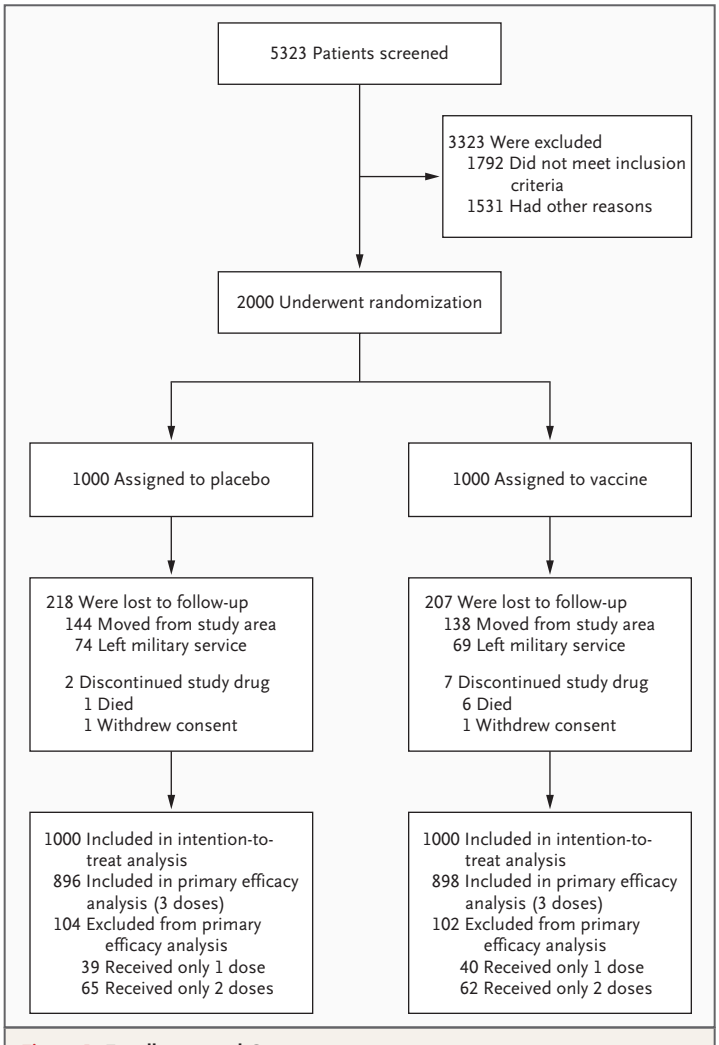

Figure 1. Enrollment and Outcomes.

RESULTS

STUDY POPULATION

From July to August 2001, 2000 healthy subjects (99.6% of whom were men), with a mean (±SD) age of 25.2±6.25 years (range, 18 to 62) were randomly assigned to receive either rHEV vaccine or placebo (Fig. 1). Follow-up ended in January 2004. The study groups (with 1000 subjects in each) were similar with respect to mean age, sex, and rates of withdrawal from the study. A total of 1566 subjects were followed for a median of 804 days.

VACCINE EFFICACY

The data and safety monitoring board reviewed 111 episodes of acute hepatitis and certified 87 definite cases of hepatitis E (see the Supplementary Appendix, available with the full text of this article at www.nejm.org, for details regarding the 24 subjects who were deemed not to have hepatitis E). Of the 87 subjects with definite hepatitis E, 84 were icteric and 3 were anicteric (all in the placebo group). The median duration of illness for the 87 subjects was 29 days (interquartile range, 23 to 39); the median maximum serum alanine aminotransferase level was 1248 U per liter (interquartile range, 756 to 1995), and the median maximum total bilirubin level was 9.0 mg per deciliter (154 μmol per liter) (interquartile range, 6.6 to 13.1 mg per deciliter [113 to 224 μmol per liter]).

The primary objective was to evaluate the efficacy of a three-dose vaccination course. During the period from 14 days after the administration of the third dose until the end of the study, hepatitis E developed in 69 subjects: 3 in the vaccine group (0.3%) and 66 in the placebo group (7.4%) ($P<0.001$ by Fisher's exact test). The efficacy of the vaccine was 95.5% (95% CI, 85.6 to 98.6) (Table 1). By logistic regression, neither age (<25 years in 1117 subjects and ≥25 years in 677 subjects) nor the level of prevaccination antibody to rHEV (≤10 WR U per milliliter in 1692 subjects and >10 WR U per milliliter in 102 subjects) had an effect on vaccine efficacy (see the Supplementary Appendix).

A secondary objective was to evaluate the efficacy of a two-dose vaccination course. During the period from 14 days after the administration of the second dose until the time of administration of the third dose, hepatitis E developed in eight subjects: one in the vaccine group

(0.1%) and seven in the placebo group (0.7%) (P=0.07 by Fisher's exact test). Among these subjects, the vaccine efficacy was 85.7% (95% CI, –16.0 to 98.2) (Table 1).

An intention-to-treat analysis was performed to estimate the vaccine's efficacy when administered during ongoing disease transmission. From randomization, HEV infection developed in 87 subjects: 9 in the vaccine group (0.9%) and 78 in the placebo group (7.8%) (P<0.001 by Fisher's exact test). Among these subjects, the efficacy of the vaccine, on the basis of the relative risk, was 88.5% (95% CI, 77.1 to 94.2) (Table 1). The cumulative incidence of HEV infection as a hazard-ratio curve, plotted for the vaccine group and the placebo group to analyze the time until infection, differed between groups; efficacy as calculated by the Cox-regression model was 89.9% (95% CI, 77.9 to 94.5) (P<0.001 by the log-rank test) (Fig. 2).

In nine subjects in the vaccine group, hepatitis E developed after the following intervals after the administration of the first vaccine dose: 1, 13, 13, 30, 194, 665, 694, 706, and 767 days. Hepatitis E developed in the first four subjects before they received the second dose; all had an acute-illness antibody pattern that was consistent with a primary response (ratio of anti-rHEV IgM to anti-rHEV immunoglobulin, >0.1), suggesting that HEV infection occurred before they received the first dose of vaccine. Infection developed in the remaining five subjects months after they had been vaccinated with the first dose; all had an acute-illness antibody pattern that was consistent with an anamnestic response (ratio of anti-rHEV IgM to anti-rHEV immunoglobulin, <0.1, with a markedly elevated level of anti-rHEV immunoglobulin), suggesting that infection occurred despite vaccination. The subject with an illness onset on day 194 had received one vaccine dose; the subject with an illness onset on day 706 had received two vaccine doses 223 days apart, and the subjects with an illness onset on days 665, 694, and 767 had received a third vaccine dose 187, 180, and 182 days, respectively, after the first dose.

VACCINE SAFETY

The two study groups had a similar rate of loss to follow-up (21.8% in the vaccine group and 20.7% in the placebo group), implying similar overall tolerability of the study treatment. The rates of reporting of symptoms in the reactogenicity subgroup when subjects were questioned by investigators were similar between groups, except for subjects who had pain at the injection site (Table 2). The proportions of subjects spontaneously reporting any adverse event were similar in the two study groups (in the reactogenicity subgroup, 28.0% in the vaccine group and 27.0% in the placebo group; in the total vaccinated cohort minus the reactogenicity subgroup, 25.2% in the vaccine group and 24.9% in the placebo group). Likewise, the proportions of subjects who spontaneously reported any adverse event that prevented them from engaging in normal activities were similar in the two groups (in the total vaccinated cohort minus

Table 1. Efficacy of the rHEV Vaccine against HEV.

Period of Observation	Subjects with HEV Infection		Vaccine Efficacy*
	Vaccine	Placebo	
	no./total no.		*% (95% CI)*
From 14 days after dose 3 until end of study (a priori primary end point)	3/898	66/896	95.5 (85.6 to 98.6)
From 14 days after dose 2 until dose 3 (a priori secondary end point)	1/960	7/961	85.7 (–16.0 to 98.2)
From 14 days after dose 2 until 14 days after dose 3 (a posteriori secondary end point)	1/960	8/961†	87.5 (0.1 to 98.4)
From dose 1 until end of study (exploratory end point)	9/1000	78/1000	88.5 (77.1 to 94.2)

* Efficacy was estimated as 1 minus the relative risk, with the 95% CI based on the Mantel–Haenszel CI for the relative risk.
† One additional case occurred 6 days after the administration of dose 3, before the surveillance period for the a priori primary end point.

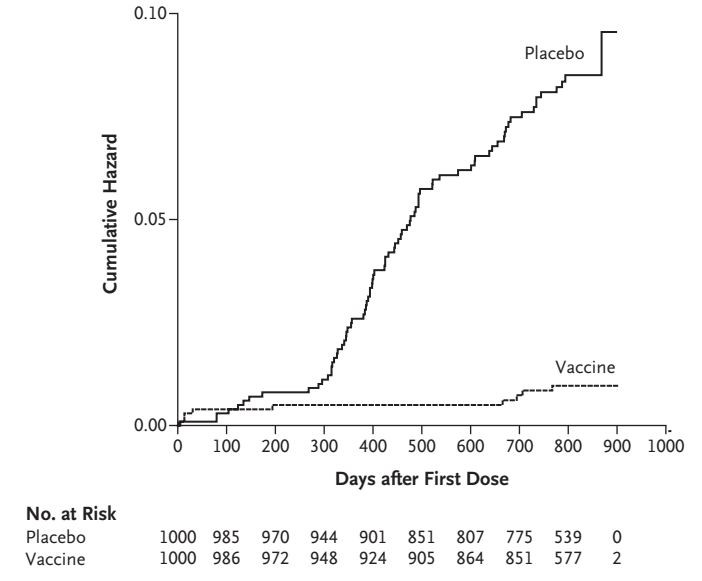

Figure 2. Cumulative Hazard of Hepatitis E.

The cumulative hazard of a first hepatitis E episode (i.e., the incidence rate) was estimated as a minus-log transformation (log data to nonlog data) of the Kaplan–Meier survival curve during the period after the administration of the first dose of study drug until the end of the study among all subjects who received at least one dose of either vaccine or placebo. The numbers below the graph are the numbers of patients in each group remaining under surveillance at 100-day intervals. The difference between subjects who received placebo and those who received vaccine was significant ($P<0.001$ by the log-rank test). Vaccine efficacy from the first dose, calculated with the Cox regression model, was 89.9% (95% CI, 77.9 to 94.5%).

the reactogenicity subgroup, 3.3% in the vaccine group and 3.0% in the placebo group).

The proportions of subjects reporting any serious adverse event, excluding acute hepatitis E, were similar in the two groups: 13.5% in the vaccine group and 13.7% in the placebo group. Subjects in the placebo group had 5.7% more serious adverse events owing to acute hepatitis E than did those in the vaccine group. The most common category of adverse events was infections (excluding hepatitis E), which accounted for 73 of 135 events in the vaccine group and 73 of 137 events in the placebo group. The most frequent diagnosis, excluding hepatitis E, was enteric fever (in 2.0% of subjects in the vaccine group and 2.4% in the placebo group). Among all serious adverse events, which were stratified according to body system and diagnosis, rates of events were similar in the two groups except for leptospirosis (0.2% in the vaccine group and 1.2% in the placebo group). However, the difference probably resulted from differential testing, since only subjects with a clinical diagnosis of hepatitis were tested for leptospirosis (see the Supplementary Appendix). Seven subjects died during the study, six in the vaccine group (four in combat, one from cholangiocarcinoma, and one from an undetermined cause 130 days after a second vaccination) and one in the placebo group (after a vehicle accident). The data and safety monitoring board did not consider any of the deaths to be related to vaccination.

ANTIBODY RESPONSE

Among subjects in the immunogenicity subgroup who received vaccine, 81.3% had a level of anti-rHEV immunoglobulin of at least 20 WR U per milliliter 1 month after the second vaccine dose, and 100% had this level 1 month after the third vaccine dose; by the end of the study, the proportion had declined to 56.3%. In contrast, the proportion of such subjects in the placebo group rose to 10.6%, reflecting the rate of HEV infection (Fig. 3A). Vaccination elicited antibody responses that differed with respect to the geometric mean concentration between the groups from 1 month after the administration of the second dose until the end of the study (Fig. 3B).

DISCUSSION

The rHEV vaccine was protective against hepatitis E during a median of 804 days. According to the primary analysis, the estimated efficacy of three doses of vaccine was 95.5%. The intention-to-treat analysis supported this finding, with an estimate that the efficacy of the rHEV vaccine after the administration of the first dose was 88.5 to 89.9%. Vaccination was conducted during active HEV transmission, affording an opportunity to evaluate the onset of protection. Before the administration of a second dose, hepatitis E developed in four subjects in the vaccine group (on days 1, 13, 13, and 30), as compared with one subject in the placebo group (on day 5). The other four subjects with hepatitis E among those who received one dose (one subject in the vaccine group and three in the placebo group) had an illness onset 104 to 288 days after vaccination. Therefore, we conclude that the vaccine has not been shown to provide any protection after one dose. Vaccination with two doses may afford protection, but the study did not establish this with certainty, since the 95%

CI included zero. Two vaccine doses may control outbreaks of hepatitis E, but this hypothesis requires confirmation.

Several lines of evidence establish that antibody to rHEV is a correlate of protection against hepatitis E. Nonhuman primates that received convalescent serum were protected from disease when challenged with HEV.[10] The convalescent serum bound to rHEV vaccine antigen, which also binds a monoclonal antibody that can neutralize infectious HEV.[20] The development of anti-rHEV immunoglobulin levels of at least 20 WR U per milliliter in 81.3% of subjects in the vaccine group 1 month after the administration of the second dose was related temporally to the apparent onset of protection, although the minimum protective level of antibody is unknown. The antibody level increased after the second dose and then declined until the administration of the third dose, but the protection persisted (Fig. 2), suggesting that a declining level of anti-rHEV immunoglobulin after the second dose does not indicate a loss of immunity. Moreover, the increase by a factor of 10 in anti-rHEV immunoglobulin levels 1 month after the administration of the third dose is evidence that the first two vaccine doses elicited immunologic memory that when boosted by a third dose provided protection against hepatitis E, even after the serum antibody level had waned. This finding is true for hepatitis B vaccine, another recombinant subunit vaccine, which confers immunity despite waning levels of antibody.[21]

The profile of adverse events associated with the administration of rHEV vaccine was similar to that of placebo, although our experience is limited with respect to the number of people at risk and the duration of observation. The symptom profile compiled in response to investigators' queries was similar to that of placebo, except that injection-site pain occurred more frequently among vaccine recipients. There were no significant differences between the groups with regard to spontaneously reported adverse events or serious adverse events. The number of deaths in the vaccine group was larger than that in the placebo group, but none of the deaths were considered to have been related to vaccination. The number of subjects was too small to exclude the possibility of rare vaccine-related adverse events.

By enrolling subjects without antibody evidence of previous HEV infection,[14] we evaluated vaccine in persons who were at greatest risk for infection. The total vaccinated cohort may have included some subjects who were immunologically primed by previous exposure but who did not have detectable antibody to rHEV. Although randomization should have distributed primed subjects equally between the groups, any priming may have offered protection against hepatitis E and an enhanced response to vaccination. Two types of evidence support the exclusion of most primed subjects. Among 80 subjects in the immunogenicity subgroup of the vaccine group, the maximum levels of anti-rHEV immunoglobulin 1 and 5 months after the administration of the second dose were 537.7 and 430.3 WR U per milliliter, respectively — levels that are inconsistent with an anamnestic response. Moreover, among 78 subjects with hepatitis E in the placebo group, 75 had ratios of anti-rHEV IgM to immunoglobulin that were consistent with a primary antibody response.[14] There-

Table 2. Rates of Symptoms Reported to Investigators (Reactogenicity Subgroup) during the 8-Day Period after the Administration of Any of Three Doses of Study Drug.

Symptom	Intensity*	Subjects Reporting Event		P Value†
		Vaccine (N = 100)	Placebo (N = 100)	
		% (95% CI)		
At injection site				
Pain	Any	82 (73.1–89.0)	68 (57.9–77.0)	0.03‡
	Grade 3	1 (0–5.4)	0 (0–3.6)	1.00
Redness	Any	24 (16.0–33.6)	19 (11.8–28.1)	0.49
	Grade 3	0 (0–3.6)	0 (0–3.6)	—
Swelling	Any	20 (12.7–29.2)	17 (10.2–25.8)	0.72
	Grade 3	0 (0–3.6)	0 (0–3.6)	—
Systemic				
Fatigue	Any	43 (33.1–53.3)	47 (36.9–57.2)	0.67
	Grade 3	0 (0–3.6)	0 (0–3.6)	—
Headache	Any	46 (36.0–56.3)	46 (36.0–56.3)	1.00
	Grade 3	0 (0–3.6)	0 (0–3.6)	—
Fever	Any	30 (21.2–40.0)	36 (26.6–46.2)	0.45
	Grade 3	1 (0–5.4)	1 (0–5.4)	1.00

* Grade 3 pain, headache, and fatigue were defined as preventing normal activities; grade 3 redness or swelling was defined as having a diameter of more than 50 mm; and grade 3 fever was defined as a temperature of more than 39.0°C.
† P values are two-sided and were calculated by Fisher's exact test. Dashes indicate that P values could not be calculated.
‡ The absolute rate difference between the vaccine group and the placebo group was 14.0% (95% CI, 2.0 to 25.8).

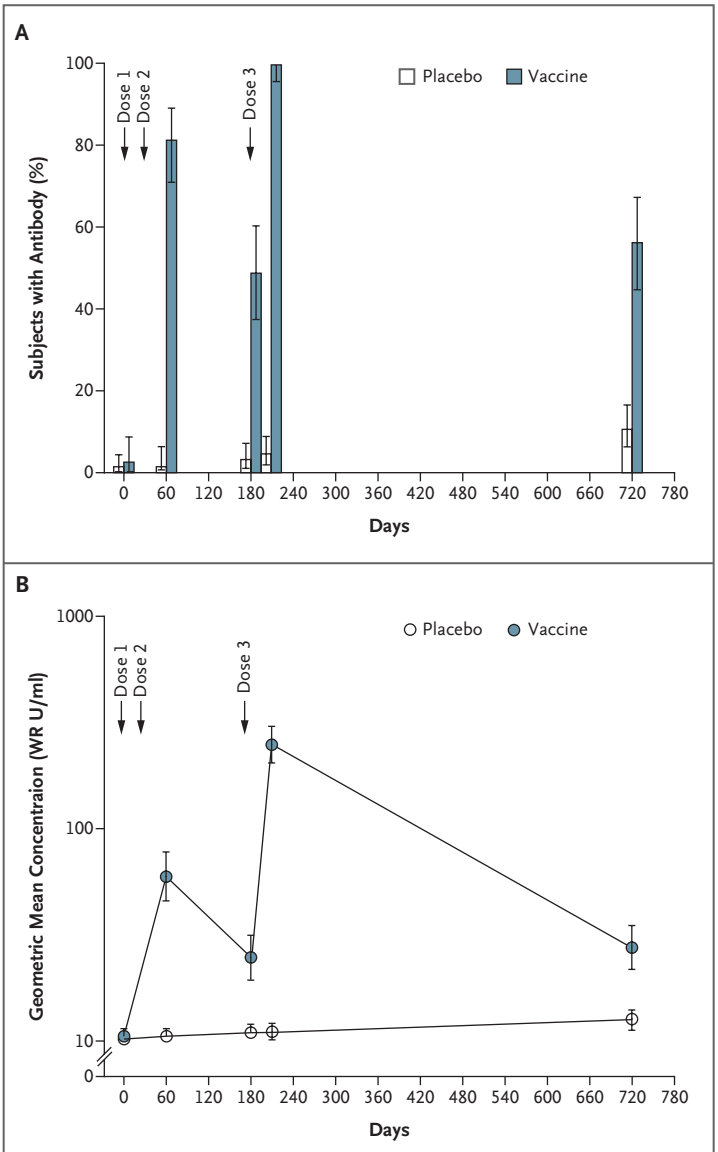

Figure 3. Antibody Response to rHEV Vaccine.

Panel A shows the proportion of subjects who had a level of antibody to rHEV of at least 20 WR U per milliliter in each study group. Panel B shows the geometric mean concentration of antibody to rHEV. In the calculation of the geometric mean concentration, values below the assay cutoff of 20 WR U per milliliter were coded as 10 WR U per milliliter. In both panels, I bars indicate 95% CIs.

fore, our results should apply to persons without previous exposure to HEV.

The contribution of HEV to overall morbidity among the subjects in our trial was substantial and supports the assertion that the burden of hepatitis E is grossly underestimated. Hepatitis E was the most common medically significant illness (including illness resulting in hospitalization, disability, or death) in the placebo group. The potential effect of rHEV vaccine to improve well-being may be substantial in adult populations with similar disease exposures.

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Dr. M.P. Shrestha, Dr. Scott, Dr. Mammen, Dr. Myint, Dr. Kuschner, Dr. S.K. Shrestha, Ms. Seriwatana, Dr. Vaughn, and Dr. Endy report being current or former employees or contractors of the U.S. Army and receiving funding through a cooperative research and development agreement with GlaxoSmithKline to conduct studies on HEV for 5 years or more before this clinical trial. Mr. Fourneau, Ms. David, Dr. Safary, and Dr. Innis report being current or former employees of GlaxoSmithKline, which has intellectual property rights in the rHEV vaccine candidate. No other potential conflict of interest relevant to this article was reported.

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. Department of Defense or the Nepalese Army.

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