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Original Articles

A Controlled Clinical Trial of the Efficacy of the Hepatitis B Vaccine (Heptavax B): A Final Report

WOLF SZMUNESS, CLADD E. STEVENS, EDITH A. ZANG, EDWARD J. HARLEY, AND AARON KELLNER

The Lindsley F. Kimball Research Institute of the New York Blood Center, and the Division of Epidemiology, Columbia University School of Public Health, New York, New York 10021

A controlled, randomized, double-blind trial in 1,083 homosexual men from New York confirmed that a highly purified, formalin-inactivated vaccine against hepatitis B prepared from HBsAg positive plasma, is safe immunogenic, and highly efficacious. Over 95% of vaccinated subjects developed antibody against the surface antigen. Vaccine-induced antibody persisted for the entire 24-month follow-up period. The attack rate of all hepatitis B virus infections (excluding conversions of anti-HBc alone) was 3.2% in vaccine recipients compared with 25.6% in placebo recipients ($p < 0.0001$). In those who received all three doses of vaccine, of 40 μg each, the protective efficacy rate was close to 100%. The vaccine protects against acute hepatitis B, asymptomatic infection, and chronic antigenemia. There is reason to assume that the vaccine is also partially effective when given postexposure.

Our initial report on the results of a vaccine efficacy trial in homosexual men (1) encompassed the first 18 months (November, 1978 to May, 1980) of the trial and a total of 14,200 persons per month of follow-up. We continued to follow the trial participants until February, 1981, when 270 hepatitis B virus (HBV) marker negative placebo recipients had been vaccinated in accordance with the study protocol. Because of the occurrence of 38 additional HBV events among participants following our initial report and an increase in the total period of follow-up to 18,000 persons per month, a reevaluation of data for the entire period, from November, 1978 to February, 1981, has been carried out.

MATERIALS AND METHODS

BRIEF DESCRIPTION OF THE PROTOCOL

The vaccine used in this study, a highly purified, formalin-inactivated preparation consisting of the 22-nm spherical particles of HBsAg was manufactured by Merck Sharp & Dohme, West Point, Pa. (2, 3).

The trial was placebo-controlled, randomized, and double-blind. Participants were recruited from approximately 13,000 homosexual men from New York, who were screened for the presence of HBV markers during our baseline studies conducted between 1974 to 1978 (4, 5). To be eligible to participate in the trial, prospective candidates had to satisfy the following criteria: be exclusively or predominantly homosexual; be negative for HBsAg, anti-HBs, and anti-HBc within 2 weeks prior to enrollment; have alanine aminotransferase (ALT) levels below 50 IU per liter; be willing to adhere to the study's vaccination and follow-up schedules during a 24-month period, and to sign an informed consent form.

The vaccine and placebo were packaged in visually indistinguishable 1-ml vials. One dose of the vaccine contained 40 μg of HBsAg protein, subtype *ad*, in an alum adjuvant (Lot 751). The placebo consisted of alum alone in the vaccine diluent. A balance between vials containing vaccine or placebo was maintained throughout the entry period. Randomization was done by means of prearranged lists of coded preparations. Both preparations were administered intramuscularly. The first injection was scheduled to be given within 2 weeks of preenrollment screening, the second 28 days later, and the third 180 days after the first. Eligibility criteria were checked prior to each injection. In those with HBV infections, no further injections were given. In partici-

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Address reprint requests to: Wolf Szmuness, M.D., the Lindsley F. Kimball Institute, The New York Blood Center, 310 E. 67th Street, New York, New York 10021.

pants with clinical or laboratory evidence of non-B viral hepatitis, injections were postponed until ALT values returned to normal. All participants kept a daily record of possible side-effects that occurred within 5 days after each injection. Ten visits were scheduled to the study clinics for blood tests during the first 2 years, once per month during the first 3 months and once every 3 months thereafter. Participants who developed evidence of hepatitis or infection were followed with biweekly blood specimens until the diagnosis was confirmed or refuted and the case was fully characterized. In order to keep the participants and study staff blind, results of testing sera for anti-HBs were not made available until the study had been decoded.

CONDUCT OF THE TRIAL

Over 1,100 men entered the study from November 1978 to October 1979. After the exclusion of those who were found to be ineligible to participate (mostly due to false-negative laboratory results in preenrollment screening), the final study sample consisted of 1,083 individuals, 549 vaccine recipients, and 534 placebo recipients.

Adherence to the study protocol was excellent throughout the entire 2-year period of the trial (Table 1). Of all acceeded individuals, 96.6% received two injections and of those eligible (the 994 who remained seronegative), 93.5% received all three injections. The study preparations in all but a few cases were administered at the prescribed intervals of time. A total of 11,297 follow-up blood specimens, more than the number scheduled by the protocol, were drawn; the mean number of follow-up specimens per subject was 9.6 ± 3.6 among the vaccine recipients, and 11.1 ± 5.0 among placebo recipients (this difference was due to the greater number of hepatitis cases among the placebo recipients).

A total of 204 participants (101 vaccine recipients and 103 placebo recipients) or 18.8% were lost, a rate much lower than the 60% anticipated. The attrition rates were higher during the first year than the second, and the rates were slightly higher, but not significantly (logrank $\chi^2 = 0.203$), among the vaccine recipients than placebo recipients. The main reasons given for dropping out were unwillingness to continue participation (28) and moving out of the study area (39); 137 dropouts could not be located.

Those who dropped out were on the average younger than those who did not, were more frequently nonwhite, less frequently had a past history of venereal diseases, and had fewer sex partners during a 6-month period prior to entry (Table 2). These differences between dropouts and nondropouts did not introduce appreciable bias into the study results.

The applied randomization procedures resulted in two treatment groups which were almost identical to each other including characteristics known to influence the risk of HBV infection in this population: age (mean age was 29 years for both groups), duration of homosexuality (mean of 10 vs. 9.7 years), mean number of different sex

TABLE 1. PROGRAM ADHERENCE OF TRIAL PARTICIPANTS

Category	Vaccine group	Placebo group	All
No. received 1 injection	549	534	1,083
2 injections (% of eligibles)	526 (95.8)	520 (97.4)	1,046 (96.6)
3 injections (% of eligibles)	473 (94.6)	456 (92.3)	929 (93.5)
Interval between 1st and 2nd injection (days):			
Mean (± S.D.)	29.9 ± 5.6	30.1 ± 6.6	30.0 ± 6.1
Median	28	28	28
Range	18–86	16–98	16–98
Interval between 1st and 3rd injection (days):			
Mean (± S.D.)	192.3 ± 34.5	188.7 ± 17.7	190.5 ± 27.6
Median	184	184	184
Range	144–541	126–330	126–541
Side-effects forms filled out and mailed:			
After 1st injection (%)	451 (82.1)	450 (84.3)	901 (83.2)
After 2nd injection (%)	370 (70.3)	375 (72.1)	745 (71.2)
After 3rd injection (%)	312 (66.0)	298 (65.4)	610 (65.7)
Follow-up visits:			
No.	5,310	5,987	11,297
Mean (± S.D.)	9.6 ± 3.6	11.1 ± 5.0	11.0 ± 4.8
Lost to follow-up:			
During first 30 days	18	26	44
30–89	14	15	29
90–269	35	36	71
270–449	25	17	42
>450+	9	9	18
Total	101	103	204

TABLE 2. COMPARISON OF 204 DROPOUTS TO 879 PARTICIPANTS WHO STAYED IN THE STUDY FOR AT LEAST 12 MONTHS

Characteristic	Dropouts	Participants	t_s	p
Age (mean ± S.D.)	26.3 ± 5.4	29.9 ± 6.3	8.19	<0.001
% nonwhite	20.9 (42/201)	11.4 (98/859)	3.33	<0.001
% with history of venereal diseases	41.7 (83/199)	51.1 (432/845)	2.39	<0.05
% with history of viral hepatitis	9.7 (19/196)	11.4 (93/817)	0.69	>0.4
No. of different sex partners during last 6 months (mean ± S.D.)	15.2 ± 19.5	18.7 ± 24.6	2.16	<0.05
% with daily alcohol intake	10.9 (22/201)	12.1 (104/857)	0.48	>0.5
% with ≥ college education	34.8 (71/204)	43.3 (373/861)	2.23	<0.05

TABLE 3. PATTERNS OF SEXUAL ACTIVITY AND FREQUENCIES OF VARIOUS CONDITIONS ACCORDING TO A 12-MONTH QUESTIONNAIRE

During last 12 months	% of vaccine recipient (n = 421)	% of placebo recipient (n = 401)
Rectal bleeding after intercourse	19.0	22.4
Rectal fissures	9.7	10.2
Cracks or tears in rectum or anal skin	16.2	13.0
Intimate sexual contact with women	11.9	11.2
Syphilis and/or gonorrhea	29.2	29.4
Amoebiasis/shigellosis	14.7	15.0
Average no. different sex partners per month:		
0-1	17.1	22.6
2-5	52.6	47.9
6-9	10.7	8.0
10-19	14.0	15.5
≥20	3.6	4.0
Mean ± S.D.	6.0 ± 6.4	6.0 ± 6.8
Most frequently used sexual technique (participant/partner):		
oral/penile	69.8	73.8
penile/oral	74.3	74.6
oral/rectal	19.7	18.5
rectal/oral	17.6	17.5
penile/rectal	53.2	48.4
rectal/penile	40.6	39.9

partners during 6 months (17.7 vs. 18.5), and past history of venereal diseases (1). In order to assess the extent and type of sexual activity of the participants during the course of the trial, as well as the incidence of diseases and conditions other than viral hepatitis, a self-administered questionnaire was filled out by 822 individuals at the time of their 12-month follow-up visit (Table 3). Between 10 and 22% of participants complained of rectal bleedings and fissures or cracks in the rectum. Our baseline studies (4, 6) had revealed that these conditions increase the HBV risk. The attack rates of syphilis and/or gonorrhea, as well as of two other sexually transmitted diseases, amoebiasis and shigellosis, were found to be unusually high—15 to 29% per annum. This survey confirmed that most participants practiced all homosexual types of intercourse, although some indicated a preferred type. The risk of exposure to an infectious partner by the trial participants appears to be considerable: participants had an average of six different partners per month. This survey demonstrated that the vaccine recipients remained almost identical to the placebo recipients with regard to the extent of their sexual activity, the types of intercourse, and the incidence of certain diseases and conditions other than hepatitis B.

DEFINITION OF EVENTS

The great majority of hepatitis cases and HBV, hepatitis A virus (HAV), and non-A, non-B events were assessed before the treatment code was broken and without access to the results of the anti-HBs test. Only the 38 events which occurred after June, 1980 were not assessed and classified under code. An event was diagnosed as "hepatitis" when ALT values were above the upper limit of normal (≥45 IU per liter) in at least two sequential blood specimens drawn within 1 to 3 weeks of each other, with one of these values more than twice the upper limit (≥90 IU per liter). Events in which ALT values were above 45 IU per liter on one occasion or more, but were always below 90 IU per liter were classified as "HBV events with evidence of minimal liver damage." Those events with serologic evidence of a viral infection but no abnormality in ALT were classified as "infection only."

A participant was considered to have had a definite HBV infection if three or more sequential blood specimens were positive for HBsAg or anti-HBc or both. Infection by HBV was considered probable when only two sequential specimens were positive for these markers and then the subject was either lost to follow-up or subsequent specimens were negative for HBsAg and anti-HBc. Infection by HAV was identified by seroconversion from antibody-negative to antibody-positive, along with the development of IgM-specific anti-HAV. Hepatitis due to cytomegalovirus and Epstein-Barr virus infections were diagnosed when antibody seroconversion coincided with the ALT elevations. Hepatitis events in which neither HBV, HAV, cytomegalovirus, nor Epstein-Barr virus were implicated were considered to be non-A, non-B hepatitis.

RESULTS

REACTOGENICITY OF THE VACCINE

A total of 1,133 side-effect reports were filled out by participants after administration of the vaccine injections. The proportion of responders was 82% following the first vaccine injection, 70% following the second, and 66% following the third. The overall incidence of reported side effects was 24.3%, including 2.6%—fever, 15.8%—sore arm, and 10.0%—other complaints. Fever was usually low grade, and in the great majority of instances its duration did not exceed 24 hours. The rate of side effects was 31.5% after the first vaccination, 18.9% after the second, and 20.2% after the third. The overall incidence of side effects in placebo recipients was 21.4% (1), which was not statistically different from the rate in vaccine recipients.

IMMUNE RESPONSE TO THE VACCINE

For the purposes of this analysis, a vaccine response was defined as a seroconversion in a vaccine recipient

from anti-HBs negativity [Ausab ratio units (RU) < 2.1] to positivity (RU ≥ 2.1) in at least two consecutive blood specimens drawn at 1 to 3 monthly intervals in the absence of HBsAg and/or anti-HBc.

As noted in our initial report (1), the vaccine response was limited to *de novo* appearance of specific antibody directed against the *ad* subtype of HBsAg used for the preparation of the vaccine. In a selected group of 50 vaccine responders twice tested, none was found to be reactive for antibody to the hepatitis B "e" antigen (anti-HBe).

Classification of immune responses to the vaccine was based on the highest RU values observed and their duration. Responses with values above 20 RU, mostly fluctuating between 100 and 300 RU, were classified as "good." Vaccine recipients with peak values of 10 to 20 RU were regarded as "fair," and those persistently below 10 RU but greater than 2.1 RU as "weak." Fully immunized vaccine recipients who had no more than one specimen with a RU above 2.1 were regarded as nonresponders to the vaccine.

Four hundred twenty one of 451 fully immunized vaccine recipients had a good (90.5%) or fair response (2.9%). Only nine vaccine recipients (2%) had a weak response and another 21 (4.7%) did not respond to the vaccine at all.

Figure 1 shows rates of antibody positive vaccine recipients and the distribution of RU values by months after the first vaccination. One month after the second injection, 76.2% of vaccine recipients were anti-HBs positive and in only 8% were the RU values ≥100. The response rate increased to 87 to 91% in the 2- to 6-month interval. Administration of the 6-month booster injection resulted in an increase of the rate to 96% at 9 months and a rise in the proportion of RU values ≥100 from 22% prior to the booster to 70% after. The overall rate of anti-HBs positive vaccine recipients remained unchanged during the entire period of follow-up: of those tested 24 months after the first injection, 98% were still antibody positive. However, the proportion with RU ≥ 100 declined from 70% at 9 months to 43% at 24 months. Similarly, median RU declined from nearly 200 at 9 or 12 months to 90 at 24 months.

Anti-HBs levels, expressed in milliInternational Units, were measured by radioimmunoassay in sera diluted serially and compared against a standard dilution curve of the World Health Organization standard for hepatitis B immune globulin (100 IU per ml) (7). All sera taken between 6 months (just prior to the third injection) and 24 months after randomization were tested on a subset of 118 vaccine recipients. These individuals were selected only because of the completeness of their follow-up and were representative of the entire group of vaccine recipients in terms of anti-HBs radioimmunoassay ratio units. Geometric mean titer (GMT) of anti-HBs mIU was 82.8 mIU per ml just prior to the 6-month booster dose of vaccine. Three months following the booster, the anti-HBs GMT was 544.1 and titers gradually declined nearly to prebooster levels over the next 18 months (Figure 2).

In order to ascertain if subjects who did not respond to the vaccine differ from those who responded to the vaccine, the two groups were compared with respect to age, race, socioeconomic class, past histories of various conditions and diseases, surgery, hospitalization, blood transfusion, duration of homosexuality, sexual promiscuity, etc. No significant differences could be discerned.

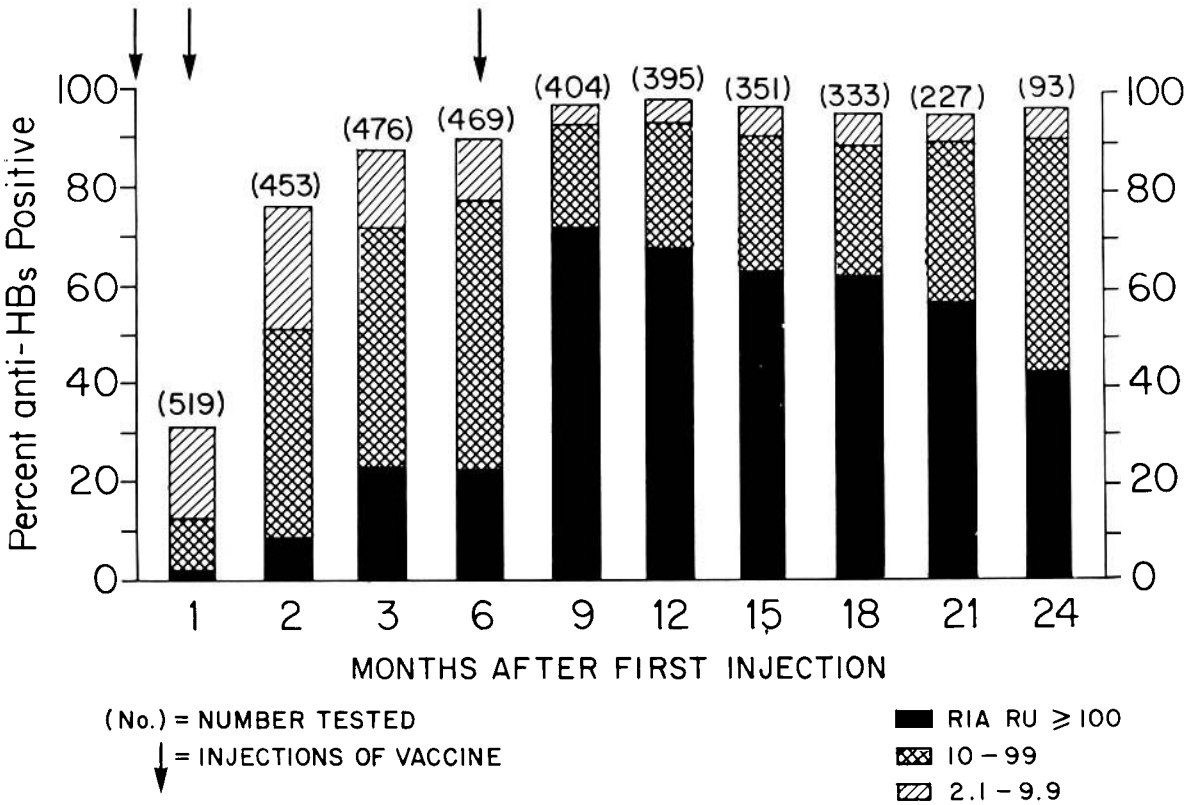

FIG. 1. Anti-HBs responses and distribution of RU values in vaccine recipients for 24 months.

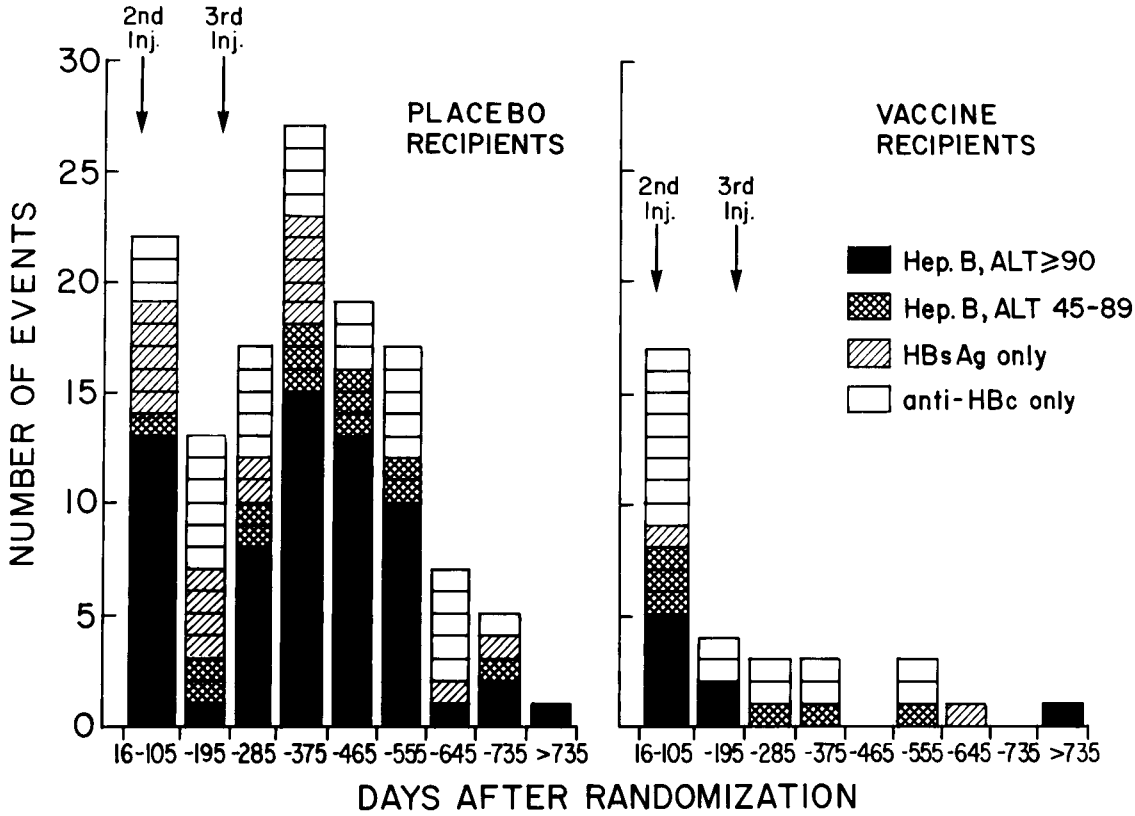

FIG. 2. GMT of anti-HBs following hepatitis B vaccination (in milliInternational Units).

Initial results of testing for HLA antigens suggest that the nonresponders may differ significantly from the responders with respect to certain antigens of the B and DR loci (P. Rubinstein, personal communication). However, a larger number of nonresponders will have to be tested to confirm this association.

Of the 187 vaccine recipients without evidence of HBV exposure who were followed for at least 18 months, only 5 or 2.7% had anti-HBs values which declined to less than 2.1 RU (range 0.9 to 1.8 RU). Two lost antibody 21 to 22 months after the first injection, one 24 months after, and two 25 to 26 months after. All of these subjects had peak anti-HBs levels <30 IU following vaccination.

ATTACK RATES OF HBV EVENTS AND THE EFFICACY OF THE VACCINE

A total of 160 HBV events occurred between Days 15 and 794 after randomization; 32 events (including two probable) in vaccine recipients and 128 (eight probable) in placebo recipients. Because only one placebo recipient and 17 vaccine recipients had so far been followed in the interval 735 to 794 days, two cases of hepatitis B which occurred in this interval (one in a vaccine recipient and one in a placebo recipient) were not included when life table methods of analysis were applied. Figure 3 presents the distribution of HBV events by type of case, time of occurrence, and treatment group. As can be seen, during the first 105 days of follow-up, the total number of events in the vaccine recipients (17) was only slightly smaller than that in placebo recipients (22). However, the types of events in the two groups were remarkably different. In the vaccine recipients, only a small proportion of all

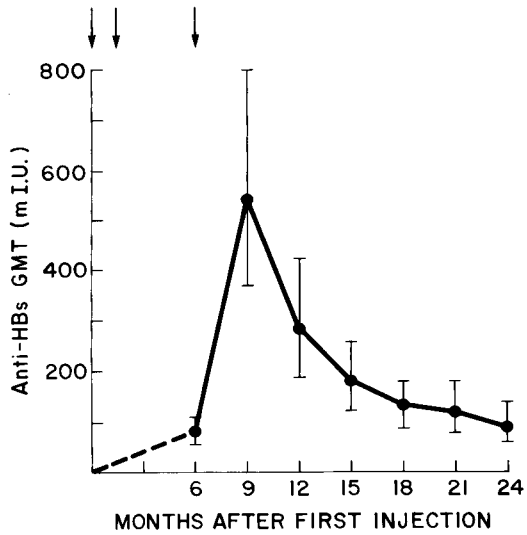

FIG. 3. Distribution of HBV events in vaccine and placebo recipients during 735 days following randomization.

events consisted of hepatitis B (5/17) while the major part (8/17) consisted of conversions for anti-HBc alone. In the placebo recipients these proportions were reversed: 14/23 and 3/23, respectively. Beginning from Day 196, the incidence of HBV events in vaccine recipients dramatically dropped (11 events vs. 93 events in placebo recipients).

Approximately 1/5 cases in placebo recipients were icteric and nearly one half were symptomatic. Ten placebo recipients (annual life table attack rate, 1.6%) developed chronic antigenemia (positive for 9 or more

months). The cases in vaccine recipients were generally milder and only one became a chronic HBsAg carrier (he developed HBV infection prior to completion of vaccination).

Because of the wide spectrum of serological, biochemical, and clinical manifestations of HBV infection, comparisons of HBV attack rates and assessment of vaccine protective efficacy were done with respect to various types of trial endpoints (not mutually exclusive).

As can be seen from data presented in Table 4, differences in life table attack rates between the two treatment groups, cumulatively for 735 days, varied from a high of 13-fold with respect to hepatitis B cases, to a low of 3.5-fold with respect to anti-HBc conversions. For all HBV events excluding anti-HBc conversions, the attack rate in placebo recipients was eight times higher than in vaccine recipients (25.6% vs. 3.2%) and if anti-HBc is included it was 5.4 times higher (34.5% vs. 6.4%). The probability that differences of this magnitude would occur by chance alone are less than 1:10,000.

Protective efficacy of the vaccine was computed by dividing the differences in attack rates between placebo and vaccine recipients by the rate in placebo recipients. Efficacy was highest with respect to hepatitis B, 92.1%, and lowest with respect to conversions for anti-HBc alone, 71.5%.

Table 5 presents attack rates for two types of endpoints and protective efficacy rates in relation to the number of vaccine doses administered. As can be seen, after the third dose of the vaccine was given, the differences in attack rates between the treatment groups increased to 20-fold and the efficacy rate increased to 95 to 100%.

High protective efficacy was seen regardless of age, race, level of education, past history of venereal diseases or viral hepatitis, and number of different sex partners during a 6-month period prior to entry in the trial (Table 6). A high level of protection was seen in participants with a large number of sex partners, i.e., those with a high risk of exposure to infective HBV carriers.

A review of data presented in Figure 3 reveals that the distribution of HBV events in placebo recipients varied somewhat during follow-up. For instance, during the 90-day period between days 286 to 375, a total of 27 events occurred, while only 13 events occurred during the 106- to 195-day interval; the corresponding life-table attack rates were 29% and 7%. Based on calculations of average daily attack rates, it has been suggested that until the mechanisms for such disparities are elucidated, the efficacy of the vaccine will not be completely established (8). Table 7 therefore compares average monthly attack rates of various HBV endpoints for the first 195 days after randomization, and beginning from the 196th day until Day 735. As can be seen, the average monthly rates were higher during the later period than the early period. However, for none of the endpoints did these differences reach statistical significance. The individuals who had HBV events during the early period of follow-up did not differ from events in the latter period with respect to such characteristics as mean age (30.3 vs. 28.9 years), mean number of sex partners during a 6-month period (26 vs. 28), and highest ALT level reached during the episode. A possible explanation for the fact that fewer HBV cases occurred during the first 6 to 7 months has been given elsewhere (9).

Vaccine Efficacy Depending on the Immune Response and Time of Administration

Of the 32 vaccinees with HBV events, 8 received only 1 injection of the vaccine prior to onset of the event, 15 received 2 injections, and only 9 completed the vaccina-

Table 4. Life Table Attack Rates of Various Endpoints (Cumulatively for 735 Days) and Protective Efficacy Rates (PER)

Endpoint[a]	Placebo group		Vaccine group		Logrank (χ^2)	p value	PER (%)
	No.	Rate	No.	Rate			
Hepatitis B	63[b]	17.6	7[b]	1.4	53.20	<0.0001	92.1
HBV infection with ALT ≥ 45 IU/liter	77	21.3	13	2.7	55.12	<0.0001	87.3
HBsAg positive	90	23.5	12	2.6	71.55	<0.0001	88.9
Anti-HBc conversions alone	32	11.9	16	3.4	7.97	<0.01	71.5
All HBV infections, excluding anti-HBc	96	25.6	14	3.2	69.80	<0.0001	87.5
All HBV infections, including anti-HBc	127	34.5	31	6.4	72.72	<0.0001	81.4

[a] Not mutually exclusive.
[b] One case which occurred after Day 735 not included.

Table 5. Protective Efficacy Rates (PER) According to Number of Vaccine Doses

Endpoint vaccine dose	Placebo group		Vaccine group		Logrank (χ^2)	p value	PER (%)
	No. of Events	LTAR[a]	No. of events	LTAR			
Hepatitis B:							
Following 1st dose	57	17.0	6	1.2	47.50	<0.001	91.8
Following 2nd dose	53	16.3	5	1.0	45.95	<0.001	93.9
Following 3rd dose	49	15.6	0	0	56.52	<0.001	100.0
All HBV infections excluding anti-HBc conversions:							
Following 1st dose	88	24.6	11	2.4	72.19	<0.001	90.2
Following 2nd dose	82	23.7	10	2.2	68.53	<0.001	90.7
Following 3rd dose	69	21.5	4	1.1	70.92	<0.001	94.9

[a] LTAR, life table attack rate.

TABLE 6. LIFE TABLE ATTACK RATES (LTAR) OF HBsAg POSITIVE EVENTS AND VACCINE EFFICACY IN SUBGROUPS OF PARTICIPANTS

Subgroup	Vaccine group		Placebo group		p value	PER[a] (%)
	At risk	LTAR	At risk	LTAR		
Age:						
<30 years	311	2.7	305	25.6	<0.001	89.4
30–39	203	3.1	193	22.9	<0.001	86.4
≥40	30	0.0	30	25.8	<0.025	100.0
No. of different sex partners—6 months:						
<10	226	1.93	225	15.23	<0.001	87.3
10–19	129	2.6	132	21.8	<0.001	88.1
≥20	184	3.5	171	38.3	<0.001	90.1
Venereal disease history						
Yes	267	4.4	255	29.6	<0.001	85.1
No	271	0.8	269	19.9	<0.001	96.0
Viral hepatitis history						
Yes	62	0.0	53	28.5	<0.001	100.0
No	462	2.9	454	24.9	<0.001	88.3
Education						
High school	138	1.0	123	20.2	<0.001	95.0
College or more	407	3.1	409	25.6	<0.001	87.9
Race						
White	468	2.1	468	24.2	<0.001	91.3
Nonwhite	78	6.1	64	26.4	<0.01	77.0

[a] PER, protective efficacy rate.

TABLE 7. AVERAGE MONTHLY HBV ATTACK RATES (%) IN TWO TIME PERIODS AMONG PLACEBO RECIPIENTS

Endpoint[a]	Days 16–195	Days 196–735	Z[b]	p
Hepatitis B	0.47	0.91	0.259	0.79
HBV infection with ALT ≥ 45 IU/liter	0.58	1.12	0.297	0.76
HBsAg positive	0.91	1.18	0.139	0.88
All HBV infection, excluding anti-HBc	0.91	1.33	0.211	0.83

[a] Not mutually exclusive.

[b] Z-test based on $\bar{x}$ probability of response and $\bar{x}$ standard errors.

tion schedule. Among these 9 fully immunized subjects, 7 were found to be nonresponders to the vaccine, 1 was a weak responder, and only 1 had responded well to the vaccine. The latter was a 23 year old with a very extensive sexual life who was anti-HBs positive with a RU of 60 to 80 on two occasions prior to converting to anti-HBc alone. No responder developed either hepatitis B or asymptomatic antigenemia. Table 8 presents HBV incidence rates for the period 196 to 735 days (after completion of the vaccination schedule) in relation to the immune response of the vaccine recipients. As can be seen, the incidence among the "good" and "fair" responders was 0.23% compared with a rate of 33.33% among the nonresponders. The incidence in the nonresponders was somewhat higher than among the placebo recipients during the same period of time, but this difference was not statistically significant.

NON-B HEPATITIS CASES

A total of 75 non-B hepatitis cases were identified during the 2-year period of follow-up (Table 9). Sixty-four per cent of the cases have been diagnosed as hepatitis type A, and 36% of cases as non-A, non-B. In four additional participants, a seroconversion to anti-HAV positivity without hepatitis has been documented. The ratio of asymptomatic to symptomatic cases of HAV in this population would thus be 1:12, much lower than ratios (1:4 to 1:5) reported in food-borne outbreaks (11). Non-B events were evenly distributed throughout the 2-year follow-up period.

Of the 235 participants who developed biochemical or serological evidence of viral hepatitis of type A, B, or non-A, non-B etiology, approximately 10% converted for antibodies to cytomegalovirus or Epstein-Barr virus agents. The exact seroconversion rates for these agents, with and without hepatitis, will be available after testing of paired sera from all participants is completed.

DISCUSSION

The classical work by Baruch Blumberg on the "Australia antigen" (10, 11) and by Saul Krugman on the MS-1 and MS-2 strains (12, 13) were the breakthroughs in the long and frustrating study of hepatitis B and laid the groundwork for a vaccine against this extremely widespread and debilitating disease. Without these pioneering studies, the development, evaluation, and licensing of present day hepatitis B vaccines would no doubt be delayed by many years.

The vaccine used in this trial was developed and evaluated in Phase I and Phase II studies by Hilleman at the Merck Sharp & Dohme Research Laboratories (2, 3). Another American vaccine, developed by Purcell and Gerin at the NIAID (14), although not yet tested for efficacy in clinical trials, appears to be similar to the Merck vaccine with respect to a number of characteristics.

TABLE 8. INCIDENCE (CRUDE) OF HBV EVENTS IN 451 VACCINEES BY TYPE OF ANTI-HBs RESPONSE (PERIOD 196–735 DAYS)

Anti-HBs response	No. of subjects	No. of HBV events	%
Vaccinees:			
Good and fair	421	1	0.23
Weak	9	1	11.11
No response	21	7	33.33
Placebo recipients	426	92	21.60

TABLE 9. NON-B HEPATITIS EVENTS

	Placebo group	Vaccine group	Total	
			No.	Rate[a]
Hepatitis A	27	21	48[b]	5.2
Non-A, non-B hepatitis	11	16	27	2.9
Total	38	37	75	

[a] Crude, in relation to 920 at risk at midpoint of follow-up.

[b] Four additional participants had anti-HAV seroconversion without hepatitis.

Two vaccines developed in France, one by Maupas (15) and the other at the Institut Pasteur in Paris (16) were also reported to be effective in studies conducted in dialysis centers (15), in Senegalese children (17), in medical personnel of dialysis centers (16), and in patients undergoing maintenance hemodialysis (18). However, the first two studies were neither truly controlled nor randomized, whereas the design and data analyses in the latter two trials are open to discussion (small sample sizes, participants scattered in a large number of centers with very few in each of them, in the great majority of centers neither vaccine or placebo recipients were presumably exposed to HBV, unexplained decline of attack rates in placebo recipients after the third month).

This study, a placebo-controlled, randomized, and double-blind trial in 1,083 healthy young men from a large metropolitan area, followed for up to 30 months, proves with a very high level of statistical confidence ($p < 0.0001$) the high efficacy of the tested vaccine. Extension of the follow-up period from an average of 18 months on which our initial report (1) has been based, to an average of 24 months in the present report, resulted in a substantial increase of HBV events in the placebo recipients (from 93 to 128 events), but in a negligible increase of events in the vaccine recipients (three, all in nonresponders to the vaccine). It should be emphasized that during the last 6 months of the trial, the absolute number of vaccine recipients at risk was ⅓ greater than placebo recipients. The protective efficacy rates in relation to all HBV events (excluding conversions for anti-HBc alone) were 90 to 91% after the first or second vaccination and 95% after the 6-month booster vaccination. In relation to hepatitis B alone, these rates were 92%, 94%, and 100%, respectively. Such high efficacy rates were seen in all subsets of vaccinees, regardless of age, race, socioeconomic background, and certain other factors known to influence HBV risk in homosexual men (Table 6). Close to 100% is also the overall protective efficacy rate, including anti-HBc conversions, if analysis is confined to vaccine recipients who exhibit a good or fair immune response: only 1 of 421 such responders, or 0.23% developed an HBV infection manifested only by appearance of anti-HBc without detectable HBsAg or ALT elevation. This nearly complete absence of any serologic evidence of HBV infection among vaccine recipients would suggest that vaccine-induced anti-HBs inhibits the penetration of HBV into liver cells thereby preventing virus replication.

The vaccine tested was not only highly efficacious in preventing disease and infection, but even in those few (32) vaccinees who did contract HBV infection, primary individuals not fully immunized or with no immune response to the vaccine, the infection in 50% of the instances was completely asymptomatic (conversion for anti-HBc alone), and in the remaining cases it was mostly anicteric and asymptomatic with relatively low ALT elevations.

Not a single fully immunized vaccine recipient developed a chronic HBsAg carrier state; the only vaccine recipient who became a carrier contracted HBV infection only 2 months after his first dose of vaccine. In sharp contrast, the yearly attack rate of chronic antigenemia in the controls was 1.6%. Assuming that the total number of susceptible homosexual men in this country is at least 1 million, one may estimate that vaccination of these susceptibles during a 5-year period (presumed duration of immunity induced by a single vaccination cycle) would prevent approximately 80,000 carrier states. It should be kept in mind that on the average, 65% of all HBsAg carriers in this population are likely to be infective as evidenced by their reactivity for the HBeAg (19).

Most vaccines are not effective when given after exposure to infection has already occurred. Even when given shortly before exposure, most are ineffective or less effective. The only exceptions are rabies vaccine and tetanus toxoid. This study provided preliminary evidence suggesting that the hepatitis B vaccine may be another exception. During the first 60 days after the initial vaccination, the total number of HBV events in vaccine recipients was only slightly lower than in placebo recipients: 11 vs. 13. However, whereas 10/13 events in the placebo recipients consisted of hepatitis B, only two vaccinees had hepatitis B and the remainder of cases were very mild ($p = 0.003$, Z test, 2-tailed). If only the first 28 days after randomization are taken into account, then the numbers of hepatitis B are 5 and 1. Obviously, in all or at least most of these early HBV events, exposure occurred either immediately prior to or soon after randomization. These findings can be most plausibly explained if one assumes that when given shortly prior to exposure or in the early period of incubation, the vaccine aborts hepatitis B or attenuates its clinical course. Of course, additional studies are required to confirm our findings concerning the vaccine's postexposure efficacy. Should these findings be confirmed, then vaccination may replace treatment with hepatitis B immune globulin (HBIG) for individuals acutely exposed to accidental inoculation with HBV-contaminated needles or other medical instruments, to infective sex partners, or of newborn infants whose mothers have acute hepatitis B in the last trimester of pregnancy, or are carriers of HBsAg. HBIG alone in these situations is only partially effective (20). A still better approach in postexposure situations, or where exposure is continuous and at a very high level, would be to combine administration of HBIG with vaccination, simultaneously or sequentially, with the hope that passive antibody will provide immediate protection while the active immune response is being elicited. Our recent studies in healthy adults have demonstrated that such an approach is both possible and advisable (21).

The immunogenicity of the vaccine tested, i.e., its ability to induce an antibody response, was found to be quite satisfactory. Following the second vaccination, 80 to 90% of subjects converted to anti-HBs positivity, with a rise of this rate to over 95% after the 6-month booster injection. This rate remained unchanged during the entire 24-month follow-up period. The very few vaccinees who lost the antibody 21 to 26 months later, were among the weak responders. In terms of actual antibody levels, the geometric mean titer reached a peak of over 500 milliInternational Units after the 6-month booster and was still over 100 units 24 months after the first injection.

Although employment of a variety of inactivation steps in the vaccine production (pepsin digestion, treatment with urea, and formalin) may have led to a less vigorous antibody response than one would desire, this did not seem to affect the protective efficacy of the vaccine: the reduction in incidence during the first months after entry was found to be greater than one would project from the timing of seroconversion rates.

Although the 21 nonresponders to the vaccine constituted merely 4.7% of the total group of vaccine recipients, they accounted for 7/9 HBV events among those with a completed vaccination regimen. At present, little is known about the nonresponders and why they do not respond to the vaccine. A much larger number of nonresponders, males and females, young and old, immune competent and immune defective, will have to be studied in order to answer these questions. As mentioned above, the few nonresponders so far tested seem to differ from the population at large with respect to certain antigens of the B and DR loci. Two other preliminary observations deserve mention: (a) of the seven nonresponders who contracted HBV infection, all but one subsequently developed anti-HBs, most with Ausab RU values greater than 100, and (b) some of the nonresponders treated 18 months later with two additional 40 μg doses of the vaccine did subsequently develop antibody (Stevens and Szmuness, unpublished data).

The immune response described in this report was induced by three doses of the vaccine, 40 μg each. Will 20-μg doses be as efficacious as 40 μg? Overwhelming evidence accumulated after our trial began indicates that the answer to this question should be positive. In studies conducted in two groups of medical staff and in young males in Greece, Krugman found that the immune response to 20-μg doses of the same Merck vaccine was exactly the same as to 40-μg doses (Krugman et al.). Similar observations have been made by Hilleman and McLean in various groups of children and adults (McLean, personal communication). In our own studies conducted in a large group of dialysis staff from 44 United States dialysis centers, the conversion rate after three 20-μg doses of the Merck vaccine was 97 to 99% (Szmuness and Stevens). Because this trial proved that the presence of anti-HBs means protection, we may conclude that vaccination with three 20-μg doses of vaccine will be as protective as with larger doses. Reducing the vaccine dose would substantially increase the supply of vaccine and reduce its cost.

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