A CONTROLLED TRIAL OF A FORMALIN-INACTIVATED HEPATITIS A VACCINE IN HEALTHY CHILDREN

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Abstract *Background.* Although inactivated hepatitis A vaccine is known to be well tolerated and immunogenic in healthy children and adults, its efficacy has yet to be established.

Methods. To evaluate the efficacy of the hepatitis A vaccine in protecting against clinically apparent disease, we conducted a double-blind, placebo-controlled trial in a Hasidic Jewish community in upstate New York that has had recurrent outbreaks of hepatitis A. At the beginning of a summer outbreak, 1037 healthy seronegative children 2 to 16 years of age were randomly assigned to receive one intramuscular injection of a highly purified, formalin-inactivated hepatitis A vaccine or placebo. A case was defined by the presence of typical signs and symptoms, a diagnostic increase in IgM antibody to hepatitis A, and a serum concentration of alanine aminotransferase at least twice the upper limit of normal. Cases occurring ≥50 days after the injection were included in the evaluation of efficacy. The children were followed for a mean of 103 days.

Results. A total of 519 children received vaccine, and 518 received placebo. The vaccine was well tolerated, with no serious adverse reactions. From day 50 after the injection, 25 cases of clinically apparent hepatitis A occurred in the placebo group and none in the vaccine group ($P<0.001$), confirming that the vaccine had 100 percent protective efficacy. Before day 21, seven cases occurred in the vaccine group and three cases in the placebo group. After that time, there were no cases among vaccine recipients and 34 cases among placebo recipients.

Conclusions. The inactivated purified hepatitis A vaccine that we tested is well tolerated, and a single dose is highly protective against clinically apparent hepatitis A. (N Engl J Med 1992;327:453-7.)

HEPATITIS A is a disease with a worldwide distribution; although rarely fatal, it is a common cause of morbidity in developed and developing nations. The annual cost of cases of hepatitis A in the United States is estimated to be over $200 million.[1] Groups at high risk include travelers, military personnel, Native Americans, children in day-care centers and their contacts, institutionalized persons, consumers of raw shellfish, and persons whose sexual practices place them at high risk.

Passive acquisition of antibodies against hepatitis A by injection of immune globulin affords protection against the clinical disease[2] but for only four to six months, necessitating the inconvenience, discomfort, and expense of repeated injections to ensure continuous protection. Since this is rarely practicable, particularly in high-risk groups, a vaccine capable of inducing long-lasting protection is desirable.

Titers of circulating antibodies against hepatitis A produced by immune globulin (measured either by neutralization assay[3] or radioimmunoassay) are low, and within three months — well within the period of protection — they become undetectable or barely detectable.[4] Thus, a vaccine that rapidly induces even low titers of hepatitis A antibody might be protective.

Since 1978, several hepatitis A vaccines have been prepared, some of which have been shown to be immunogenic in marmosets, chimpanzees, and humans.[5-12] The isolation, growth, and serial passage of hepatitis A virus in cell culture by Provost and Hilleman[6] in 1979 led to the development of a live attenuated vaccine and also a prototype, formalin-inactivated vaccine derived from virus propagated in cell culture, which proved to be immunogenic and efficacious in marmosets.[9] A single dose of live attenuated variant F′ vaccine, derived from strain CR326F of the hepatitis A virus, was found to be well tolerated and immunogenic in healthy adults.[11] Further passage and adaptation of this F′ variant in MRC-5 cell cultures produced seed virus used to manufacture the current preparation of inactivated hepatitis A vaccine.[12]

Both three-dose regimens (reinjection after one or two months and after six months) and two-dose regimens (reinjection after six months) of the inactivated vaccine have been evaluated in healthy adults and children.[4,13-16] The vaccine has been shown to be well tolerated and immunogenic, and a single dose induces high titers of antibodies within two to four weeks.[4,13] Geometric-mean antibody levels increase about 10-fold with each additional injection.[13] IgM antibody to hepatitis A can be detected shortly after the first or second injection.[13]

In the light of the safety and tolerability of the formalin-inactivated vaccine in more than 1200 adults and 400 children, we conducted a double-blind, placebo-controlled trial in a community of Hasidic Jewish children with a high rate of hepatitis A. The community is characterized by rapid growth and large families (averaging more than six members per family). Hepatitis A is primarily a childhood illness in this population; 68 percent of persons more than 19 years of age have detectable levels of antibody to the virus.[17] Previous epidemiologic studies have revealed strong

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seasonal trends in incidence (peaking during the summer and winter) and a year-to-year repetition of hepatitis A epidemics. The occurrence of hepatitis A correlated with the presence of children three to five years old in a household and with a pattern of early schooling (from three years of age) in an environment similar to that of day-care centers.

Methods

Vaccine and Placebo

The vaccine and placebo were prepared at Merck Research Laboratories (West Point, Pa.). The vaccine was prepared with modifications of a previously described technique[12] that make possible the large-scale manufacture of this vaccine. In brief, MRC-5 cell monolayers were established in a commercial medium (Nunc Cell Factories, Nunc, Roskilde, Denmark), infected with the attenuated strain CR326F', and maintained for several weeks by regular feeding. At the appropriate time, infected MRC-5 monolayers were lysed by exposure to detergent, and the antigen in the supernatant buffer was recovered by decantation and concentrated by ultrafiltration. Thereafter, the vaccine antigen was highly purified and inactivated with formalin according to essentially the same techniques as previously described. A single lot of aqueous vaccine adsorbed to aluminum hydroxide and stored at 2°C to 8°C was used in this study. Each 0.6-ml dose of vaccine contained 25 units of hepatitis A virus antigen on radioimmunoassay against a purified-virus reference standard. This dose was formerly expressed as 400 ng of virus antigen.[9,13] Like the vaccine, each dose of the placebo — aluminum hydroxide diluent — contained 300 μg of aluminum and thimerosal at a 1:20,000 dilution.

Study Participants

The study protocol was approved by the Western Institutional Review Board (Olympia, Wash.). Children 2 to 16 years old at the time of prevaccination serologic screening who were residents of the Kiryas Joel community in Monroe, New York, and who were expected to be available for follow-up were enrolled after consent was obtained from their parents or guardians. Children were excluded if they were seropositive for hepatitis A antibodies, were immunodeficient, had had a seizure within the past year, were known to be allergic to any component of the vaccine, had received immune globulin during the 6 months before the study started, had received any other hepatitis A vaccine, had received any other vaccine within the previous 15 days, or had any other condition that the investigators judged might interfere with the evaluation of study objectives.

After the epidemiologic pattern of disease had been taken into account, vaccination was planned to begin in June 1991 to allow as many seronegative children as possible to seroconvert before the expected summer–fall outbreak.

After screening, seronegative children received a single 0.6-ml intramuscular injection containing either vaccine or placebo. Blood samples were obtained on the day of vaccination and one month later.

Randomization and Blinding

Children were assigned to receive vaccine or placebo according to a schedule for randomly assigning numbers that was based on the sequential order of injection. The randomization code was not revealed to any study personnel, the manufacturer's research staff for hepatitis A, or the participants and their parents or guardians until the termination of the study. When labeled with the numbers, the vials of vaccine and placebo were indistinguishable.

Monitoring of Adverse Reactions and Cases of Hepatitis A

Each participant was observed for at least 15 minutes after injection for any immediate allergic reactions. The parent or guardian was asked to record the child's oral temperature and any systemic reactions or reactions at the injection site on a vaccination report card four hours after injection and daily for the next four days. Study personnel were to be notified immediately in case of any unexpected or severe reactions. If a report card was not returned on time, a report was obtained by telephone.

Clinically apparent cases of hepatitis A were detected both through active surveillance by semimonthly telephone calls to each child's parent or guardian and through direct reporting of possible cases by the parent or guardian. Children presenting with any signs or symptoms of hepatitis A were examined by the primary investigator, and a blood sample was obtained; this sample was tested for IgM antibody to hepatitis A virus, and serum alanine aminotransferase and total bilirubin were measured. Children were followed by study personnel until a definitive diagnosis was made and their illness had resolved.

Independent Monitoring Committee

An independent committee was appointed to monitor the progress of the trial, the safety and tolerability of the vaccine and placebo, and the accrual of cases of hepatitis A among the participants and to determine when the study should be terminated. The committee determined whether each clinical case reported met the case definition.

Case Definition

A clinical case of hepatitis A disease was defined by the following features: a diagnostic level of IgM antibody to the virus; a serum alanine aminotransferase level at least twice the upper limit of normal during an episode of illness, with no other obvious cause; and one or more of the clinical signs or symptoms consistent with hepatitis A — i.e., dermal, scleral, or faucial icterus associated with a serum total bilirubin level of at least 2.0 mg per deciliter (≥35 μmol per liter), fatigue, malaise, abdominal pain, emesis, an oral temperature of 38.3°C or higher (≥101°F) without any other cause, clay-colored stools, or dark urine.

Evaluation of Efficacy

Interim analyses were planned by the monitoring committee so that the study could be stopped if efficacy was demonstrated. Clinical cases of hepatitis A occurring before the 50th day after the first injection were excluded from the primary analysis of efficacy in order to eliminate from consideration children who were already infected before the injection.[18] Only clinical cases of disease that met the case definition and occurred 50 days after the first injection or later could be considered in any determination of whether to stop or continue the trial. The committee could stop the study if the lower bound of a one-sided 95 percent confidence-interval estimate of efficacy was 47.6 percent or more. The committee reserved the option to make a point estimate of efficacy after the trial ended; this estimate would include cases accrued at various times less than 50 days after injection, along with the corresponding 95 percent confidence interval (lower bound, one-sided).

Laboratory Studies

Serum samples from potential study participants were screened at Merck Research Laboratories for antibodies to hepatitis A by radioimmunoassay of the eluate of blood obtained by finger stick (20 μl) and collected on dried filter paper, according to a modified format[11,13] (and unpublished data) of an assay for the hepatitis A virus antibody (HAVAB, Abbott Laboratories, North Chicago). During the blinded phase of the trial, serum from patients in whom hepatitis A was suspected was tested for IgM antibody to the virus (HAVAB-M, Abbott Laboratories) by an independent commercial laboratory, and the level of alanine aminotransferase and bilirubin was measured by this laboratory. Serum samples obtained on the day of the first injection and one month later were tested for hepatitis A antibody with the modified HAVAB assay[11,13]; the results were expressed in milli-International Units per milliliter, in accordance with the standard reference serum of the World Health Organization, and titers ≥10 mIU per milliliter were considered to show

seropositivity. All testing was done in a blinded manner at Merck Research Laboratories after the code was broken by the committee.

Statistical Analysis

The annual incidence of hepatitis A was estimated from epidemiologic data to be at least 3 percent among the children of this community. If the vaccine had an efficacy of 80 percent, enrolling 600 children in each study group would provide a power of 95 percent for rejecting the null hypothesis that the attack rates of hepatitis A disease would be equal in the vaccine and placebo groups.

Efficacy was calculated with the following formula: 1 − (observed attack rate in the vaccine recipients/observed attack rate in the placebo recipients). The attack rate in each group was calculated by dividing the number of children initially seronegative according to their antibody level on day 0 (or their status on screening, for the 77 children from whom a sample was not obtained on day 0) by the number of children with a confirmed clinical case of hepatitis A. To determine the confidence intervals for efficacy, the number of cases of clinical disease in each group was assumed to follow a Poisson distribution, with parameters lambda v for the vaccine group and lambda p for the placebo group. Under this assumption, the number of vaccine cases, V, has a binomial distribution (T,u) conditional on T, the total number of cases, with u = lambda v/(lambda v + lambda p). Exact confidence intervals were computed for u and transformed into confidence intervals for efficacy.

The Type I error rate for an interim analysis was less than 0.4 percent. If the true efficacy of the vaccine was 80 percent or 90 percent, an interim analysis would have a power of at least 53 percent or 85 percent, respectively, to detect a difference between the vaccine and placebo groups. In all other comparisons, a P value ≤ 0.05 was considered to denote statistical significance.

Contingency tables were analyzed with Fisher's exact test or a chi-square test.

Results

From June 24 to November 5, 1991, 1037 children were enrolled in the trial; 519 children received one injection of vaccine, and 518 received one injection of placebo. Thirty-five percent of the children screened for the study were found to have detectable levels of hepatitis A antibody and were excluded. The vaccine and placebo groups were similar in sex ratio, age at first injection, and length of follow-up (Table 1).

Adverse Reactions

There were no serious adverse reactions during the study. Adverse reactions were mild and self-limited and consisted mainly of local reactions at the injection site (pain, tenderness, swelling, warmth, or rubor), occurring in 42 of the 515 vaccine recipients evaluated (8 percent) and 44 of the 510 placebo recipients evaluated (9 percent) (P = 0.82) within 24 hours of vaccination. Oral temperatures ≥38.3°C (≥101°F) were observed in five vaccine recipients and seven placebo recipients. No severe or fulminant cases of hepatitis A or deaths occurred during the trial.

Efficacy

A total of 34 clinical cases of hepatitis A (18 cases occurring ≥50 days after injection and 16 cases <50 days after injection) were reported through November 5, 1991. The monitoring committee met on November 6 for the first interim analysis of the data. The analysis showed that the vaccine had a high degree of efficacy, and the committee recommended that the study be terminated as soon as vaccine could be provided for the placebo recipients. Case accrual continued in a blinded fashion until November 19, 1991, when vaccination of the placebo recipients began. An additional 10 cases (7 diagnosed ≥50 days and 3 <50 days after injection) were reported from November 6 through November 18. The committee met again on December 12 to review the additional cases and reach a final assessment of the vaccine's efficacy. The final analysis of the 25 cases occurring ≥50 days after injection showed that all 25 cases occurred in placebo recipients and none in vaccine recipients (P<0.001) (Table 2 and Fig. 1).

Table 1. Selected Characteristics of the Study Groups.*

Characteristic	Vaccine Recipients (N = 519)	Placebo Recipients (N = 518)
Age at first injection (yr)		
Mean	7.99	7.84
Median	7.44	7.31
Range	2–16	2–16
Sex (M/F)	267/252	268/250
Mean follow-up (days)	104	102

*None of the differences between the groups were significant.

All 25 placebo recipients with hepatitis A had IgM antibody to the virus, alanine aminotransferase levels more than twice the upper limit of normal (mean, 1383 U per liter; range, 240 to 2850 [mean, 23,511 nmol per second per liter; range, 4080 to 48,450]), and symptoms typical of the disease. Thirteen of the 25 children had icterus, confirmed by elevation of the serum bilirubin concentration. Among all placebo recipients, 3 cases occurred between days 5 and 18 after injection and 34 cases between days 21 and 137.

Among the vaccine recipients, seven cases occurred between days 5 and 18 after injection and none after day 21. All vaccine recipients with hepatitis A had IgM antibody to the virus, alanine aminotransferase levels more than twice the upper limit of normal (mean, 1579 U per liter; range, 196 to 4100 [mean,

Table 2. Results of the Efficacy Analysis of Inactivated Hepatitis A Vaccine.*

Days after Injection	Cases of Hepatitis A		Efficacy Estimate	P Value	95% CI†
	Vaccine	Placebo			
	cases/no. evaluated‡		%		
50–137	0/498	25/496	100	<0.001	87.3
21–46§	0/498	9/505	—	—	—
5–18§	7/505	3/508		—	—

*Three vaccine recipients and one placebo recipient were excluded from this analysis because they had received immune globulin at their parents' request.

†CI denotes a one-sided confidence interval, lower bound.

‡Children initially seropositive according to modified HAVAB[11,13] assay on day 0 are excluded from this table.

§No cases were reported from days 0 to 4, on day 19 or 20, or from days 47 to 49.

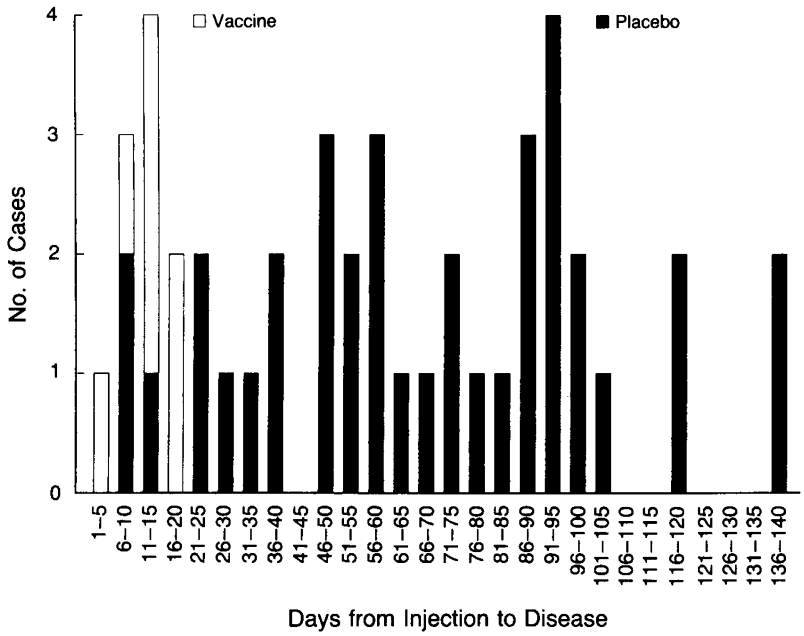

Figure 1. Distribution of Cases of Clinical Hepatitis A in the Vaccine and Placebo Groups, According to the Length of Time since Injection.

26,843 nmol per second per liter; range, 3332 to 69,700]), and symptoms typical of the disease; three of the seven children had icterus.

Serologic Responses

Of the 305 initially seronegative vaccine recipients who were studied one month after vaccination and did not have clinical hepatitis A, all but 1 child had detectable antibody, with a geometric mean titer of 42 mIU per milliliter. Regression of the natural log titer on age showed a significant decrease in titer with increasing age ($P<0.001$).

Discussion

The results of this randomized, double-blind trial confirm that the rapid induction of antibody (as measured by the neutralization test and radioimmunoassay) by this vaccine in previous studies correlates with protection against clinically apparent hepatitis A.[4] Previous studies[4] with the inactivated hepatitis A vaccine showed that the level of antibodies induced by one dose matched (and soon exceeded) the level measured three months after the administration of immune globulin, when there is still passive protection against clinically apparent disease. The correlation between the ability of the radioimmunoassay and that of the neutralization test[3] to detect seropositivity developing after one injection of this vaccine in healthy young recipients is close to 100 percent three to four weeks after injection.[13] Our study confirms that the antibody response associated with seroconversion parallels the start of protection. Similar seroconversion rates have been observed among adults given two doses of vaccine.[15]

The antigenicity of strains of hepatitis A virus from many sources has been found to be strongly conserved.[19,20] Thus, the vaccine should prove protective against strains of all geographic origins.

The fact that an outbreak of hepatitis A was ongoing in the community before vaccination began does not permit precise determination of the minimal interval between vaccination and exposure to wild virus required to ensure protection against clinical disease. Some participants had probably been exposed and were in the incubation phase of the disease before they received the injection. This probably accounts for the cases that occurred in the vaccine recipients within the first three weeks after their inoculation. The best indicator of protection — a detectable antibody titer — has been documented as early as two weeks after one dose of vaccine.[4,13] In studies of healthy adults, a second (booster) dose of vaccine at six months has been shown to induce very high antibody titers,[14] with a decay curve predicting that high titers will persist for more than seven years (unpublished data). Studies being carried out two years after initial vaccination show that antibody levels continue to be high.

We plan to give participants in this study a booster dose after 6, 12, or 18 months. Although further studies of the long-term continuation of protection are ongoing, one study of natural cases of hepatitis A has suggested that otherwise healthy persons with prior exposure to the virus are protected from clinical disease after reexposure to the virus, even when their antibody titers have become undetectable.[21] This suggests that after seroconversion, a single dose of vaccine might confer long-lasting protection against hepatitis A. No cases of hepatitis A with onset $\geq$21 days after injection have occurred among the vaccine recipients in this study during the 10-month follow-up period, although some cases have continued to occur among persons in the community who did not participate in the study, indicating that the virus was present.

Our study shows that this vaccine against hepatitis A prevents the clinical disease in children; it does not show whether the vaccine will also prevent subclinical infection. The only means by which subclinical infection could have been detected was repeated serologic monitoring of the levels of IgM antibody to the virus in the study participants. This obviously was not feasible in a trial conducted in children. At the one point before the end of the trial when blood was tested (one month after injection), only three cases of asymptomatic infection were detected in the placebo group — a number inadequate for analysis.

The vaccine that we used should replace immune globulin as the agent for preexposure prophylaxis against hepatitis A and may merit trials for use in

postexposure prophylaxis. Routine use of this vaccine in healthy, susceptible persons planning to visit areas with a high incidence of hepatitis A, children in day-care centers, members of groups at high risk, and food handlers could substantially decrease the morbidity and mortality associated with this disease. The early protection afforded by this vaccine should make it of special practical benefit to travelers, military personnel, and people who live in frequently affected communities.

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