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SUMMARY FOR BASIS OF APPROVAL

Reference No. 85-053

Drug Licensed Name: **Hepatitis B Vaccine (Recombinant)**

Mfr: **Merck Sharp & Dohme (MSD)**

Drug Trade Name: **RECOMBIVAX HB®**

Hepatitis B Vaccine (Recombinant), RECOMBIVAX HB, is a non-infectious subunit viral vaccine derived from synthetic hepatitis B surface antigen (HBsAg) produced in yeast cells. A plasmid containing a portion of hepatitis B virus gene coding for HBsAg is cloned into yeast, and the vaccine for hepatitis B is produced from cultures of this recombinant yeast strain.

I. INDICATIONS FOR USE:

RECOMBIVAX HB is indicated for immunization against infection caused by all known subtypes of hepatitis B virus (HBV). The vaccine has been shown to be effective in inducing an immune response (anti-HBs) in initially seronegative adults and children. It has been shown to be effective in preventing chronic hepatitis B infection among infants of carrier mothers when used in conjunction with one dose of hepatitis B immune globulin.

RECOMBIVAX HB will not prevent hepatitis caused by other agents such as hepatitis A virus, non-A, non-B hepatitis viruses or other viruses known to infect the liver.

Vaccination is recommended for those persons who are or will be at increased risk of infection with all known subtypes of hepatitis B virus, including persons employed in a variety of health care occupations, patients requiring frequent and/or large volume blood transfusions or clotting factor concentrates, residents and staff of institutions for the mentally handicapped, intimate contacts of persons with persistent hepatitis B antigenemia, infants born to HBsAg positive mothers, persons at increased risk due to their sexual practices, and users of illicit injectable drugs. Additional studies are in progress in dialysis patients.

Studies are ongoing to determine the need and timing for revaccination.

II. DOSAGE AND ADMINISTRATION:

RECOMBIVAX HB consists of hepatitis B surface antigen which is produced in yeast cells. The isolated and purified antigen is adsorbed onto aluminum hydroxide as an adjuvant, and thimerosal is added as a preservative. A 1.0 ml dose of the adult formulation of the vaccine

contains 10 mcg of hepatitis B surface antigen adsorbed onto 0.5 mg of aluminum hydroxide; a 0.5 ml dose of the pediatric formulation contains 5 mcg of hepatitis B surface antigen adsorbed onto 0.25 mg of aluminum hydroxide. All formulations of vaccine contain 1:20,000 thimerosal as preservative. The vaccine has been treated with formaldehyde prior to adsorption onto alum.

Primary vaccination consists of three injections of vaccine, with the second and third injections given 1 and 6 months, respectively, after the first. Adults and children above 10 years of age are given 10 mcg (1.0 ml) of hepatitis B surface antigen per injection, while children from birth to 10 years of age receive 5 mcg (0.5 ml) of hepatitis B surface antigen per injection. Infants born to HBsAg positive mothers should receive at birth Hepatitis B Immune Globulin in conjunction with the first dose of RECOMBIVAX HB in different sites. All injections are given intramuscularly in the deltoid muscle in adults and children or in the anterolateral thigh muscle in infants and neonates, except those given to persons with hemophilia or similar disorders which are given subcutaneously. Data suggest that injections given in the buttocks are less effective in producing an immune response, perhaps since injections in the buttocks may frequently be given into fatty tissue instead of into muscle.

III. MANUFACTURING AND CONTROLS:

A. MANUFACTURING AND CONTROLS

The organism, Saccharomyces cerevisiae, strain (b)(4) (b)(4), which is utilized for the production of HBsAg, contains a plasmid containing a gene for the adw subtype of HBsAg. The culture is grown in a Yeast Extract/Soy Peptone/Dextrose (YEHD) medium at (b)(4) The fermentations are (b)(4)

(b)(4)

(b)(4)

(b)(4)

The final container is tested for sterility, general safety, (b)(4) thimerosal, (b)(4) aluminum (b)(4) and potency in mice (b)(4) (b)(4)

The manufacturer submitted for evaluation samples and protocols of five final container lots of vaccine derived from five different bulk lots produced initially at production scale. These lots met the release specifications listed at the time of their manufacture. Subsequently, modifications to the release specifications have been incorporated into the license application. These include a (b)(4) yeast impurity specification from (b)(4) to (b)(4) and a change in the (b)(4) specification for the mouse potency test from 3.0 mcg/ml to 1.5 mcg/ml. The specification requires that (b)(4) (b)(4) Additional lots have been submitted for release which when tested by the manufacturer meet all of the current release specifications.

B. STABILITY STUDIES

The recommended storage temperature of the vaccine, adsorbed onto alum is 2-8°C. Stability of the vaccine was monitored by the demonstration of potency in an in vivo mouse model and by (b)(4) (b)(4) (b)(4) of the vaccine was studied through (b)(4) (b)(4) at 2-8°C. and (b)(4) to 24 months at 2-8°C. No significant differences in potency which would indicate a loss in the immunizing potential of the product were observed throughout the period. Other studies are in process. Accelerated stability studies at (b)(4) were carried out. By the mouse potency assay, statistically significant degradation was noted only at (b)(4) By (b)(4) measurable loss of antigen occurred at temperatures (b)(4) (b)(4)

The product will have an expiration dating of twenty-four months at 2-8°C. The package insert recommends storage at 2-8°C. which is supported by the stability studies. Merck has committed to conduct ongoing stability studies.

C. VALIDATION

The major equipment used in the manufacture and filling of the vaccine has been validated at the Merck & Co., Inc., West Point, PA, facilities. In addition, appropriate specifications have been established for monitoring environmental conditions for critical work areas in this facility by the Environmental Control Department, MSD. Validation analyses for product potency and purity are performed at MSD. The test methods were found to be suitable for control and regulatory purposes.

D. LABELING

The labeling, including the package insert, has been reviewed for compliance with 21 CFR 610.60, 610.61, 610.62, 201.56 and 201.57 and found satisfactory. The container label includes a warning statement indicating "Do Not Inject Intravenously", a caution statement that federal law prohibits dispensing without prescription, a statement to "Shake Well Before Using", a statement to store at 2-8°C. (35.6 - 46.4°F) and a warning statement "Do Not Freeze." A statement to see the accompanying circular for dosage instructions is also included.

The package insert (copy attached) contains appropriate statements concerning product description, clinical pharmacology, indications and use, contraindications, warnings, precautions, adverse reactions, how supplied, dosage and administration and information on the storage of the vaccine.

E. ESTABLISHMENT INSPECTION

A pre-license inspection of the MSD biological production facilities in West Point, PA, was conducted May 12-14, 1986. No objectionable practices or exceptions to the regulations were observed.

F. ENVIRONMENTAL IMPACT ANALYSIS REPORT

An environmental assessment for the manufacture and use of RECOMBIVAX HB was completed to address the environmental impact considerations of 21 CFR, Part 25. The information provided for this environmental assessment supports the finding of no significant environmental impact. (Exhibit 2)

IV. PHARMACOLOGY, BIOCHEMISTRY AND SEROLOGY:

RECOMBIVAX HB is composed of HBsAg which is the product of a plasmid containing a portion of the hepatitis B virus gene that codes for HBsAg and which was derived from plasma of a donor infected with hepatitis B virus, subtype adw. This plasmid has been cloned into yeast. (b)(4)

(b)(4)

Serological studies have been performed to evaluate the anti-HBs antibodies raised in recipients of yeast-derived vaccine. Cross-adsorption studies were performed on anti-HBs in five recipients of yeast-derived vaccine four months post-vaccination and in six recipients of plasma-derived vaccine three months post-vaccination. In all five samples from yeast vaccine recipients 99-100% of the anti-HBs antibodies were adsorbed by both yeast-derived and plasma-derived antigen. In the six samples from plasma-derived vaccine recipients, 99-100% of the anti-HBs antibodies were adsorbed by plasma-derived HBsAg and 87-99% by yeast-derived antigen. The mean affinity constants obtained against a synthetic cyclic peptide derived from the HBsAg sequence were 4×10^7 for antibodies from both plasma-derived vaccine recipients and yeast-derived vaccine recipients.

An inhibition assay using a monoclonal antibody that had been shown to protect chimpanzees from hepatitis B infection showed 38% inhibition (10-69%) of the monoclonal antibody by samples from 10 yeast-derived vaccinees and 54% inhibition (18-99%) by samples from 10 plasma-derived vaccinees.

Avidity constants against entire HBsAg ranged from 4 to 8×10^{10} in six samples at 3 months post-vaccination from plasma-derived vaccinees and 1 to 16×10^{10} in six samples from yeast-derived vaccinees.

Comparison of the proportions of the anti-a and anti-d components of the anti-HBs response showed that at 7 months post-vaccination 95% of the anti-HBs was anti-a and 5% anti-d in 27 samples of yeast vaccine recipients and 93% anti-a and 7% anti-d in 8 samples from plasma-derived vaccine recipients.

These serological studies show that although the antibodies induced by yeast-derived and plasma-derived antigen are comparable, 1) yeast-derived antigen is slightly less capable of adsorbing antibody induced by plasma-derived antigen, 2) the antibody induced by yeast-derived antigen is somewhat less reactive in a cross inhibition assay with a protective monoclonal antibody and 3) the antibodies induced by yeast-derived antigen show greater variability in their avidity constants.

V. MEDICAL:

A. GENERAL INFORMATION

Hepatitis B virus is one of several viruses (hepatitis A, hepatitis B and several non-A, non-B hepatitis) causing a systemic infection with pathologic changes in the liver. It is a major cause of acute and chronic hepatitis and cirrhosis and has been implicated in the etiology of primary hepatocellular carcinoma worldwide. There is no effective treatment for hepatitis B infection. Six to 10% of young adults infected with hepatitis B in the United States fail to eliminate the virus and become persistently infected (chronic HBsAg carriers). It is estimated that there are 0.7 to 1.0 million chronic carriers of hepatitis B virus in the United States and more than 170 million in the world.

In the United States and Northern Europe, hepatitis B virus infects mainly adults, while children are most affected in developing areas of the world. In both cases, the virus is maintained in populations primarily by transfer of infection from chronic carriers. Such spread is effected through blood transfusion, exposure to contaminated needles or instruments, through sexual contact and by spread from carrier mother to infant in the perinatal period.

Hepatitis B surface antigen is the main component of the outer envelope of the 42 nm hepatitis B virus. Excess HBsAg is also produced in particles that are 18-22 nm in diameter. HBsAg has been found in the blood and other clinical specimens including saliva, urine, bile and feces of infected persons.

Antibodies to HBsAg (anti-HBs) have been shown to be protective against infection with HBV. A safe and effective hepatitis B vaccine comprised of hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of the virus is commercially available. An attractive alternative to human plasma as a source of HBsAg is the use of recombinant DNA technology to effect synthesis of HBsAg by a culture of microorganisms. Vaccine prepared from yeast by recombinant DNA technology was shown to be safe and antigenic in monkeys and chimpanzees and also protective in chimpanzees subsequently challenged with infectious hepatitis B virus.

B. CLINICAL STUDIES

From July 1983 to January 1986 RECOMBIVAX HB was administered to approximately 3800 participants enrolled in 50 clinical studies to assess immunogenicity and safety. The populations included in the studies are summarized in Table 1. In addition, the four studies in infants born to carrier mothers were designed to assess protection from chronic infection.

The vaccine was administered as a series of three intramuscular injections. The first two injections were given one month apart followed by a third or booster injection given six months after the first dose.

Vaccine recipients were asked to report their temperature and any injection site or systemic sequelae that occurred within a five day period following each injection of vaccine.

Post-vaccination blood samples were obtained for the determination of antibody to hepatitis B surface antigen (anti-HBs), other hepatitis B virus serologic markers (HBsAg, anti-HBc), serum alanine aminotransferase (ALT) activity, and in some instances, antibody to yeast antigens.

1. SAFETY

The vaccine was proven non-infectious for man in a human safety test in which a single 1.0 ml dose of vaccine containing 10 mcg of HBsAg was administered to each of five initially seronegative persons who were followed serologically for 6 months for appearance of markers of hepatitis B infection. No markers were detected.

RECOMBIVAX HB has been well tolerated. There have been no serious or alarming reactions directly attributable to vaccine reported among subjects who participated in the clinical studies. The types and incidence of complaints which were reported within five days following administration of 3258 injections of vaccine to 1252 healthy adults who participated in clinical studies for which analysis has been completed are summarized in Table 2. Injection site and systemic complaints were reported following 17% and 15% of the injections, respectively. Comparable rates of systemic reactions were observed in controlled clinical studies using plasma-derived vaccine in both the immunized and placebo groups. The most frequent specific injection site reactions were soreness, pain and tenderness. The most frequent systemic complaints were fatigue/weakness and headache.

In the clinical trials, no cases of anaphylaxis, severe bronchospasm or laryngeal edema were reported. There were 3 reports of urticaria, one of facial edema and 16 reports of "rash". Antibodies to yeast have been observed both pre- and post-immunization. Testing for serum IgG and IgE antibodies to yeast proteins in individuals with allergic reactions indicated no correlation between antibody responses to yeast antigens and allergic reactions.

The frequency of clinical complaints reported within five days following administration of 231 injections of vaccine to 80 healthy children (3 months to 11 years) for which analysis has been completed are summarized in Table 3. Systemic complaints including fatigue, weakness, diarrhea and irritability were reported following 14% of the injections. Injection site complaints consisting principally of soreness were reported following 2% of the injection.

2. IMMUNOGENICITY

Clinical studies have demonstrated that Hepatitis B Vaccine (Recombinant) induces protective levels of antibody in greater than 90% of healthy individuals who received the recommended three-injection regimen. A protective antibody level has been defined as 10 or more milli-International Units/ml (mIU/ml) as determined by (b)(4).

Anti-HBs responses of 511 healthy adults 20-69 years of age, 83 healthy children, and 53 dialysis patients are summarized in Table 4. The doses used were 3 x 10 mcg for adults, 3 x 5 mcg for children and 3 x 40 mcg for dialysis patients.

Antibody response to the vaccine is age dependent. The younger the vaccinee, the greater the likelihood of an immune response developing. Antibody seroconversion rates for children 1 to 10 years of age were 100% with Geometric Mean Titer (GMT) of 15,966 mIU/ml. Seroconversion rates for adults ranged from 95% to 99% for those 20 to 39 years of age and 91% for those 40 years of age or older. The Geometric Mean Titers (GMT) were 1707 mIU/ml for the 20-29 year age group and 484 mIU/ml for the 40-49 year age group. Immunocompromised persons respond less well to the vaccine than do healthy individuals. Sixty-eight percent of predialysis and dialysis patients who received three 40 mcg doses of vaccine developed protective level of anti-HBs and had a GMT of 178 mIU/ml.

Preliminary data from a double-blind, randomised, controlled study in healthy adults comparing this product and the currently licensed plasma-derived vaccine show at nine months comparable seroconversion rates of 91% (40/44) for the

recombinant vaccine and 93% (38/41) for the plasma-derived one. The GMT (402 mIU/ml) seen in these recipients of the recombinant vaccine was less than half that seen in the recipients of the plasma-derived vaccine (1676 mIU/ml).

3. EFFICACY

The protective efficacy of RECOMBIVAX HB has been demonstrated in neonates born to mothers positive for both HBsAg and HBeAg. In two clinical studies of infants who received the recommended one injection of hepatitis B immune globulin at birth followed by a three injection regimen of vaccine, efficacy in prevention of chronic hepatitis B infection was 93% in 40 infants at 6 months in one study and 93% in 57 infants at nine months in the other study.

VI. ADVISORY PANEL CONSIDERATION.

Data concerning the manufacture, safety and efficacy of Hepatitis B Vaccine (Recombinant) for the prevention of hepatitis B were discussed at the Vaccines and Related Biological Products Advisory Committee meeting on June 7, 1984, October 4, 1984 and April 3, 1986.

VII. APPROVED PACKAGE INSERT

A copy of the approved package insert is attached. (Exhibit 1)

Daljit K. Gill

Daljit K. Gill, M.D.
Chairman

Ira Berkower

Ira Berkower, M.D.

Neil Goldman

Neil Goldman, Ph.D.

Barbara C. Meyer

Barbara C. Meyer

Elizabeth B. Paul

Elizabeth B. Paul

Linda A. Smallwood

Linda A. Smallwood, Ph.D.

TABLE 1

PERSONS INCLUDED IN CLINICAL STUDIES OF HEPATITIS B VACCINE (RECOMBINANT) BETWEEN JULY 1983 AND JANUARY 1986

Populations	No. Vaccinated (≥1 Injection)
Health Care Personnel/ Other Healthy Adults	2414
Healthy Teenagers	165
Healthy Infants/Children	258
Dialysis/Predialysis Patients	288
Infants of Carrier Mothers	289
Other Groups	447
Mentally retarded institutionalized patients	
Patients with thalassemia, hemophilia, or sickle cell anemia	
Hyporesponders or nonresponders to plasma-derived vaccine	
Preimmune adults	
Chronic carriers of HBsAg	

TABLE 2

FREQUENCY OF CLINICAL COMPLAINTS WITHIN 5 DAYS FOLLOWING ADMINISTRATION OF 3255 INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) TO 1252 HEALTHY ADULTS

Clinical Complaint	% of Injections With Complaint
INJECTION SITE	
Injection site reactions consisting principally of soreness, and including pain, tenderness, pruritis, erythema, ecchymoses, swelling, warmth, and nodule formation.	16.7
BODY AS A WHOLE	
Fatigue/weakness	4.2
Headache	4.1
Fever (≥100°F)	3.2
Malaise	1.2
Sweating	0.5
Achiness	0.4
Sensation of warmth	0.4
Lightheadedness	0.3
Chills	0.2
Flushing	0.2
DIGESTIVE SYSTEM	
Nausea	1.8
Diarrhea	1.1
Vomiting	0.3
Abdominal pains/cramps	0.3
Dyspepsia	0.2
Diminished appetite	0.1
RESPIRATORY SYSTEM	
Pharyngitis	1.2
Upper respiratory infection	1.0
Rhinitis	0.8
Influenza	0.3
Cough	0.2

TABLE 2
(Continued)

FREQUENCY OF CLINICAL COMPLAINTS WITHIN 5 DAYS FOLLOWING ADMINISTRATION OF 3255 INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) TO 1252 HEALTHY ADULTS

Clinical Complaint	% of Injections With Complaint
NERVOUS SYSTEM	
Vertigo/dizziness	0.5
Paresthesia	0.1
INTEGUMENTARY SYSTEM	
Pruritis	0.3
Rash (non-specified)	0.2
Urticaria	0.1
MUSCULOSKELETAL SYSTEM	
Arthralgia including monoarticular	0.5
Myalgia	0.4
Back pain	0.2
Neck pain	0.2
Shoulder pain	0.2
Neck stiffness	0.2
HEMIC/LYMPHATIC SYSTEM	
Lymphadenopathy	0.2
UROGENITAL SYSTEM	0.2
CARDIOVASCULAR SYSTEM	0.2
PSYCHIATRIC/BEHAVIORAL	
Insomnia/Disturbed Sleep	0.1
SPECIAL SENSES	
Earache	0.2

TABLE 3

FREQUENCY OF CLINICAL COMPLAINTS WITHIN 5 DAYS FOLLOWING ADMINISTRATION OF 231 INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) TO 80 HEALTHY CHILDREN

Clinical Complaint	% of Injections With Complaint
INJECTION SITE	
Injection site reactions consisting principally of soreness	2.2
BODY AS A WHOLE	
Fatigue/weakness	3.0
Headache	0.8
Sweating	0.4
Bruise from venipuncture	0.4
Illness	0.4
DIGESTIVE SYSTEM	
Diarrhea	2.0
Vomiting	1.3
Diminished appetite	0.4
Loose stool	0.4
Nausea	0.4
Teething	0.4
RESPIRATORY SYSTEM	
Upper respiratory infection	2.6
Pharyngitis	0.8
Rhinitis	0.8
Cough	0.4
Croup	0.4
INTEGUMENTARY SYSTEM	
Papular Rash	0.8
Rash (non-specified)	0.4
Urticaria	0.4

TABLE 3
(Continued)

FREQUENCY OF CLINICAL COMPLAINTS WITHIN 5 DAYS FOLLOWING ADMINISTRATION OF 231 INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) TO 80 HEALTHY CHILDREN

Clinical Complaint	% of Injections With Complaint
PSYCHIATRIC/BEHAVIORAL	
Irritability	1.7
Insomnia/Disturbed Sleep	0.4
INFECTIOUS SYNDROMES	
Viral infection	1.7
SPECIAL SENSES	
Otitis media	0.4

TABLE 4

ANTIBODY RESPONSES AT 7/8 MONTHS AMONG HEALTHY INDIVIDUALS AND DIALYSIS PATIENTS WHO RECEIVED THREE INJECTIONS OF HEPATITIS B VACCINE (RECOMBINANT) AT 0, 1 AND 6 MONTHS

				% Seroconversion	GMT(mIU/ml)
Population	Age	No.	Dose	mIU/≥10	mIU/ml≥10
Healthy Individuals	1 - 11 yrs.	14	5 mcg	100	15966.0
	12 - 19 yrs.	69	10 mcg	100	2913.4
	20 - 29 yrs.	344	10 mcg	99	1737.0
	30 - 39 yrs.	111	10 mcg	95	730.0
	≥40 yrs.	56	10 mcg	91	586.5
Dialysis Patients	≥20 yrs.	53	40 mcg	68	178.1

BRIEF SUMMARY OF YEAST RECOMBINANT HEPATITIS B VACCINE CLINICAL REPORT

I. CLINICAL AND SEROLOGIC DATA

Study Population	Number Vaccinated ≥1 Injection	Number Vaccinated 3 Injections	Clinical Reports ≥1 Injection	Clinical Reports 3 Injections	Serologic Data ≥1 Injection	Serologic Data 3 Injections
Health Care Personnel/ Other Healthy Adults	2414	1442	1626	990	1616	1048
Healthy Teenagers	165	165	165	165	165	165
Healthy Infants/ Children	258	122	220	100	213	97
Dialysis/Predialysis Patients	288	196	286	184	258	166
Other Groups	736	362	581	110	633	80

II. IMMUNOGENICITY

Antibody responses across all dose levels used are summarized below:

Study Populations	% with Anti-HBs After 3 Injections Minimal Titer (S/N ≥2.1)	Fully Protective Titer (mIU/ml ≥10)
Health Care Personnel/ Other Healthy Adults	98	96
Healthy Teenagers	100	98
Healthy Infants/Children	100	100
Dialysis/Predialysis * Patients	94	88

*Figures apply to patients that received three 40 mcg doses in the deltoid. See SUMMARY - DIALYSIS AND PREDIALYSIS PATIENTS for discussion of other regimens that were less immunogenic.

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III. CLINICAL REACTIONS

There have been no reports of serious adverse experiences attributable to vaccination. Clinical reactions following vaccination have been mild and transient consisting mostly of soreness at the injection site, fatigue/weakness, headache, and nausea. Complaint frequencies across all dose levels used are summarized below:

Study Populations	% of Injections Followed by Clinical Complaints			
	Local (Injection Site)	Systemic	Any Complaint	Temperature ≥100°F (Oral)
Health Care Personnel/ Other Healthy Adults	17	15	27	3
Healthy Teenagers	5	2	6	0.2
Healthy Infants/Children	2	9	11	11
Dialysis/Predialysis Patients	3	8	10	5

IV. EFFICACY

Passive-active prophylaxis consisting of hepatitis B immune globulin and yeast recombinant hepatitis B vaccine was 98% effective in preventing chronic hepatitis B infection among infants born to mothers positive for both HBsAg and HBeAg (59 infants evaluated at six months).

GENERAL SUMMARY

Clinical studies with the yeast recombinant hepatitis B vaccine were initiated in July 1983. This document includes data from studies concerned with the vaccine's safety, immunogenicity and efficacy which were generated to support a license for the vaccine in the United States. Summaries and analyses across studies of clinical complaints and serologic responses are based on data encoded within the project database by October 15, 1985. However, several individual study summaries are derived from more recent data that have not yet been entered in the database.

VACCINE

A total of 28 lots of yeast recombinant hepatitis B vaccine have been prepared by Merck and Co., Inc., according to procedures developed in the Merck, Sharp and Dohme Research Laboratories. Eighteen of the lots are in use in human clinical trials (see Appendix I). All clinical data received to date indicate that the vaccine is safe. One of the lots (C-J625) was made using (b)(4) procedure and was (b)(4) The clinical and serologic data relating to this lot will be summarized separately, because this procedure will not be used in making commercial vaccine (see section entitled (b)(4) VACCINE). The remainder of the lots were made using a (b)(4) procedure and are in clinical trials under BB IND 1925.

CLINICAL STUDIES

Table 1 lists 50 clinical studies involving the yeast recombinant hepatitis B vaccine produced by the (b)(4) procedure that are currently in progress.

In most of the studies, participants receive the vaccine as an intramuscular injection administered at 0, 1 and 6 months. However, chronic carriers of HBsAg and certain groups of dialysis patients receive a total of 6 doses of vaccine administered at monthly intervals, while persons with prior immunity and subjects in the study designed to demonstrate noninfectivity of the vaccine are given only a single dose of vaccine. Patients with hemophilia receive the vaccine as a subcutaneous injection. Each dose of vaccine (total mcg of HBsAg administered at a given time) is generally contained within a single injection. However, each 40 mcg dose given to dialysis and predialysis patients consists of a pair of 20 mcg injections.

The numbers of subjects who have received first, second and third injections of the yeast recombinant hepatitis B vaccine are shown by population in Table 2. A total of 3861 participants have received one or more injections of vaccine, while 2309 individuals have completed a 3 dose regimen of vaccination.

Vaccinees in all studies are asked to record their temperature daily and to record any local or systemic complaints that they may have for 5 days following each injection of vaccine. Table 2 also shows by population the number of subjects for whom post vaccination clinical reports are currently available. Clinical reports following the first injection have been received for 2878

vaccinees, while 1571 reports are available for subjects who have received 3 doses of vaccine.

Postvaccination blood samples are obtained for the determination of antibody to hepatitis B surface antigen (anti-HBs), other hepatitis B virus serologic markers, alanine aminotransferase (ALT), and antibody to yeast antigens. Table 2 also shows by population the number of subjects for whom postvaccination anti-HBs data are available. Anti-HBs titers are known for 1551 subjects following 3 doses of vaccine and are available for an additional 1334 individuals following only the first or second injection of vaccine.

IMMUNOGENICITY

Anti-HBs Assay

Immune responses to vaccine are measured using a radioimmunoassay (b)(4) (b)(4) to detect antibody (anti-HBs) specific for the hepatitis B virus surface antigen (HBsAg). Two different cutoff values have been utilized in determining a positive antibody response; one to indicate seroconversion, the other an attempt to define a minimum level of antibody clearly indicative of protection from clinical infection. The lower cutoff is taken as a ratio of sample counts to negative control counts (S/N) $\geq$2.1. The higher cutoff defines as positive a sample having an anti-HBs titer in milli-International Units/ml (mIU/ml) $\geq$10. Anti-HBs titers expressed as S/N ratios cannot be converted directly into units of mIU/ml. However, the two scales of measurement are fairly similar at low titers (i.e. S/N of $\leq$10 is approximately the same as an mIU/ml of $\leq$10). There is a developing concensus that views an anti-HBs titer of S/N or mIU/ml $\geq$10 as fully adequate for protection against hepatitis B. (Centers for Disease Control: Recommendations for protection against viral hepatitis. MMWR 34 (22):313-335, June 7, 1985)

Anti-HBs responses among healthy, initially seronegative persons receiving yeast recombinant hepatitis B vaccine (b)(4) procedure) at 0, 1 and 6 months, and for whom post vaccination anti-HBs are available in units of mIU/ml, are summarized in Tables 3 to 6. Additional tabulations and discussions of antibody responses for these and other groups will be found in the population-specific summaries. Very brief accounts of the immune responses of each population are given in the following paragraphs of this general summary.

Health Care Personnel/Other Healthy Adults

Thirty-six studies are in progress involving 2414 health care personnel or other healthy adults. Participants receive a dose of the recombinant vaccine (2.5, 5, 10 or 20 mcg) at 0, 1 and 6 months. Fourteen hundred and forty-two (1442) persons have completed a 3 injection regimen of vaccination. Anti-HBs responses following the third injection have been measured for 1048 subjects and responses following only one or two injections have been measured for an additional 568 vaccinees.

Tables 3 to 6 summarize the anti-HBs responses of 801 adults, 20-69 years of age, who received 2.5, 5, 10 or 20 mcg doses of vaccine, and for whom data are available reported in units of mIU/ml. At 7/8 months (1-2 months after the third injection), 97-100% of the vaccinees had an anti-HBs titer of S/N $\geq$2.1, while 89-97% achieved a protective titer of mIU/ml $\geq$10 (Table 5). At 12 months,

92-97% of the vaccinees still had an anti-HBs titer of S/N ≥2.1, while 74-90% (86-90% of those receiving doses of 10 mcg or more) had titers of mIU/ml ≥10 (Table 6).

The level of anti-HBs attained after 3 injections of vaccine does increase with dose level (Table 5). Age and sex also influence the antibody response to vaccine. Anti-HBs levels are inversely related to age, while females tend to develop higher antibody titers than males (see SUMMARY - HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS for statistical analysis of these factors).

For healthy adults as a group, a vaccination regimen consisting of three 10 mcg doses is sufficient to induce fully protective titers of antibody (mIU/ml ≥10) in 97% of the vaccinees.

Healthy Teenagers

The vaccine has been administered at 0, 1 and 6 months to 165 seronegative, healthy teenagers (all male military recruits mostly 17-19 years of age). Subjects received 2.5, 5 or 10 mcg doses. All of the vaccine recipients had anti-HBs titers of S/N >2.1 by 7 months regardless of dose level. Using a cutoff of mIU/ml >10, 100% of subjects receiving 10 or 5 mcg doses were antibody positive, while 94% of those receiving 2.5 mcg doses had antibody at that time. Response level (titer) was found to increase significantly with dose level (see SUMMARY - HEALTHY TEENAGERS for details of the statistical analysis). At each dose level, the geometric mean antibody titers attained by teenage subjects following 3 doses of vaccine were greater than those developed by young adults (Table 5). At 12 months, 100% of those who received 10 or 5 mcg doses of vaccine have antibody, while 91% of those who received 2.5 mcg doses continue to have protective levels of anti-HBs.

Healthy Infants/Children

To date, a total of 258 healthy infants and children, 3 months to 11 years of age, who were negative for hepatitis B markers, have been vaccinated with hepatitis B recombinant vaccine. Seven to 8 month serology data are available on 97 infants and children. Antibody responses to 5, 2.5 and 1.25 mcg doses of the vaccine administered at 0, 1 and 6 months were evaluated. The vaccine was very immunogenic in this population. Seroconversion (S/N ≥2.1) exceeded 94% after 2 doses regardless of dose level. Protective levels of antibody (mIU/ml >10) were induced in 100% of vaccine recipients, one month after the third injection, regardless of dose level administered. Statistical analysis of data from study 809 showed that both log dose level and the age of the child were related to antibody titer (see SUMMARY - HEALTHY CHILDREN for details of the statistical analysis). Titers increased with log dose level, and younger children had higher titers than older children. As shown in Table 5, the GMT of anti-HBs at 7/8 months in children receiving 2.5 or 5 mcg doses of vaccine (based on study 809 only) were higher than those developed by teenagers receiving comparable dosages. At 12 months, all children surveyed still had titers of mIU/ml >10.

Dialysis and Predialysis Patients

Five studies are in progress involving 288 patients with chronic renal insufficiency. Two hundred ten patients are receiving dialysis treatments (dialysis patients), while 78 are not yet receiving such treatments (predialysis

patients). Predialysis patients receive an injection of the yeast recombinant hepatitis B vaccine (10, 20, or 40 mcg dose) at 0, 1, and 6-months. Dialysis patients receive an injection of the vaccine (20, 40 or 100 mcg dose) either at 0, 1, and 6 months or according to a more intensified regimen (20 or 40 mcg dose) at 0, 1, 2, 3, 4 and 5 months. In four of the studies, patients received the vaccine as an intramuscular injection in the deltoid. However, in one study, vaccine was administered in the buttock.

One hundred forty-seven dialysis patients and 52 predialysis patients have completed a three injection regimen of vaccination, and 34 dialysis patients have completed a six injection regimen. Serologic data following the last injection of vaccine are currently available for 50 predialysis and 84 dialysis patients who received three injections of vaccine and 32 dialysis patients on the six injection regimen. Because of the multiplicity of regimens utilized, antibody responses are summarized below in tabular form:

Patient Group	Regimen (# Doses)	Dose (mcg)	Inject. Site (B/D)	% with Anti-HBs (# Evaluated) 7/8 Months S/N ≥2.1	7/8 Months mIU/ml ≥10	12 Months S/N ≥2.1	12 Months mIU/ml ≥10
Predialysis	3	10	D	15 (13)	15 (13)	8 (12)	0 (12)
		20	D	68 (19)	58 (19)	71 (14)	50 (14)
		40	D	67 (18)	61 (18)	40 (10)	40 (10)
Dialysis	3	20	D	59 (29)	48 (29)	52 (29)	41 (29)
		40	D	94 (17)	88 (17)	81 (21)	71 (21)
		40	B	64 (36)	58 (36)	65 (37)**	54 (37)**
	6	20	B	56 (16)*	44 (16)*	50 (18)**	44 (18)**
		40	B	69 (16)*	69 (16)*	67 (15)**	60 (15)**

* 6 months
** 10 months
B = buttock
D = Deltoid

Serologic data are currently available following two injections of vaccine for dialysis patients receiving 100 mcg doses. At three months, 68% (19/28) had antibody (S/N ≥2.1), while 25% had a fully protective titer (mIU/ml≥10).

In summary, predialysis and dialysis patients do not respond to the vaccine as well as healthy adults. Responses to the vaccine among patients improved with increasing dose and were better with administration in the deltoid as opposed to the buttock. Responses to the three injection and intensified six injection regimens of vaccination appear to be similar.

Mentally Retarded Institutionalized Patients

One study is in progress including 202 mentally retarded individuals. Participants receive a 10 mcg or 20 mcg dose of the recombinant vaccine at 0, 1 and 6 months. Two hundred persons have completed a three injection regimen of vaccination. Anti-HBs responses following only one injection are available for 201 vaccinees. At 1 month 19-20% had an anti-HBs titer of S/N ≥2.1, while 8-11% achieved a protective titer of mIU/ml ≥10.

Thalassemics/Hemophiliacs

Thirty-one thalassemic children (<16 years of age) have received intramuscular injections of yeast recombinant hepatitis B vaccine in a single study. Among 15 children who received three 5 mcg doses, 89% had at least minimal evidence of anti-HBs at 7 months (S/N $\geq$2.1), while 78% had fully protective titers (S/N $\geq$10). Twelve children have received three 2.5 mcg doses of vaccine. At 7 months, all had titers of S/N $\geq$10.

Fifteen patients with hemophilia have been vaccinated subcutaneously in a single study. Twelve subjects under 20 years of age who received two 5 mcg doses all had protective levels of antibody by 3 months (mIU/ml $\geq$10). Three patients $\geq$20 years of age have received 10 mcg doses of vaccine. At 3 months, 2 of these patients had seroconverted (S/N $\geq$2.1), but neither had achieved a protective level of antibody (mIU/ml $\geq$10).

Nonresponders/Hyporesponders/Transient Responders

Six studies are in progress involving 55 healthy adults and 26 dialysis patients who failed to develop detectable anti-HBs after three injections of plasma-derived hepatitis B vaccine. The studies also include five healthy adults who were hyporesponders or transient responders to the plasma-derived vaccine. Nonresponders receive an injection of the yeast recombinant vaccine (10 or 20 mcg doses for healthy individuals and 40 mcg doses for dialysis patients) at 0, 1, and 6 months. Hyporesponders and transient responders receive a single injection containing 10 mcg of the yeast recombinant hepatitis B vaccine.

Thirty nonresponders (24 healthy adults and six dialysis patients) have completed the three injection regimen of vaccination. Anti-HBs (S/N $\geq$2.1) was detectable in 79% (11/14) of the adults measured at 7-9 months, while 50% had protective titers (mIU/ml $\geq$10). Two of four dialysis patients monitored at 7-9 months developed antibody titers of mIU/ml $\geq$10.

Three of four hyporesponders/transient responders had protective titers of anti-HBs one month after receiving a dose of the yeast recombinant vaccine.

Preimmune Adults

Two studies are being conducted to examine the response of adults, who have been documented to have hepatitis B antibody at some time in the past, to a single 5 or 10 mcg booster injection of yeast recombinant hepatitis B vaccine. Sixty-three persons have received a 10 mcg dose of vaccine. Ninety-seven percent of those participants whose anti-HBs responses were measured approximately one month following the booster demonstrated a boost in titer at that time. One individual who was antibody negative just prior to the booster injection failed to develop detectable antibody. Twenty-eight individuals received a 5 mcg booster injection. All of 25 participants tested at one month after the injection demonstrated a boost in anti-HBs titer.

Chronic Carriers

One study is being conducted to determine whether vaccination can eliminate the carrier state. Eighteen adult chronic carriers (positive for HBsAg for at least one year) have been scheduled to receive six 10 mcg doses of recombinant hepatitis B vaccine at monthly intervals. Three participants have received all

six doses; eighteen have received at least four doses. Administration of the remaining doses continues in progress. To date, none of the carriers has become negative for HBsAg.

Anti-HBs Subtype Specificity

Four major subtypes of the hepatitis B virus are known with respect to the antigenic composition of HBsAg. The subtypes are designated adw, adr, ayw, and ayr. All of the subtypes have the common antigenic determinant a, and anti-HBs specific for the a determinant of HBsAg would be expected to be protective regardless of the subtype of the challenging virus.

The immunizing component of the yeast recombinant hepatitis B vaccine is HBsAg of subtype ad. Assays were performed to ascertain that anti-HBs induced by the vaccine in human subjects is largely specific for the a determinant of HBsAg. Postvaccination serum samples with anti-HBs titers of 25 mIU/ml or more from subjects in several studies were tested to determine the percentage of antibody specific for the a and d determinants of HBsAg. Table 7 shows the results of these assays. Antibody specific for the a determinant predominates. By 3 months (2 months after the second dose of vaccine) the mean percentage of anti-a in all sera tested was 90%. The percentage of anti-a continued to increase with time and reached 95% at 7/8 months (1 to 2 months after the third dose of vaccine).

SAFETY

The vaccine has been well tolerated. There have been no reports of serious or alarming reactions attributable to vaccine. To date there have been 7 reactions that are possibly related to the vaccine. Five of these reactions are described in table 8 which lists reports of experiences among vaccine recipients that have been filed with the OoBRR. The other two reactions which are not described in Table 8 are summarized below:

1. A 23 year old female developed hives within 24 hours of receiving the first injection of vaccine. The hives were described as one large 3-4 inch lesion, pruritic, with several satellite lesions on the back and several small lesions on the legs. All symptoms resolved by day 4 post vaccination. Within 24 hours of receiving the second injection of vaccine the subject developed small hives on the back, arms, and left hand. All symptoms resolved by day 4 post vaccination. The individual received her third injection of vaccine with no evidence of hives. In the past, the subject developed hives during administration of contrast dye (for CAT scan). There is no other allergic history.

2. A 40-year old female developed a few ecchymotic flat lesions on the lateral aspect of her breasts, bilaterally, four days after the first injection of vaccine. Over the following two days the lesions increased. Vomiting occurred on the third day. All symptoms disappeared over the next 36 hours, and the subject has remained well. There was no fever, and WBC, Hgb, platelets, and coagulation profile were normal. The patient has no history of allergies to exogenous substances. No further vaccine was administered to this patient.

Table 9 summarizes the most frequent injection site or systemic complaints reported by healthy adult vaccine recipients. Injection site and systemic complaints were reported with frequencies of 17% and 15%, respectively. The most frequent specific injection site reactions were soreness, pain, and tenderness. The most frequent specific systemic complaints were fatigue/weakness and headache (see SUMMARY-HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS for a more detailed listing of clinical complaints).

In addition to monitoring clinical complaints, recipients of the yeast recombinant hepatitis B vaccine were also followed for antibody to yeast antigen, elevations of alanine aminotransferase, and acquisition of the hepatitis B virus serologic markers HBsAg and anti-HBc. Since the yeast recombinant hepatitis B vaccine does not involve intact hepatitis B virus at any stage of its formulation, and it also cannot contain core antigen, post-vaccination assays for HBsAg and anti-HBc were included only to detect possible breakthrough hepatitis B infections or infections that might have been in an early stage of incubation when vaccination was initiated.

Antibody to Yeast Antigen

In order to look for antibody to components of the yeast used to prepare the vaccine, sera from vaccine recipients were tested by radioimmune assay. The yeast antigens utilized in the assay were derived from the parent strain of S. cerevisiae used for the production of HBsAg. This strain does not contain the gene for HBsAg. Sera from 133 vaccine recipients (adults and children) were tested for antibodies to yeast antigen. One hundred percent of individuals tested had anti-yeast IgG in both pre and postvaccination sera. The titers in prevaccination sera ranged from 12,000 to 104,000 antibody units. Postvaccination anti-yeast IgG titers fluctuated over time with some increasing and others decreasing. However, a statistical test failed to show any significant trend in postvaccination anti-yeast titers of antibody (Table 10) There was also no association found between changes in the titer of anti-yeast antibody and the incidence of clinical complaints following vaccination (Table 10).

The most prominent yeast antigen found in preparations of the yeast recombinant hepatitis B vaccine is designated P60. Antibody to P60 is detected and semi-quantitated using a Western blot assay. Prevaccination and 3 month postvaccination sera from 42 individuals have been assayed for antibody to P60. There were no statistically significant associations between the level of antibody to P60 and the incidence of clinical complaints following vaccination (Table 11).

Alanine Aminotransferase (ALT)

All subjects enrolled in a clinical study have pre-vaccination ALT levels determined. To date, one or more post-vaccination levels have been obtained in most individuals. Thirty-one subjects, whose pre-vaccination ALT levels were normal, had elevated levels of this enzyme (1.5 - 7.0 times the upper limit of normal) at some time during a 7-8 month period of observation following vaccination. Elevations were transient in 22 cases. For 3 subjects, transient elevations in ALT were attributed to infectious mononucleosis, cholecystitis, or non A non B hepatitis. In all other instances, a reason for the ALT elevation was not ascertained. None of the subjects has shown any clinical or serologic signs (HBsAg or anti-HBc) of hepatitis B. For the remaining 9 subjects, one

participant's follow-up serum sample showed a decreasing ALT, and the other individuals have no follow-up sera available. These 9 individuals have shown no clinical or serologic signs of hepatitis B.

Two additional subjects had fluctuations in ALT levels. In both cases the prevaccination samples were elevated (1.5 - 2 times the upper limit of normal). After vaccination, the levels returned to normal, increased, and then began to decrease. In one case, a 4.5-fold increase in ALT was noted at 2 months after vaccination. At 3 months the ALT level was 2-fold higher than normal. In the second case a 3.5-fold increase in ALT was seen at 6 months. AT 7 months it was 2-fold higher than normal. No reason for the ALT elevation could be ascertained. No follow-up sera are available. Neither participant has been reported to show any clinical or serologic signs of hepatitis B.

Sporadic transaminase elevations may result from a variety of causes including minor muscle trauma (such as that caused by exercise and by intramuscular injections), common infection (including viral and mycoplasmol infections), drugs (including aspirin), and alcoholic beverages. In a previous clinical trial of plasma-derived hepatitis B vaccine, about one percent of the vaccine and the placebo recipients had elevated ALT levels at each testing. The elevations were sporadic; those with an elevated ALT at any given time were generally not the ones with an elevation at the next testing time. Elevations among recipients of the yeast recombinant vaccine have been similarly sporadic and of low incidence. We do not believe that the transaminace elevations that have occurred are likely to have been caused by the yeast recombinant hepatitis B vaccine.

HBsAg

The Interim Submission reported 2 initially seronegative vaccine recipients for whom a single postvaccination serum sample gave a marginally positive test for HBsAg (S/N $\geq$2.1).

In one case, the 3 month postvaccination serum from a healthy teenager tested just above the cutoff for HBsAg (S/N = 2.11). However, the prevaccination, 1, 6, and 7 month postvaccination samples were negative for HBsAg. The individual had normal ALT levels and all serum samples were negative for anti-HBc. It seems likely that the low positive test was spurious.

The second case is an adult health care professional. The subject's 6 month postvaccination serum gave a low positive test for HBsAg (S/N = 2.4). However, a subsequent retest of this serum sample tested negative for HBsAg. The prevaccination sample and all other postvaccination samples through 8 months of follow-up have been negative for HBsAg and anti-HBc and all samples have had normal ALT levels.

Anti-HBc

A total of 18 participants had serum samples positive for anti-HBc at some time during the study period. Five of the individuals had prevaccination samples positive, while 13 had positive postvaccination samples. A brief description of each case follows.

Healthy Adults

Two subjects had prevaccination serum samples positive for anti-HBc. In one case, the anti-HBc was transient. In the other case, all but one serum sample taken after vaccination remained positive. Serum samples for these individuals have remained negative for HBsAg and there has been no report of clinical illness.

One healthy adult was reported in the Interim Submission to have had a 2 month postvaccination serum sample positive for anti-HBc. The same serum sample was reported negative on retest. All subsequent samples through 12 months were negative. In two additional adults, the 6 and 8 month serum samples, respectively, were borderline positive for anti-HBc. All previous serum samples were negative. Both subjects remained HBsAg negative, and there has been no report of clinical illness. Repeat testing will be done and follow-up samples are pending.

Predialysis Patients

In the Interim Submission serum samples from 6 predialysis patients were reported positive for anti-HBc at some time during the 7 month observation period. Four of the 6 were transiently positive. Of the remaining 2 patients, one was negative on retest, and one on retest was positive for anti-HBc of the IgG class but negative for anti-HBc of the IgM class.

Dialysis Patients

Three dialysis patients had prevaccination serum samples which tested positive for anti-HBc. For one patient the positive anti-HBc was transient. Anti-HBc persisted in the other two patients. None of the patients was reported to have developed clinical illness or become HBsAg positive.

Three dialysis patients were reported to have one or more serum samples positive for anti-HBc postvaccination. In one case, the positive anti-HBc was transient. In the second case, the 9 month sample was positive. In the third case, the 3 and 6 month samples were positive. Further samples were not available. None of the patients was reported to have developed clinical illness.

Other Populations

The 8 month serum sample from a patient with hemophilia was reported positive for anti-HBc. The pre, 1 and 6 month samples were negative. The patient has been anti-HBs positive since 2 months. The patient has remained HBsAg negative and there has been no report of clinical illness.

The small percentage of vaccine recipients with serum samples positive for anti-HBc may reflect both the frequency of false positives seen with this assay and the fact that predialysis, dialysis and hemophiliac patients receive transfusions of blood and blood products at varying intervals during the course of their disease. Where possible retesting will be done and follow-up samples obtained.

EFFICACY

Four studies have been initiated to evaluate the efficacy of yeast recombinant hepatitis B vaccine in preventing chronic hepatitis B antigenemia in healthy infants born to mothers who are positive for HBsAg and either positive or negative for HBeAg. Two of the studies are being conducted in China, one is in Hong Kong, and one is in the United States. In 3 of the studies, infants receive a single injection of hepatitis B immunoglobulin immediately after birth followed by injections of yeast recombinant hepatitis B vaccine (5 mcg dose) at 0, 1 and 6 months. One of these studies also includes infants that receive HBIG plus plasma-derived hepatitis B vaccine (10 mcg dose). Two of the studies being conducted in China include groups of infants that receive a three injection regimen of yeast recombinant hepatitis B vaccine alone (5 or 10 mcg dose), and one study has a group that receives plasma-derived hepatitis B vaccine (20 mcg) without any HBIG.

To date, 412 infants have been enrolled in the 4 studies, 289 of these in groups receiving the yeast recombinant hepatitis B vaccine. No serious adverse experiences related to the vaccine have been reported.

Data are currently available for 59 infants, born to mothers positive for both HBsAg and HBeAg, who receive a single dose of HBIG and three 5 mcg doses of the yeast recombinant vaccine. A single infant in this group was HBsAg positive at 6 months. This infant was already antigen positive at birth. Based on these data, the efficacy of this passive-active prophylaxis in preventing chronic hepatitis B vaccine is estimated to be 98%.

COMPARISON OF RECOMBINANT AND PLASMA DERIVED VACCINES

The only hepatitis B vaccine currently licensed in the United States (HEPTAVAX-B) is comprised of noninfectious HBsAg that has been purified from the plasma of chronically infected persons. By contrast, the investigational recombinant hepatitis B vaccine is made from HBsAg produced by a strain of baker's yeast (S. *cerevisiae*) containing that portion of the hepatitis B virus gene which codes for surface antigen. HBsAg purified from yeast is essentially the same as that from human plasma including its particle appearance. Unlike the plasma-derived HBsAg the yeast HBsAg is not glycosylated. The recombinant HBsAg vaccine is adsorbed to alum as is the plasma-derived product.

A direct comparison of the two vaccines with respect to immunogenicity and clinical complaints will be available from two studies. One is a small (56 participants) randomized study (#807). The results for this study are presented in the appropriate study summary (see SUMMARY-HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS). The other is a double blind study in which 300 healthy adult male homosexuals will receive three doses of either yeast recombinant (10 mcg dose) or plasma-derived (20 mcg dose) hepatitis B vaccine. This study was initiated recently. The first injection of vaccine has been administered to 197 subjects, while 113 have received the second of three scheduled injections. Assays for hepatitis B serologic markers will not be done on any samples until subjects have received all injections of vaccine. However, interim clinical reports submitted following the first two injections have been examined by the clinical monitor at Merck and complaints and elevated temperatures tallied according to the type of hepatitis B vaccine (recombinant or plasma-derived) that was administered.

Clinical complaints from the study involving homosexuals are summarized in Table 12. All reactions have been mild and transient. Among recipients of plasma-derived vaccine, 39% reported injection site reactions while 31% had systemic complaints within a 5 day period following vaccination. Recipients of recombinant vaccine reported injection site reactions following 32% of the injections, while 24% had systemic complaints. Local complaints consisted almost exclusively of soreness at the injection site for recipients of either vaccine. The most frequent systemic complaints following injection of recombinant vaccine were fatigue/weakness (6%), arthralgia (6%), and nausea (4%), while the most frequent systemic complaints following injection of the plasma-derived vaccine were fatigue/weakness (16%), arthralgia (7%), and headache (6%).

Further comparison of the antibody and clinical responses to the plasma-derived and yeast recombinant hepatitis B vaccine is possible using data from multiple ongoing studies involving the recombinant vaccine and historical data obtained in earlier studies with the plasma-derived vaccine. This type of comparison is described below and demonstrates that both recombinant and plasma-derived vaccines are well tolerated and highly immunogenic. Tables 13 to 17 compare the anti-HBs responses of health care personnel and other healthy adults who received 10 mcg doses of yeast recombinant hepatitis vaccine in the current clinical trials program with similar subjects who received 20 mcg doses of plasma-derived hepatitis B vaccine in earlier studies. Seroconversion rates among adults 20-49 years of age, after 3 injections of vaccine, were 94% or greater for either vaccine (Table 15). The GMTs of responders in this age range were 1554.0 mIU/ml (approximate conversion from (b)(4) units) and 1282.3 mIU/ml for recipients of plasma-derived and recombinant vaccines, respectively.

The percentages of both plasma-derived and recombinant vaccine recipients developing anti-HBs (S/N $\geq$2.1) declined with increasing age. The geometric mean titers of responders also varied inversely with age. Although 94 - 99% of the vaccinees ages 20-49 years of age had anti-HBs after 3 injections of vaccine, the frequency of seroconversion in subjects 50-59 years of age was 90% among recipients of recombinant vaccine and 85% for those who received plasma-derived vaccine. The geometric mean titers of anti-HBs at 7/8 months in persons receiving recombinant vaccine ranged from 1707 mIU/ml for the 20-29 year age group to 442 mIU/ml in the 50-59 year age group. The GMT for recipients of plasma-derived vaccine was 2830 mIU/ml for the 20-29 year age group and 306 mIU/ml for the 50-59 year age group (Table 15).

Table 16 shows the distribution of antibody titers achieved by healthy adult vaccinees of all ages following 3 injections of either yeast recombinant or plasma-derived hepatitis B vaccine. Among recipients of the recombinant vaccine, 98% had at least minimal evidence of antibody (S/N $\geq$2.1), while 97% developed fully protective levels of anti-HBs (mIU/ml $\geq$10). Eighty-nine percent of the vaccinees had a titer of mIU/ml $\geq$100, while 58% had a titer of mIU/ml $\geq$1000. A fairly similar distribution of titers was characteristic of persons receiving the plasma-derived vaccine. Ninety-five percent seroconverted for anti-HBs (S/N $\geq$2.1), while 92% developed fully protective levels of antibody (mIU/ml $\geq$10). Seventy-eight percent of the plasma-derived vaccine recipients had a titer of mIU/ml $\geq$100, while 53% had a titer of mIU/ml $\geq$1000.

Tables 17 and 18 summarize the anti-HBs status of recombinant and plasma-derived vaccine recipients at 12 months. The GMTs of responders at 12 months are 2 to 5-fold lower than those observed at 7/8 months. However, when tallied across

all age groups, 90% of the recombinant vaccinees and 92% of the recipients of plasma-derived vaccine retained fully protective titers (mIU/ml ≥10) at 12 months (Table 18). Sixty-five percent of the recombinant vaccine recipients had titers of mIU/ml ≥100 at 12 months, while 25% still had titers of mIU/ml ≥1000. Among vaccinees who received the plasma-derived vaccine, 70% had titers of mIU/ml≥100 at 12 months, while 37% retained titers of mIU/ml ≥1000.

Table 19 shows the frequencies of local injection site complaints, any type of clinical complaint, and elevated temperatures reported by health care personnel and other healthy adults following vaccination with the yeast recombinant hepatitis B vaccine in current studies compared with the frequencies of such complaints among similar subjects in earlier studies of plasma-derived hepatitis B vaccine. With either vaccine, the frequencies of complaints were somewhat lower following the second and third injections. Over all injections, the frequencies of injection site complaints and any type of complaint were 12% and 20%, respectively for plasma-derived vaccine, while the use of recombinant vaccine was followed by reports of injection site complaint or any type of complaint with frequencies of 17% and 27%, respectively. All complaints were mild, transient in nature and consisted most frequently of injection site soreness, fatigue/weakness and headache. The frequency of elevated temperature (≥100°F, oral) reported by healthy adults during a 5 day period following vaccination was approximately 3%, both for recipients of plasma-derived vaccine and of yeast recombinant vaccine (Table 19).

Clinical studies with the recombinant vaccine demonstrate its safety and immunogenicity. A comparison with historical data obtained using plasma-derived hepatitis B vaccine shows that 10 mcg doses of the recombinant vaccine and 20 mcg doses of the plasma-derived vaccine yield similar seroconversion rates and GMTs in healthy adult recipients. Using historical data from past studies involving the plasma-derived vaccine, clinical reactions appear to be somewhat more frequent following injection of the recombinant vaccine as compared to the plasma-derived vaccine. However, in one contemporary double-blind study involving both vaccines, clinical complaints were more frequent among recipients of the plasma-derived as compared to the recombinant vaccine. Both vaccines were well tolerated with postvaccination reactions being of a mild and transient nature.

Table 1

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced By the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Healthy Adults	779-1*	Bishop	Merck & Co., PA	11/16/83	In progress	C-K444	10 mcg	0,1,6 mos.	30 (26)	100 (17/17)	94 (16/17)	7/8
Healthy Adults	809-1	Plotkin, Starr	Philadelphia	6/19/84	In progress	C-K444	10 mcg	0,1,6 mos.	20 (18)	100 (11/11)	100 (11/11)	7/8
Healthy Adults	839	Bishop	Merck & Co., PA	7/31/84	In progress	C-K444	10 mcg	Day 0	10 (5)	25 (1/4)	0 (0/4)	6
Healthy Adults	882	Iino	Japan	12/84	In progress	C-L215	10 mcg	0,1,6 mos.	50 (40)	100 (40/40)	NA	7
Healthy Adults (Male Homosexuals)	894	Polk	Baltimore	4/85	In progress	C-K563	10 mcg	0,1,6 mos.	350 (87)	NA	NA	--
						H-B-Vax C-M252	20 mcg	0,1,6 mos.	(88)	NA	NA	--
Healthy Adults	898	Bishop	Merck & Co., PA	11/18/85	In progress	C-M125	20 mcg	0,1,6 mos.	20 (2)	NA	NA	--
						C-M126	10 mcg	0,1,6 mos.	20 (1)	NA	NA	--
Healthy Adults	907	Iino	Japan	5/7/85	In progress	C-L215	10 mcg/IM	0,1,6 mos.	62 (62)	98 (54/55)	NA	7
							10 mcg/SC	0,1,6 mos.	62 (62)	97 (56/58)	NA	7
Healthy Adults	904	Kessler	Chicago	10/85	In progress	C-M718	10 mcg	0,1,6 mos.	50 (50)	NA	NA	--
						C-L217	10 mcg	0,1,6 mos.	50 (50)	NA	NA	--
Healthy Adults (Male Homosexuals)	900	Zuckerman	London, UK	8/85	In progress	C-M126	10 mcg	0,1,6 mos.	200 ( )	NA	NA	--
Health Care Personnel	792-1	Dienstag	Boston	5/84	In progress	C-K564	10 mcg	0,1,6 mos.	30 (35)	96 (27/28)	93 (26/28)	9
Health Care Personnel	794	Alter	Bethesda	4/18/84	In progress	C-K444	10 mcg	0,1,6 mos.	30 (41)	97 (35/36)	94 (34/36)**	7/8

NA = Not Available
*Suffix number indicates addendum to initial study protocol.
**This percentage is that with S/N ≥10, rather than mIU/ml ≥10.

31531/1
1/9/86

Table 1 (Cont.)

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced By the (b) (4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Health Care Personnel	794-1	Alter	Bethesda	6/84	In progress	C-K444	5 mcg	0,1,6 mos.	30 (30)	84 (21/25)	76 (19/25)**	7/8
Health Care Personnel	795-2	Deinhardt	W. Germany	12/1/84	In progress	C-L215	10 mcg	0,1,6 mos.	300 (97)	99 (79/80)	99 (79/80)	7/8
						C-K564	10 mcg	0,1,6 mos.	(148)	100 (76/76)	100 (76/76)	7/8
Health Care Personnel	798	Hollinger	Houston	4/11/84	In progress	C-K446	20 mcg	0.1,6 mos.	35 (36)	100 (35/35)	91 (32/35)	7/8
							10 mcg	0,1,6 mos.	35 (37)	97 (34/35)	97 (35/36)	7/8
							5 mcg	0,1,6 mos.	35 (36)	97 (35/36)	83 (30/36)	7/8
Health Care Personnel	801	Septimus	Houston	2/16/84	In progress	C-K444	10 mcg	0,1,6 mos.	25 (22)	100 (21/21)	100 (21/21)	7/8
Health Care Personnel	803	Judson	Denver	1/16/84	In progress	C-K444	10 mcg	0,1,6 mos.	30 (31)	85 (22/26)	85 (22/26)	7/8
Health Care Personnel	807	Schalm	Netherlands	4/4/84	In progress	C-K444	10 mcg	0,1,6 mos.	30 (31)	100 (31/31)	100 (31/31)	7/8
						H-B Vax 1510J	20 mcg	0,1,6 mos.	30 (25)	100 (22/22)	100 (22/22)	7/8
Health Care Personnel	808	Sampliner	Tucson	4/3/84	In progress	C-K444	10 mcg	0,1,6 mos.	25 (25)	96 (22/23)	96 (22/23)	7/8
Health Care Personnel	811	Grob	Switzerland	4/10/84	In progress	C-K446	10 mcg	0,1,6 mos.	11 (11)	86 (6/7)	83***(5/6)	7/8
Health Care Personnel	813	Davidson	NYC	2/1/84	In progress	C-K444	10 mcg	0,1,6 mos.	50 (62)	97 (38/39)	97 (38/39)	7/8
Health Care Personnel	813-1	Davidson	NYC	2/84	In progress	C-K444	5 mcg	0,1,6 mos.	50 (60)	94 (44/47)	91 (43/47)	7/8
Health Care Personnel	813-2	Davidson	NYC	5/84	In progress	C-K444	2.5 mcg	0,1,6 mos.	50 (61)	100 (40/40)	97 (39/40)	7/8
Health Care Personnel	813-3	Davidson	NYC	1/85	In progress	C-L220	10 mcg	0,1,6 mos.	50 (62)	95 (37/39)	92 (36/39)	6
Health Care Personnel	813-4	Davidson	NYC	2/85	In progress	C-L220	5 mcg	0,1,6 mos.	50 (61)	93 (41/44)	80 (35/44)	6

**This percentage is that with S/N ≥10, rather than mIU/ml ≥10.
***Based on 6 subjects (5 responders) for whom numeric titers are available.
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Table 1 (Cont.)

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine
Produced By the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Health Care Personnel	813-5	Davidson	NYC	6/85	In progress	C-M125	20 mcg	0,1,6 mos.	50 (7)	NA	NA	--
						C-M126	10 mcg	0,1,6 mos.	50 (7)	NA	NA	--
Health Care Personnel	816	Plotkin, Starr	Philadelphia	5/15/84	In progress	C-K446	10 mcg	0,1,6 mos.	25 (8)	80 (4/5)	80 (4/5)	7/8
Health Care Personnel	835	Lemon	Chapel Hill	10/26/84	In progress	C-K564	10 mcg	0,1,6 mos.	30 (29)	100 (19/19)	100 (19/19)	7-9
Health Care Personnel	838	Deinhardt	W. Germany	6/7/84	In progress	C-K733	10 mcg	0,1,6 mos.	25 (22)	94 (16/17)	94 (16/17)	7/8
Health Care Personnel	859	Clumeck	Belgium	3/12/85	In progress	C-K563	10 mcg	0,1,6 mos.	50 (31)	80 (24/30)	53 (16/30)	3
Health Care Personnel	860	Laufs	W. Germany	12/28/84	In progress	C-K563	10 mcg	0,1,6 mos.	100 (60)	100 (56/56)	100 (56/56)	7/8
Health Care Personnel	869	Rankin, Coates	Canada	5/85	In progress	C-L217	10 mcg	0,1,6 mos.	150 (71)	32 (22/68)	12 (8/68)	1
Health Care Personnel	871	Oon	Singapore	1/26/85	In progress	C-K564	10 mcg	0,1,6 mos.	30 (31)	97 (28/29)	97 (28/29)	7/8
Health Care Personnel	880	Wormser	Valhalla, NY	4/1/85	In progress	C-L215	10 mcg	0,1,6 mos.	50 (50)	86 (31/36)	64 (23/36)	6
						C-L216			50 (43)	100 (20/20)	100 (20/20)	6
						C-L217			50 (54)	88 (23/26)	81 (21/26)	6
						C-L219			50 (47)	90 (19/21)	81 (17/21)	6
						C-L220			50 (43)	97 (38/39)	90 (35/39)	6
Health Care Personnel	883	Plotkin, Starr	Philadelphia	11/13/84	In progress	C-L220	10 mcg	0,1,6 mos.	25 (28)	100 (24/24)	96 (23/24)	7/8
							5 mcg	0,1,6 mos.	25 (25)	100 (20/20)	95 (19/20)	7/8
Health Care Personnel	885	Liebowitz	Miami	7/85	In progress	C-L215	10 mcg	0,1,6 mos.	50	NA	NA	--
						C-L216			50	NA	NA	--
						C-L217			50 (50)	NA	NA	--
						C-L219			50 (50)	NA	NA	--
						C-L220			50 (50)	NA	NA	--
Health Care Personnel	889	Perillo	St. Louis	6/19/85	In progress	C-K937	10 mcg	0,1,6 mos.	50 (88)	.17 (14/82)	6 (5/82)	1
Health Care Personnel	834	Rizzetto	Italy	8/85	In progress	C-K564	10 mcg	0,1,6 mos.	30 (25)	NA	NA	--

Table 1 (Cont.)

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced By the (b) (4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Health Care Personnel	841	Zuckerman	United Kingdom	5/85	In progress	C-K563	10 mcg	0,1,6 mos.	100	NA	NA	--
Health Care Personnel	891	Hu	China	12/85	In progress	C-K564	10 mcg	0,1,6 mos.	100 (25)	NA	NA	--
						H-B-Vax 0027L	20 mcg	0,1,6 mos.	100 (25)	NA	NA	--
Health Care Personnel	912	Shimizu	Japan	9/2/85	In progress	C-L220	10 mcg/IM	0,1,6 mos.	87 (87)	75 (56/75)	NA	2
							10 mcg/SC	0,1,6 mos.	88 (88)	59 (43/73)	NA	2
Health Care Personnel	914	Burette	Belgium	11/21/85	In progress	C-M126	10 mcg	0,1,6 mos.	20 (20)	NA	NA	--
Health Care Personnel	815	Schalm	Netherlands	12/85	In progress	C-K937	10 mcg	0,1,6 mos.	30	NA	NA	--
							20 mcg	0,1,6 mos.	30	NA	NA	--
						H-B-VAX 2277K	20 mcg	0,1,6 mos.	30	NA	NA	--
Health Care Personnel	867	Crovari	Italy		Planned	C-K564	10 mcg	0,1,6 mos.	30	NA	NA	--
Health Care Personnel	899	DeBac	Italy		Planned	C-K564	10 mcg	0,1,6 mos.	30	NA	NA	--

Table 1

Clinical Studies of Hemophiliacs, Thalassemic Children and Patients With Sickle Cell Anemia
Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine			# Subjects Planned (Vaccinated)	% with anti-HBs		Time (Months)
						Lot	Dose	Regimen		S/N ≥2.1	mIU/ml ≥10	
Hemophiliacs	861	Gill	Milwaukee	11/8/84	In progress	C-K564	10 mcg	0,1,6 mos.	2 (3)	100 (2/2)	0 (0/2)	3
							5 mcg	0,1,6 mos.	25 (12)	100 (8/8)	100 (8/8)	3
Thalassemic Children	799	Stevens	NYC	9/4/84	In progress	C-K444	5 mcg	0,1,6 mos.	25 (15)	89 (8/9)	78 (7/9)	7/8
							2.5 mcg	0,1,6 mos.	25 (16)	82 (9/11)	64 (7/11)	6
Patients with Sickle Cell Anemia	861-1	Gill	Milwaukee	7/85	In progress	C-K564	5 mcg	0,1,6 mos.	10 (4)	NA	NA	--

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Table 1

Clinical Studies of Healthy Teenagers, Children and Infants Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Healthy Teenagers	819	Papaevangelou	Greece	5/12/84	In progress	C-K564	10 mcg	0,1,6 mos.	55 (55)	100 (52/52)	100 (52/52)	7/8
						C-K732	5 mcg	0,1,6 mos.	55 (55)	100 (54/54)	100 (54/54)	7/8
						C-K732	2.5 mcg	0,1,6 mos.	55 (55)	100 (53/53)	94 (50/53)	7/8
Healthy Children	809	Plotkin, Starr	Philadelphia	2/2/84	In progress	C-K444	5 mcg	0,1,6 mos.	20 (22)	100 (14/14)	100 (14/14)	7/8
							2.5 mcg	0,1,6 mos.	20 (17)	100 (10/10)	100 (10/10)	7/8
	809-2	Plotkin, Starr	Philadelphia	6/19/84	In progress	C-K732	2.5 mcg	0,1,6 mos.	15 (15)	100 (11/11)	100 (11/11)	7/8
							1.25 mcg	0,1,6 mos.	25 (26)	100 (14/14)	100 (14/14)	7/8
Healthy Children/ Infants	865	Yeoh	Hong Kong	2/1/85	In progress	C-K734	5 mcg	0,1 mos.	100 (90)	96 (23/24)	88 (21/24)	8
							5 mcg	0,1,6 mos.	100 (88)	100 (21/21)	100 (21/21)	8
Healthy Children	891	Hu	China	12/85	In progress	C-K564	5 mcg	0,1,6 mos.	100 (25)	NA	NA	—
						H-B Vax 0027L	10 mcg	0,1,6 mos.	100 (25)	NA	NA	—
Healthy Children	843	Oon	Singapore		Planned	C-K734	5 mcg	0,1,6 mos.	30	NA	NA	—
						C-M127	2.5 mcg	0,1,6 mos.	30	NA	NA	—
						C-M128	1.25 mcg	0,1,6 mos.	30	NA	NA	—
						C-M129	0.6 mcg	0,1,6 mos.	30	NA	NA	—

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Table 1

Clinical Studies of Dialysis/Predialysis Patients and Mentally Retarded Patients Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Dialysis Patients	816	Plotkin, Starr	Philadelphia	5/15/84	Inprogress	C-K446	40 mcg	0,1,6 mos.	25 (36)	80 (16/20)	75 (15/20)	7/8
							20 mcg	0,1,6 mos.	25 (39)	57 (16/28)	46 (13/28)	7/8
Dialysis Patients	838	Deinhardt	W. Germany	6/7/84	Inprogress	C-K733	40 mcg	0,1,6 mos.	50 (51)	64 (23/36)	58 (21/36)	7/8
Dialysis Patients	838-1	Deinhardt	W. Germany	11/84	Inprogress	C-K733	40 mcg	0,1,2,3,4, 6 mos.	20 (20)	67 (10/15)	60 (9/15)	10
							20 mcg	0,1,2,3,4, 6 mos.	20 (20)	50 (9/18)	44 (8/18)	10
Dialysis Patients	825	Alter	Washington	4/10/85	Inprogress	C-L915	100 mcg	0,1,6 mos.	30 (44)	68 (19/28)	25 (7/28)*	3
Predialysis Patients	789	Hamilton	Durham	5/23/84	Inprogress	C-K446	40 mcg	0,1,6 mos.	20 (15)	71 (5/7)	57 (4/7)*	7/8
							20 mcg	0,1,6 mos.	20 (14)	86 (6/7)	57 (4/7)*	7/8
						H-B Vax	40 mcg	0,1,6 mos.	20 (16)	67 (4/6)	67 (4/6)*	7/8
Predialysis Patients	811	Grob	Switzerland	4/10/84	Inprogress	C-K446	40 mcg	0,1,6 mos.	20 (13)	64 (7/11)	64 (7/11)	7/8
							20 mcg	0,1,6 mos.	20 (14)	58 (7/12)	58 (7/12)	7/8
							10 mcg	0,1,6 mos.	20 (14)	15 (2/13)	15 (2/13)	7/8
						H-B Vax	40 mcg	0,1,6 mos.	20 (11)	50 (4/8)	38 (3/8)	7/8
							20 mcg	0,1,6 mos.	20 (11)	25 (2/8)	25 (2/8)	7/8
Predialysis Patients	838-3	Deinhardt	W. Germany	1/85	Inprogress	C-K733	40 mcg	0,1,6 mos.	10 (8)	13 (1/8)	0 (0/8)	1
Mentally Retarded	889	Perrillo	St. Louis	6/19/85	Inprogress	C-K937	20 mcg	0,1,6 mos.	125 (101)	20 (20/100)	11 (11/100)	1
							10 mcg	0,1,6 mos.	125 (101)	19 (19/101)	8 (8/101)	1
Mentally Retarded	815	Schalm	Netherlands	12/85	Inprogress	C-K937	10 mcg	0,1,6 mos.	30	NA	NA	--
							20 mcg	0,1,6 mos.	30	NA	NA	--
						H-B-Vax 2277K	20 mcg	0,1,6 mos.	30	NA	NA	--

*This percentage is that with S/N≥10, rather than mIU/ml ≥10.

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Table 1

Clinical Studies of Nonresponders and Hyporesponders, Chronic Carriers of HBsAg, and Preimmune Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Nonresponders to Plasma Vaccine (Healthy Adults)	794-2	Alter	Bethesda	6/84	In progress	C-K444	10 mcg 5 mcg	0,1,6 mos. 0,1,6 mos.	10 (11) (1)	88 (7/8) 100 (1/1)	63 (5/8) 0 (0/1)	7/8 7/8
Nonresponders to Plasma Vaccine (Dialysis Patients)	816	Plotkin, Starr	Philadelphia	5/14/84	In progress	C-K446	40 mcg 20 mcg	0,1,6 mos. 0,1,6 mos	4 (4) 5 (5)	33 (1/3) 25 (1/4)	33 (1/3) 25 (1/4)	7/8 3
Nonresponders to Plasma Vaccine (Healthy Adults)	817	Bishop	Merck & Co., PA	3/21/84	In progress	C-K444	10 mcg	0,1,6 mos.	20 (4)	0 (0/2)	0 (0/2)	7/8
Nonresponders to Plasma Vaccine (Healthy Adults)	854	Dienstag	Boston	10/4/84	In progress	C-K564	10 mcg	0,1,6 mos.	20 (14)	58 (7/12)	25 (3/12)	6
Nonresponders to Plasma Vaccine (Dialysis Patients)	875	Johnson	Duluth	7/85	In progress	C-K937 H-B Vax	40 mcg 40 mcg	0,1,6 mos. 0,1,6 mos.	20 (17) 20 (18)	38 (5/13) 47 (7/15)	15 (2/13) 47 (7/15)	2 2
Hyporesponders to Plasma Vaccine	854	Dienstag	Boston	10/4/84	In progress	C-K564	10 mcg	Day 0	20 (2)	NA	50 (1/2)	1
Chronic carriers of HBsAg	854	Dienstag	Boston	10/4/84	In progress	C-K564	10 mcg	0,1,2,3,4, 5 mos.	15 (18)	0 (0/18)**	0 (0/18)**	--

**This percentage (proportion) refers to the number of chronic carriers who became seronegative for HBsAg after vaccination with recombinant vaccine.

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Table 1 (Cont.)

Clinical Studies of Nonresponders and Hyporesponders, Chronic Carriers of HBsAg, and Preimmune Adults Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine			# Subjects Planned (Vaccinated)	% with anti-HBs		Time (Months)
						Lot	Dose	Regimen		S/N ≥2.1	mIU/ml ≥10	
Transient Responders	854	Dienstag	Boston	10/4/84	In progress	C-K564	10 mcg	Day 0	15 (3)	NA	67 (2/3)	1
Non-responders/ Hypo-responders	874	Tong	California	9/85	In progress	C-K563	10 mcg	0,1,6 mos.	40 (26)	36 (9/25)	NA	1
Preimmune Adults	813-6	Davidson	NYC	7/85	In progress	C-M126	10 mcg	Day 0	100 (31)	97 (29/30)*	NA	1
Preimmune Adults	813-7	Davidson	NYC	7/85	In progress	C-M126	5 mcg 10 mcg	Day 0 Day 0	25 (28) 25 (28)	NA NA	100 (28/28)* 100 (28/28)*	1/2 1/2
Preimmune Adults	817	Bishop	Merck & Co.	3/21/84	In progress	C-K444	10 mcg	Day 0	20 (5)	100 (5/5)*	100 (5/5)	1/8

*This percentage (proportion) refers to the number of preimmune subjects (naturally acquired or vaccine-induced, as indicated) who exhibited a boost in anti-HBs titer after receiving recombinant vaccine.

Table 1

Clinical Studies of Neonates Born to Carrier Mothers Receiving Yeast Recombinant Hepatitis B Vaccine Produced by the (b)(4) Method (BB IND 1925)

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine Lot	Vaccine Dose	Vaccine Regimen	# Subjects Planned (Vaccinated)	% with anti-HBs S/N ≥2.1	% with anti-HBs mIU/ml ≥10	Time (Months)
Neonates of HBeAg+ Mothers	864	Stevens	NYC/LA/SF	9/1/84	In progress	C-K732	5 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	80 (134)	100 (47/47)	NA	6
Neonates of HBeAg+ Mothers	862	Yeoh	Hong Kong	2/85	In progress	C-K734	5 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	150 (40)	NA	100 (24/24)	3
						H-B Vax 1032K 2455J 0027L 1507J	10 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	75 (28)	NA	100 (19/19)	3
Neonates of HBeAg+ Mothers	878	Sun	China	7/85	In progress	C-K564	5 mcg	0,1,6 mos. +0.5 ml HBIG at birth	30 (30)	NA	NA	--
					Planned	C-K564	5 mcg	0,1,6 mos. (No HGIB)	70			
Neonates of HBeAg+ Mothers	892	Hu	China	12/85	In Progress	C-K564	5 mcg	0,1,6 mos.	50 (5)	NA	NA	--
							10 mcg	0,1,6 mos.	50 (5)	NA	NA	--
						H-B Vax 0027L	10 mcg	0,1,6 mos.	50 (5)	NA	NA	--
							20 mcg	0,1,6 mos.	50 (5)	NA	NA	--
Neonates of HBeAg - Mothers	862	Yeoh	Hong Kong	2/85	In progress	C-K734	5 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	(75)	NA	100 (41/41)	3
						H-B-VAX 1032K 2455J 0027L 1507J	10 mcg	0,1,6 mos. + 0.5 ml HBIG at birth	(85)	NA	100 (42/42)	3

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Table 2

List of Number Vaccinated with
Yeast Recombinant Hepatitis B Vaccine, Clinical Reports, and
Post-Vaccination Anti-HBs Data by Population Group

NA = Not Applicable

Population Group	Vaccinations Injection #			Clinical Reports Injection #			Anti-HBs Data Injection		
	1	2	3	1	2	3	1	2	3
Health Care Personnel/Other Healthy Adults	2414	2286	1442	1626	1508	990	1616	1436	1048
Healthy Teenagers	165	165	165	165	165	165	165	165	165
Healthy Infants/Children	258	222	122	220	191	100	213	189	97
Dialysis/Predialysis Patients	288	287	196	286	264	184	258	230	166
Mentally Retarded Institutionalized Patients	202	201	200	202	201	--	202	--	-
Thalassemic Children	31	31	27	30	30	5	31	27	14
Hemophiliacs	15	15	6	13	10	6	15	15	6
Patients with Sickle Cell Anemia	4	4	--	--	--	--	--	--	--
Nonresponders to Plasma-Derived Vaccine									
Healthy Adults	55	54	24	30	28	24	52	25	14
Dialysis Patients	26	24	6	25	24	6	20	21	4
Hyporesponders/Transient Responders to Plasma-Derived Vaccine	5	NA	NA	5	NA	NA	4	NA	NA
Preimmune Adults	91	NA	NA	48	NA	NA	88	NA	NA
Chronic Carriers of HBsAg	18	18	18	18	18	18	18	18	18
Infants of Carrier Mothers									
$HBsAg^+/HBeAg^+$	214	157	73	135	114	43	133	110	19
$HBsAg^+/HBeAg^-$	75	73	30	75	73	30	70	41	--
T O T A L	3861	3537	2309	2878	2626	1571	2885	2277	1551

Table 3
Antibody Responses at 3 Months Among Healthy
Initially Seronegative Persons Receiving Yeast Recombinant
Hepatitis B Vaccine at 0,1 and 6 Months

Age (Years)	1.25 mcg				2.5 mcg				5 mcg				10 mcg				20 mcg			
	% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*	
	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10
1-11	100 (7/7)	86 (6/7)	52.7	77.5	100 (16/16)	81 (13/16)	77.3	130.5	100 (10/10)	100 (10/10)	189.3	189.3								
12-19					91 (49/54)	67 (36/54)	31.8	63.3	100 (54/54)	94 (51/54)	107.9	127.4	100 (56/56)	100 (54/56)	189.2	215.4				
20-29					84 (43/51)	65 (33/51)	37.6	66.1	83 (118/142)	67 (95/142)	34.0	57.5	92 (359/388)	83 (323/388)	67.9	90.9	84 (16/19)	58 (11/19)	21.5	64.9
30-39					100 (4/4)	25 (1/4)	7.5	12.7	50 (8/16)	31 (5/16)	18.4	46.7	78 (87/112)	61 (68/112)	38.7	70.7	94 (15/16)	56 (9/16)	9.5	19.9
40-49									67 (2/3)	0 (0/3)	3.6	--	75 (21/28)	54 (15/28)	47.9	126.8				
50-59					100 (1/1)	100 (1/1)	73.6	73.6					82 (14/17)	65 (11/17)	21.6	31.3				
60-69													75 (3/4)	25 (1/4)	5.9	24.2				

*Responders only.

24101/1
12/26/85

Table 4

Antibody Responses at 6 Months Among Healthy Initially Seronegative Persons Receiving Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months

Age (Years)	1.25 mcg				2.5 mcg				5 mcg				10 mcg				20 mcg			
	% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*	
	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10
1-11	100 (21/21)	90 (19/21)	75.9	100.7	96 (26/27)	93 (25/27)	145.2	163.2	100 (19/19)	100 (19/19)	308.4	308.4								
12-19					94 (48/51)	71 (36/51)	31.3	59.4	100 (54/54)	100 (54/54)	107.5	107.5	100 (74/74)	99 (73/74)	162.9	169.3				
20-29					86 (45/52)	69 (36/52)	33.4	51.4	88 (125/142)	72 (102/142)	43.3	71.2	96 (403/419)	90 (379/419)	96.4	115.8	90 (17/19)	79 (15/19)	58.1	86.8
30-39					75 (3/4)	75 (3/4)	22.9	22.9	46 (6/13)	31 (4/13)	11.4	22.9	89 (110/124)	79 (98/124)	53.4	70.7	93 (14/15)	80 (12/15)	25.8	34.5
40-49									78 (2/3)	33 (1/3)	10.5	35.5	88 (30/34)	74 (25/34)	44.6	71.2				
50-59					100 (1/1)	100 (1/1)	15.5	15.5					81 (13/16)	69 (11/16)	42.4	59.8				
60-69													100 (3/3)	33 (1/3)	13.1	112.8				

*Responders only.

2410I-3
12/26/85

00027

Table 5

Antibody Responses at 7/8 Months Among Healthy
Initially Seronegative Persons Receiving Yeast Recombinant
Hepatitis B Vaccine at 0, 1, and 6 Months*

	1.25 mcg				2.5 mcg				5 mcg				10 mcg				20 mcg			
	% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*	
Age (Years)	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10
1-11	100 (17/17)	100 (17/17)	2059.3	2059.3	100 (20/20)	100 (20/20)	5454.0	5454.0	100 (14/14)	100 (14/14)	15866.0	15866.0								
12-19					100 (53/53)	94 (50/53)	846.3	1131.8	100 (54/54)	100 (54/54)	2553.4	2553.4	100 (69/69)	100 (69/69)	2913.4	2913.4				
20-29					100 (54/54)	96 (52/54)	270.2	316.1	98 (96/98)	94 (92/98)	357.5	423.7	99 (341/344)	99 (340/344)	1707.0	1737.0	100 (19/19)	84 (16/19)	527.3	1373.7
30-39					100 (3/3)	100 (3/3)	217.0	217.0	92 (12/13)	54 (7/13)	15.1	46.6	96 (106/111)	95 (105/111)	693.5	730.0	100 (16/16)	94 (15/16)	553.2	744.7
40-49									100 (3/3)	100 (3/3)	96.5	96.5	97 (33/34)	91 (31/34)	484.5	655.9				
50-59					100 (1/1)	100 (1/1)	21.8	21.8					90 (17/19)	90 (17/19)	442.0	442.0				
60-69													100 (3/3)	100 (3/3)	919.0	919.0				

*Includes some responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

00028

24101-5
1/11/86

Table 6

Antibody Responses at 12 Months Among Healthy
Initially Seronegative Persons Receiving Yeast Recombinant
Hepatitis B Vaccine at 0, 1, and 6 Months

Age (Years)	1.25 mcg				2.5 mcg				5 mcg				10 mcg				20 mcg			
	% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*		% with Anti-HBs		GMT (mIU/ml)*	
	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10
1-11	100 (9/9)	100 (9/9)	819.2	819.2	100 (18/18)	94 (17/18)	2808.6	3925.0	100 (13/13)	100 (13/13)	3481.8	3481.8								
12-19					92 (49/53)	91 (48/53)	498.1	541.1	100 (54/54)	100 (54/54)	498.2	498.2	100 (55/55)	100 (55/55)	560.5	560.5				
20-29					95 (40/42)	90 (38/42)	148.6	177.6	96 (77/80)	81 (65/80)	121.7	226.2	98 (115/118)	93 (110/118)	342.7	419.3	95 (18/19)	84 (16/19)	258.2	449.3
30-39					100 (4/4)	75 (3/4)	57.1	116.6	64 (7/11)	18 (2/11)	7.9	63.4	94 (74/79)	86 (68/79)	235.4	322.7	100 (16/16)	88 (14/16)	119.2	297.9
40-49									100 (2/2)	100 (2/2)	70.2	70.2	91 (21/23)	91 (21/23)	238.3	238.3				
50-59					100 (1/1)	0 (0/1)	5.5	——					88 (15/17)	82 (14/17)	150.9	202.2				
60-69													100 (2/2)	100 (2/2)	233.5	233.5				

*Responders only.

62000

24101/7
12/26/85

Table 7

Percentages of Anti-HBs Specific for a and d Determinants of HBsAg in Post-Vaccination Sera

Time (Months)	Number of Samples	% Anti-a		% Anti-d	
		Range	Mean	Range	Mean
1	26	0-100	68	0-100	31
3	97	33-100	90	0-63	10
6	44	58-100	93	0-37	7
7/8	38	81-100	95	0-19	5

Table 8

Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
779	(b) (6)	1925	C-K444	10 mcg	(b) (6) (b) (6) (b) (6)	(b) (6)	11/15/84	A forty-one year old female developed headache, swollen face and rash within several hours after receiving the third injection of vaccine. Headache and swollen face resolved in one day, and the rash faded over four days. No clinical complaints were reported by this individual following the first and second injections of vaccine. She received her first and second injection of vaccine as scheduled, while the third injection was not administered until 11 months after the first injection. The individual does have a history of allergies.	Yes
789		1925	2449H (HEPTAVAX)	40 mcg	(b) (6) (b) (6)		10/19/84	This 30-year old male subject had congenital polycystic renal and liver disease. He had a history of recurrent hemorrhaging from esophageal varices. He was admitted to hospital for hemorrhage of esophageal varices. Death was due to subsequent infection, multisystem organ failure and shock.	No
789		1925	C-K446	20 mcg	(b) (6) (b) (6)		6/19/85	This 58-year old male subject had a history of hypertension and chronic renal failure (predialysis). He died at home approximately 4 months after receiving his second injection of vaccine. The Inv. stated the patient was lost to follow-up. Cause of death is unknown.	Unlikely
798		1925	C-K446	10 mcg	(b) (6) (b) (6) (b) (6)		11/19/84	A 32-year old male subject had an elevated ALT level at the time of his 3rd injection. On (b) (6) the patient reported his urine had been dark orange in color for the previous 7-8 days. The patient became anorexic and began to vomit. Jaundice was apparent. Diagnosis: Non-A, Non-B hepatitis.	No
801		1925	C-K444	10 mcg	(b) (6)		5/29/84	This 26-year old female became aware that she was pregnant after receiving one injection of vaccine. The vaccine was administered approximately 1 month after conception. She experienced a spontaneous abortion at 18 weeks after fetal death *in utero*. No microscopic examination was completed on the fetus. The subject previously delivered two healthy infants without complication of pregnancy. She had no known allergies.	Possibly**

* Clinical investigator's assessment.
**Clinical monitor's assessment.

3018I/1

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
801	(b) (6)	1925	C-K444	10 mcg	(b) (6) (b) (6) (b) (6)	(b) (6)	3/85	A 35-year old female subject complained of headache one day after receiving the third injection of vaccine. The headache persisted for three days and was accompanied by a sore throat and swollen eyes. She was admitted to hospital on (b) (6) with a diagnosis of clinical viral meningitis. She recovered without sequelae.	Probably Not
803		1925	C-K444	10 mcg	(b) (6)		2/7/84	A 43-year old male patient experienced sudden onset of biparietal headache, upset stomach, confusion and expressive aphasia 2 days after receiving the 1st injection of vaccine. His neurologic exam and vital signs were within normal limits. A CAT scan of the head was also normal. His WBC was slightly elevated with a shift to the left. By (b) (6) symptoms resolved spontaneously. The patient has a history of multiple childhood allergies.	No
811		1925	C-K446	20 mcg	(b) (6) (2 injections)		4/22/85	This 28-year old male with underlying renal disease and recently initiated hemodialysis, died approximately one month after administration of vaccine. The investigator reported death was due to vasculitis.	
816		1925	C-K446	40 mcg	(b) (6) (b) (6) (b) (6)		5/17/85	This 57-year old female hemodialysis patient with severe diabetes mellitus, hypertriglyceridemia, hyperkalemia, atherosclerotic cardiovascular disease and anemia, expired approximately 6 months after administration of the 3rd injection of vaccine. Death was due to myocardial infarction.	No
816		1925	C-K446	20 mcg	(b) (6) (b) (6) (b) (6)		4/15/85	This 57-year old male subject had a history of coronary artery disease with angina and end-stage renal disease (3x/week hemodialysis). Death was due to myocardial infarction.	No
816		1925	C-K446	40 mcg	(b) (6) (b) (6)		2/5/85	This 49-year old male patient had end-stage renal disease (3x/week hemodialysis). Death was due to respiratory arrest, aspiration asphyxia, end-stage renal and coronary artery disease.	No

*Clinical investigator's assessment.

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
816	(b) (6)	1925	C-K446	40 mcg	(b) (6) (b) (6)	(b) (6)	2/5/85	The patient, a 79-year old male, had end-stage renal disease (3x/week hemodialysis). Death was caused by cardiac arrest, atherosclerosis, end-stage renal disease, and multiple myeloma.	No
816		1925	C-K446	20 mcg	(b) (6)		1/22/85	This 71-year old female patient had a history of chronic renal failure, Parkinson's Disease, dementia, and abdominal aneurysm. The patient received biweekly hemodialysis. Her death was due to cardiopulmonary arrest, uremia, chronic renal failure, and abdominal aortic aneurysm without rupture.	No
816		1925	C-K446	40 mcg	(b) (6) (b) (6)		1/22/85	This 49-year old male patient had a history of cardiac myopathy and chronic renal failure (3x/week hemodialysis). His death was due to cardiac arrest, pulmonary edema, and end-stage kidney disease.	No
816		1925	C-K446	20 mcg	(b) (6) (b) (6)		2/5/85	The 53-year old female subject had a history of hypertension, diabetes mellitus, cirrhosis, severe renal osteodystrophy and end-stage renal disease (3x/week hemodialysis). Death was caused by congestive heart failure, renal failure, and severe arteriosclerosis.	No
816		1925	C-K446	20 mcg	(b) (6) (b) (6) (b) (6)		1/22/85	This 63-year old male hemodialysis patient with ESRD and severe peripheral vascular disease, was hospitalized for a left femoral-popliteal bypass and lumbar sympathectomy approximately 2 months after administration of his 3rd injection of vaccine. His hospital course was complicated by postoperative blood loss, hypotension and hyperkalemia. He subsequently experienced a respiratory arrest requiring resuscitative measures. Post resuscitation, the patient was comatose and decerebrate. His condition further deteriorated and he died 4 days after admission to the hospital.	No

*Clinical investigator's assessment.

3018I-3
1/19/86

Table B (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
816	(b) (6)	1925	C-K446	40 mcg	(b) (6) (b) (6)	(b) (6)	2/5/85	This 37-year old female subject had a history of diabetes mellitus and end-stage renal disease (2x/week hemodialysis). Her death was caused by sepsis, end-stage renal disease, acute respiratory distress syndrome, infected dialysis graft, and diabetes mellitus.	No
825		1925	C-L915	100 mcg	(b) (6)		5/14/85	This 31-year old male hemodialysis patient with ESRD, diabetes mellitus and hypertension, died 18 days after administration of his first injection of vaccine. The cause of death was reported as cardiac arrhythmia secondary to end-stage renal disease.	No
825		1925	C-L915	100 mcg	(b) (6) (b) (6)		9/11/85	This 73-year old female hemodialysis patient with ESRD, diabetes mellitus, hypertension, and hypo-parathyroidism, was hospitalized 5 days after administration of her 2nd injection of vaccine for a possible CVA. On the day of admission, the patient had been receiving her schedule dialysis treatment during which she complained of left-sided weakness. Eight days after hospitalization, the patient expired. Death was reported to be due to a CVA secondary to diabetes associated vascular disease.	No
838		1925	C-K733	40 mcg	(b) (6) (b) (6) (b) (6) (b) (6) (b) (6)		4/8/85	This 70-year old male subject had a history of coronary artery disease and end-stage renal disease. His death was due to acute myocardial infarction.	No
838		1925	C-K733	40 mcg	(b) (6) (b) (6) (b) (6)		10/17/85	This 46-year old male dialysis patient with a history of diabetes mellitus and diabetic nephropathy, died 2 months after administration of his 3rd injection of vaccine. Death was due to cardiac arrest secondary to hyperkalemia.	No

*Clinical investigator's assessment.

3018I-4
1/19/86

00034

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
861	(b) (6)	1925	C-K564	10 mcg	(b) (6) (b) (6) (b) (6)	(b) (6)	10/28/85	This 42-year old male with hemophilia type A was hospitalized one day post his 3rd injection of vaccine for melena and lightheadedness. His past medical history was significant for recurrent GI bleeding, duodenal and antral gastric ulcers, and multiple hemarthroses. On admission to the hospital an endoscopy was performed which showed a hemorrhaging telangiectasic site in the distal atrum of the stomach. The patient received 4 units of whole blood and daily cryoprecipitate infusions. He was discharged after 5 days when there was no further clinical or laboratory evidence of GI bleeding.	No
864		1925	C-K732	5 mcg	(b) (6) (b) (6) (b) (6)		6/24/85	The neonatal male received HBIG and his first injection of vaccine at birth (b) (6) . On the fifth and sixth days post-vaccination, he had a temperature of 38°C. The infant received tylenol and his temperature returned to normal. He received his second and third injections of vaccine without temperature elevation.	Unlikely
864		1925	C-K732	5 mcg	(b) (6) (b) (6) (b) (6)		6/24/85	This male neonate received one dose of HBIG at birth (b) (6) . He developed physiologic jaundice on day 4 (b) (6) after birth. The jaundice resolved by day 7. The first injection of vaccine was administered on (b) (6) The infant received the second and third injections of vaccine without local or systemic complaints.	Unlikely
864		1925	C-K732	5 mcg	(b) (6) (b) (6) (b) (6)		6/24/85	On the first day of life, this female neonate had a fever of 101.7°F. The child received one dose of HBIG at birth. The following day her temperature was normal and she received her first injection of vaccine. There were no local or systemic complaints after the first, second or third injections of vaccine.	Unlikely
864		1925	C-K732	5 mcg	(b) (6) (b) (6)		6/24/85	This male neonate was reported to have developed jaundice during the post-natal period. He had received one dose of HBIG at birth (b) (6) and his first injection of vaccine three days later. His second injection of vaccine was administered on (b) (6)	Unlikely

*Clinical investigator's assessment.

30181-5
1/19/86

00035

Table B (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
864	(b) (6)	1925	C-K732	5 mcg	(b) (6)	(b) (6)	9/19/85	This one day old full-term male infant with apgar scores of 9 at both 1 and 5 minutes was entered into study 864. He received one injection of Hep-B-Gammagee on the day of birth and his 1st injection of vaccine the following day. The infant did well until two days post-delivery when poor feeding was noted. A cardiac evaluation revealed a murmur and possible atrial septal defect. His clinical condition deteriorated requiring intubation and the administration of pressor and diuretic agents. The infant died on (b) (6) after circulatory collapse and the onset of arrhythmias. An autopsy revealed intracranial, renal and hepatic hemorrhage, hypoplasia of the left auricle and ventricle, a patent foramen ovale, an atrial septal defect, and aspiration pneumonia.	No
869		1925	C-L217	10 mcg	(b) (6)		9/24/85	Nine hours after administration of vaccine, this 46-year old female health care worker experienced generalized pruritis (without rash) which increased in intensity over the subsequent 6 hours. Pruritis continued during the next 24 hours accompanied by irritability, nausea, and parathesia in the area beneath the left breast. These symptoms resolved on the 2nd and 3rd days post-vaccination. However, the participant reported that her extremities felt stiff and heavy. Her past medical history is significant for parathesias which occurred one year prior to vaccination after a mass was surgically removed from her breast. The investigator felt that the subject's reaction had an emotional component and was not related to vaccine.	No

*Clinical investigator's assessment.

30181-6
1/19/86

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
875	(b) (6)	1925	2277K Heptavax	40 mcg	(b) (6) (b) (6)	(b) (6)	9/24/85	This 53-year old female hemodialysis patient with an 18 month history of widely metastasized adenocarcinoma of the breast in addition to COPD, HTN, uremic pericarditis and renal failure, was entered into study 875 and randomized to receive plasma derived hepatitis B vaccine. Thirty-nine days after administration of the 2nd injection of vaccine the patient died of respiratory arrest.	No
875		1925	C-K937	40 mcg	(b) (6) (b) (6)		9/13/85	Forty-seven days after administration of the 2nd injection of vaccine, this 66-year old female patient was hospitalized for an infarcted bowel. Exploratory surgery was performed and the following day the patient expired.	No
875		1925	C-K937	40 mcg	(b) (6)		9/4/85	A 32-year old male hemodialysis patient received a 20 mcg intramuscular injection of vaccine into each deltoid (total dose 40 mcg). The patient's left arm subsequently became swollen, stiff and sore. These symptoms persisted for one week and then subsided. The patient did not receive any further injections.	Possible**
875		1925	C-K937	40 mcg	(b) (6)		9/4/85	Three days after administration of the first injection of vaccine, this 72-year old male hemodialysis patient developed generalized achiness and a headache. Forty-eight hours after onset of these symptoms, he developed a flu-like syndrome with a temperature of 100°F. The patient did not receive any further vaccine injections.	Possible**
875		1925	2277K Heptavax	40 mcg	(b) (6)	unk	9/4/85	A 70-year old male dialysis patient developed an unspecified illness, requiring hospitalization, following administration of the first injection of vaccine. The investigator stated the "illness" was not related to vaccine. The patient did not receive additional vaccine injections.	No

*Clinical investigator's assessment.
**Clinical monitor's assessment.

3018I-7
1/19/86

00037

Table 8 (Cont.)
Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study #	Case #	BB-IND	Lot of Vaccine	Dose	Dates Administered	Date of Event	Date Reported	Summary of Event	Vaccine* Related
880	(b) (6)	1925	C-L215	10 mcg	(b) (6) (b) (6)	(b) (6)	5/6/85	This 25-year old female subject recorded a temperature of 100.1°F several days after administration of a second injection of vaccine. A CBC completed at that time revealed a normal WBC with a normal differential but a platelet count greater than 1 x $10^6/mm^3$ was noted. Bone marrow examination revealed numerous megakaryocytes. A pre-existing myeloproliferative disorder is considered the most likely diagnosis	Unlikely
883		1925	C-L220	10 mcg	(b) (6) (b) (6)		4/30/85	The subject is a dental student who developed persistent cough and tiredness. He was seen by a physician approximately 139 days after his second injection of vaccine and was tentatively diagnosed as having chronic lymphatic leukemia.	No
889		1925	C-K937	10 mcg	(b) (6)		9/24/85	Fourteen hours after administration of the 1st injection of vaccine, this 37-year old female noted facial warmth and flushing lasting 45 minutes. She subsequently developed facial urticaria. The urticaria were treated with cold packs. All symptoms subsided within 12 hours. The subject received Benadryl prior to the second and third injections and had no post-vaccination reactions. She has no known known history of allergies.	Probably**

*Clinical investigator's assessment.
**Clinical monitor's assessment.

Table 9

Most Frequent Complaints (≥1.0%) Reported by 1252 Health Care Personnel and Other Healthy Adults During a Five-Day Period Following 3255 Injection of Yeast Recombinant Hepatitis B Vaccine

Type of Complaint	Frequency as %
Local (Injection Site)	
Soreness	8
Pain	5
Tenderness	3
Pruritis	1
Systemic	
Fatigue/Weakness	4
Headache	4
Nausea	2
Diarrhea	1
Malaise	1
Pharyngitis	1
Upper Respiratory Infection (Nos)	1

Table 10

Statistical Tests Regarding Anti-Yeast Antibody

1. Test for Trend in Antibody Titer (Log Titer)

	Time			
	Prevaccination	Post First Injection	Post Second Injection	Post Third Injection
Mean Log Titer	10.6	10.6	10.8	11.0
Std. Error	0.05	0.07	0.06	0.19
Number Tested	131	70	90	12

Conclusion: No significant trend in Log Titer ($p = 0.70$)

2. Test of Association between Change in Anti-Yeast Antibody (Pre vs. Postvaccination Titers) and Incidence of Clinical Complaints (Logistic Regression Model Controlled for Age and Sex)

Test	χ^2 (1 d.f.)	p
Post First Injection	0.14	0.71
Post Second Injection	0.04	0.84

Conclusion: No association between change in anti-yeast antibody and incidence of clinical complaints

Table 11

Statistical Test of Association between Antibody to a Specific Yeast Antigen (P60) and Incidence of Clinical Complaints*

Table of p Values

Level of Antibody to P60	Clinical Complaints			
	Post First Injection	Post Second Injection	Post Third Injection	Anytime
3 Months (2 Months Post First Injection)	0.49	0.60	0.95	0.76
Change in Antibody to P60 from Prevaccination to 3 Months	0.42	0.49	0.97	0.82

* Mantel Haenzel Test with Responses Corrected for Study and Prevaccination Level of Antibody to P60. Test significant for $p < 0.05$.

Table 12

Percentage (Proportion) of Healthy Adult Male Homosexuals with Clinical Complaints Following Injections of Yeast Recombinant (10 mcg Dose) or Plasma-Derived Hepatitis B Vaccine (20 mcg Dose) in Study B94

Type of Complaint	Vaccine	First Injection	Second Injection	Both Injections
Local (Injection Site)	Plasma-Derived	42 (37/88)	35 (24/67)	39 (61/155)
	Recombinant	30 (25/83)	35 (21/60)	32 (46/143)
Systemic	Plasma-Derived	35 (31/88)	25 (17/67)	31 (48/155)
	Recombinant	29 (24/83)	18 (11/60)	24 (35/143)
Any	Plasma-Derived	61 (54/88)	51 (34/67)	57 (88/155)
	Recombinant	51 (42/83)	47 (28/60)	49 (70/143)
Temperature ≥ 100°F (oral)	Plasma-Derived	2 (2/84)	0 (0/67)	2 (2/151)
	Recombinant	5 (4/83)	7 (4/57)	6 (8/140)

Table 13

Anti-HBs Responses at 3 Months Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine at 0, 1 and 6 Months

Age (Years)	Recombinant Vaccine - 10 mcg		Plasma-Derived Vaccine - 20 mcg	
	% with Anti-HBs*	GMT (mIU/ml)**	% with Anti-HBs*	GMT (mIU/ml)**
20 - 29	92 (359/388)	68	91 (436/477)	107
30 - 39	78 (87/112)	39	88 (277/315)	46
40 - 49	75 (21/28)	48	80 (124/156)	28
50 - 59	82 (14/17)	22	61 (66/108)	27

* S/N $\geq$2.1

** Responders only; titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b)(4) titer + 4.

3086I/1
1/11/86

Table 14

Anti-HBs Responses at 6 Months Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine at 0, 1 and 6 Months

Age (Years)	Recombinant Vaccine - 10 mcg		Plasma-Derived Vaccine - 20 mcg	
	% with Anti-HBs*	GMT (mIU/ml)**	% with Anti-HBs*	GMT (mIU/ml)**
20 - 29	96 (403/419)	96	95 (434/459)	148
30 - 39	89 (110/124)	53	93 (273/293)	56
40 - 49	88 (30/34)	45	88 (128/146)	40
50 - 59	81 (13/16)	42	76 (81/107)	39

* S/N $\geq$2.1

** Responders only; titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b)(4) titer + 4.

Table 15

Anti-HBs Responses at 7/8 Months Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine at 0, 1 and 6 Months+

Age (Years)	Recombinant Vaccine - 10 mcg		Plasma-Derived Vaccine - 20 mcg	
	% with Anti-HBs*	GMT (mIU/ml)**	% with Anti-HBs*	GMT (mIU/ml)**
20 - 29	99 (341/344)	1707	98 (412/421)	2830
30 - 39	96 (106/111)	694	95 (261/274)	1050
40 - 49	97 (33/34)	484	94 (134/142)	528
50 - 59	90 (17/19)	442	85 (87/102)	360

+ Includes some responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine

* S/N $\geq$2.1

** Responders only; titer in mIU/ml for recipients of plasma-derived vaccine recipients approximated as (b)(4) titer ÷ 4.

3086I/3
1/11/86

TABLE 16

Distribution of Anti-HBs Titers at 7/8 Months
Among Health Care Personnel and Other Healthy Adults
Receiving Yeast Recombinant or Plasma-Derived
Hepatitis B Vaccine at 0, 1, and 6 Months

	% (Proportion) with Titer	
Anti-HBs Titer	Recombinant Vaccine 10 mcg	Plasma-Derived Vaccine 20 mcg
S/N ≥2.1	98 (498/509)	95 (930/983)
mIU/ml ≥10	97 (494/509)	92 (900/983)
mIU/ml ≥100	89 (451/509)	78 (772/983)
mIU/ml ≥1000	58 (294/509)	53 (519/983)

* Titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b) (4) titer + 4.

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1/11/86

Table 17

Anti-HBs Responses at 12 Months Among Health Care Personnel and Other Healthy Adults Receiving Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine at 0, 1 and 6 Months

Age (Years)	Recombinant Vaccine - 10 mcg		Plasma-Derived Vaccine - 20 mcg	
	% with Anti-HBs*	GMT (mIU/ml)**	% with Anti-HBs*	GMT (mIU/ml)**
20 - 29	98 (115/118)	343	99 (233/236)	954
30 - 39	94 (74/79)	235	97 (67/69)	441
40 - 49	91 (21/23)	238	87 (33/38)	117
50 - 59	88 (15/17)	151	87 (46/53)	116

* S/N $\geq$2.1

** Responders only; titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b)(4) titer + 4.

30861/4
1/11/86

TABLE 18

Distribution of Anti-HBs Titers at 12 Months
Among Health Care Personnel and Other Healthy
Adults Receiving Yeast Recombinant or Plasma-Derived
Hepatitis B Vaccine at 0, 1, and 6 Months

	% (Proportion) with Titer	
Anti-HBs Titer	Recombinant Vaccine 10 mcg	Plasma-Derived Vaccine 20 mcg
S/N ≥2.1	95 (225/237)	95 (400/422)
mIU/ml ≥10	90 (213/237)	92 (387/422)
mIU/ml ≥100	65 (155/237)	70 (294/422)
mIU/ml ≥1000	25 (60/237)	37 (157/422)

*Titer in mIU/ml for recipients of plasma-derived vaccine approximated as (b)(4) titer ÷ 4.

Table 19

Percentage (Proportion) of Health Care Personnel and Other Healthy Adults With Clinical Complaints During a 5 Day Period Following Injections of Yeast Recombinant or Plasma-Derived Hepatitis B Vaccine

Type of Complaint	Vaccine	First Injection	Second Injection	Third Injection	All Injections
Local (Injection Site)	Plasma-Derived	13 (92/687)	10 (67/650)	11 (55/480)	12 (214/1817)
	Recombinant	20 (248/1252)	14 (157/1162)	17 (139/841)	17 (544/3255)
Any Complaint	Plasma-Derived	24 (164/687)	18 (119/650)	18 (87/480)	20 (370/1817)
	Recombinant	34 (426/1252)	23 (263/1162)	23 (196/841)	27 (885/3255)
Temperature >100°F (oral)	Plasma-Derived	3 (18/681)	3 (20/640)	2 (10/467)	3 (48/1788)
	Recombinant	4 (45/1217)	3 (28/1111)	4 (27/769)	3 (100/3097)

APPENDIX I

Lot Numbers of Vaccine Used in Clinical Trials

Lots of the yeast recombinant hepatitis B vaccine used in the clinical trials summarized in this report are identified by an alpha-numeric code consisting of two or three segments. In the Interim Submission (Report #2) issued in August 1985, many lots of vaccine were identified in text and tables using either the prefix or internal segments. In the present report, all lots are identified by the 5 digit suffix segment. To facilitate cross reference between the Interim Submission and the present report, the complete lot number for each lot of vaccine in use is listed below:

934/C-J625

972/C-K444

974/C-K446

978/C-K563

979/C-K564

985/C-K732

986/C-K733

987/C-K734

993/C-K937

81990D/18066/C-L215

817668/18067/C-L216

81991D/18068/C-L217

81992A/18070/C-L219

81954I/18071/C-L220

89303/1005/C-L915

89426/22930/C-M718

85860/22123/C-M125

85861/22124/C-M126

IMMUNE AFFINITY
VACCINE

SUMMARY - IMMUNE AFFINITY VACCINE

Recombinant hepatitis B vaccine from one lot (934/C-J625) produced by an immune affinity purification procedure has been administered to 75 initially seronegative health care personnel and other healthy adults in 3 studies (Table 1), with 72 of these completing a 3 injection regimen of vaccination. The serologic and clinical data relating to this lot are summarized separately because this procedure will not be used for the commercial product.

Table 2 shows the anti-HBs responses in persons immunized at 0, 1, and 6 months with 10 mcg doses of vaccine produced by the immune affinity procedure. All vaccinees developed protective levels of anti-HBs (mIU/ml $\geq$10) 7-8 months post the first injection of vaccine. The geometric mean titer was 1607.0 mIU/ml. Twelve months after the first injection of vaccine, 96% of the vaccinees still had titers $\geq$10 mIU/ml. However, the geometric mean titer declined to 422 mIU/ml.

There have been no serious or alarming reactions attributable to the immune affinity purified vaccine. While one adverse experience report has been filed with the OoBRR (Table 3), the reaction noted did not appear to be related to the vaccine. There was also one subject whose 2, 3, and 4 month post-vaccination sera were positive for anti-HBc. His pre-vaccination blood sample and his 1, 5, 6, and 7 month blood samples tested negative for anti-HBc. The subject has been positive for anti-HBs since one month following the first injection of vaccine. None of his blood samples have been positive for HBsAg. All samples had normal levels of AST and ALT.

Table 4 shows the frequencies of clinical complaints reported following 206 injections of the vaccine. Reports of injection site discomfort and systemic complaints were made with frequencies of 50% and 15%, respectively. The frequencies of specific injection site complaints are shown in Table 5. The most frequent complaints were soreness (34%), pain (7%), and tenderness (5%). The frequencies of specific systemic complaints by body system are shown in Table 6. Complaints occurring at frequencies of $\geq$1% were fatigue/weakness (4%), headache (2%), pharyngitis (2%), malaise (1%), rhinitis (1%), upper respiratory infection (not otherwise specified) (1%), nausea (1%), and diarrhea (1%).

Table 1

Clinical Studies of Health Care Personnel and Other Healthy Adults Receiving

Yeast Recombinant Hepatitis B Vaccine Produced by An Immune Affinity Method

Population	Study #	Investigator	Location	Date Initiated	Status	Vaccine			% Subjects Planned (Vaccinated)	% with Anti-HBs		Time (Months)
						Lot	Dose	Regimen		S/N ≥2.1	mIU/ml ≥10	
Healthy Adults	779	Bishop	Merck & Co., PA	7/13/83	In progress	C-J625	10 mcg	0,1,6 mos.	15 (15)	100(14/14)	100(14/14)	12 mos.
Health Care Personnel	792	Dienstag	Boston	11/10/83	In progress	C-J625	10 mcg	0,1,6 mos.	30 (30)	96(25/26)	96(25/26)	12 mos.
Health Care Personnel	795	Deinhardt	West Germany	11/21/83	In progress	C-J625	10 mcg	0,1,6 mos.	30 (30)	96(26/27)	93(25/27)	12 mos.

00053

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1/6/86

Table 2

Antibody Responses Among Health Care Personnel and Other Healthy Adults Following Vaccinatio at 0, 1, and 6 Months with 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Time (Months)	% with Anti-HBs		GMT (mIU/ml)		
			All Vaccinees	Responders	
	S/N ≥2.1	mIU/ml ≥10		S/N ≥2.1	mIU/ml ≥10
1	36 (15/70)	9 (6/70)	1.0	7.0	26.5
2	79 (8/73)	63 (46/73)	16.1	38.4	64.5
3	96 (67/70)	76 (53/70)	30.8	37.4	62.7
6	97 (69/71)	89 (63/71)	52.9	67.5	79.7
7/8	100 (70/70)	100 (70/70)	1607.0	1607.0	1607.0
9	100 (60/60)	97 (58/60)	1024.5	1024.5	1228.4
12	97 (65/67)	96 (64/67)	317.9	393.8	422.0

Studies: 779, 792, 795

Table 3

Adverse Experiences to Yeast Recombinant Hepatitis B Vaccine

Study-Case No. No.	BB-IND	Lot of Vaccine	Dose	Date(s) Administered	Date of Event	Date Reported	Summary of Event	Vaccine Related *
(b)(6)	(b)(4)	C-J625	10 mcg	(b)(6)	(b)(6)	1/15/85	A 30 year-old male subject was noted to have a serum ALT of 170 on (b)(6) (three months after receiving the third dose of vaccine). One week later, the serum ALT was 139. The subject's pre-vaccination ALT was 47. All sera remained negative for anti-HBc and HBsAg. The subject had been taking two antimalarial drugs, Chloroquine and Fansidar, for 2 months prior to the (b)(6) bleeding. During that time, he had been visiting East Africa.	No

* Clinical investigator's assessment.

00055

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1/21/86

Table 4

Percentages of Health Care Personnel and Other Healthy Adults With Clinical Complaints During a 5-Day Period Following 206 Injections of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Studies: 779, 792, 795

Type of Complaint	Dose 1	Dose 2	Dose 3	All
Local (Injection Site)	55 (39/71)	44 (31/70)	51 (33/65)	50 (103/206)
Systemic	22 (16/71)	13 (9/70)	9 (6/65)	15 (31/206)
Any Complaint	63 (45/71)	47 (33/70)	54 (35/65)	55 (113/206)

Studies: 779, 792, 795

Table 5

Frequency of Local (Injection Site) Complaints Occurring Within 5 Days Among Health Care Personnel and Other Healthy Adults Following 206 Injections of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Number of Vaccine Recipients: 71

Studies: 779, 792, 795

Complaint	Number	Frequency as %
Soreness	71	34
Pain	15	7
Tenderness	11	5
Stiffness/Tightness	4	2
Swelling	4	2
Ecchymosis	2	1
Erythema	2	1
Pruritis	2	1
Numbness	1	0.5
Pigment Change	1	0.5
Skin Mottled/Peeling	1	0.5
Parasthesia	1	0.5
Papule	1	0.5
Warmth	1	0.5

Table 6

Frequency of Systemic Complaints by Body System Occurring Within 5 Days Among Health Care Personnel and Other Healthy Adults Following 206 Injections of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Number of Vaccine Recipients: 71

Studies: 779, 792, 795

Body System/Complaint	Frequency as % (Number)	Body System/Complaint	Frequency as % (Number)
Whole Body/General	8 (17)	Infectious Syndromes	1 (2)
Fatigue/Weakness	4 (9)	Herpes Labialis, Recurrent	0.5 (1)
Headache	2 (5)	Viral Infection, Nos	0.5 (1)
Malaise	1 (3)		
Sensation of Warmth, General	0.5 (1)		
Respiratory	5 (11)	Hemic/Lymphatic	0.5 (1)
Pharyngitis	2 (5)	Lymphadenopathy, Cervical	0.5 (1)
Rhinitis	1 (3)		
Upper Respiratory Infection. Nos	1 (3)		
Cough	0.5 (1)	Musculoskeletal	0.5 (1)
Sinusitis	0.5 (1)		
Laryngitis	0.5 (1)	Myalgia	0.5 (1)
Digestive	2 (5)		
Nausea	1 (3)	Organs of Special Sense	0.5 (1)
Diarrhea	1 (2)		
Dyspepsia/Heartburn	0.5 (1)	Conjunctivits	0.5 (1)
Abdominal Pain/Cramps	0.5 (1)		

Table 7

Percentages of Health Care Personnel and Other Healthy Adults With Elevated Temperatures During a 5-Day Period Following 190 Injections of Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625

Studies: 779, 792, 795

Temperature	Dose 1	Dose 2	Dose 3	All
≥ 100°F	4 (3/70)	2 (1/63)	4 (2/57)	3 (6/190)
≥ 101°F	1 (1/70)	2 (1/63)	4 (2/57)	2 (4/190)

Immune Affinity Vaccine

Study 779 - West Point, PA - Dr. R. Bishop

Healthy adults receive 10 mcg injections of vaccine from one of two lots at 0, 1, and 6 months.

Fifteen adults have received 3 injections of vaccine from lot C-J625 produced by the immune affinity method. At 7/8 months, 100% (15/15) of the participants seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for these responders was 1758.1 mIU/ml. Among the participants with serology data at 12 months, 100% (12/12) were positive for anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 402.3 mIU/ml. No serious or alarming reactions attributable to vaccine have been reported. Subjects continue to be followed for persistence of antibody.

Refer to the summary in health care personnel and other healthy adults for responses of subjects vaccinated in this study with vaccine produced using the (b) (4) method.

Study 792 - Boston, MA - Dr. J. Dienstag

Initially seronegative health care personnel receive 10 mcg injections of vaccine from one of two lots at 0, 1, and 6 months.

Thirty persons have received 2 injections of vaccine from lot C-J625 produced by the immune affinity method, and 27 of these have received the third injection. One hundred percent (26/26) of the participants seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at nine months. The GMT for these responders was 1400.1 mIU/ml. At 12 months, 96% (25/26) of the subjects were positive for anti-HBs (mIU/ml ≥10) with a GMT of 329.8 for all vaccinees. There have been no reports of serious or alarming reactions attributable to vaccine. Subjects continue to be followed for persistence of antibody.

Refer to the summary on health care personnel and other healthy adults for responses of subjects vaccinated in this study with vaccine produced using the (b) (4) method.

Study 795 - West Germany - Dr. F. Deinhardt

The study population consists of health care personnel and other healthy adults who are initially negative for hepatitis B serologic markers. Participants receive 10 mcg injections of vaccine at 0, 1, and 6 months from one of three vaccine lots.

Immune Affinity Vaccine

Study 795 - West Germany - Dr. F. Deinhardt (Contd)

Thirty persons have received 3 injections of lot C-J625 vaccine produced by the immune affinity method. At 7/8 months, 100% (29/29) of the subjects seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for these responders was 1735.7 mIU/ml. Ninety-three percent (25/27) of the participants were positive for anti-HBs (mIU/ml ≥10) at 12 months. The GMT for all vaccinees at that time was 271.5 mIU/ml.

Refer to the summary in health care personnel and other healthy adults for responses of subjects vaccinated in this study with vaccine produced using the (b)(4) method.

STUDY 779

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 779
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among healthy adults who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 934/C-J625 (10 mcg HBsAg/ml) Lot 972/C-K444 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Robert P. Bishop, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486
SECONDARY INVESTIGATORS:	E. P. Avancena, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486 Joseph C. Rogers, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486 Joseph P. Romano, M.D. Health Services Merck Sharp and Dohme Rahway, NJ 07065
STUDY LOCATION:	Merck Sharp and Dohme West Point, PA 19486
DATE INITIATED:	July 13, 1983
DATE COMPLETED:	In progress

Study 779

STUDY PROCEDURE:

The study population consists of 41 healthy adults of either sex (excluding pregnant women) employed at Merck and Co., Inc., who were initially negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

Eligible participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine produced by either the immune affinity or the (b)(4) procedure at 0, 1 and 6 months. Study participants are asked to take and record their temperatures for five days after each injection of vaccine and to record any local or systemic complaints that they may experience.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before vaccination. Post-vaccination blood samples (10-15 ml) are obtained monthly for seven months and at 9, 12 and 24 months following the first injection of vaccine. Samples are assayed for HBsAg, anti-HBc, anti-HBs and ALT, and these may be assayed for antibody to antigens in yeast extract. Samples with an anti-HBs titer $\geq$ 25 mIU/ml units are tested to determine the relative proportions of anti-a and anti-d activity.

STUDY RESULTS:

HEALTHY ADULTS (Immune Affinity Vaccine):

10 mcg Lot 934/C-J625 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
15	15	15

Study 779

RESULTS: (Cont.)

2. Serologic Results:

Serologic data are available for 15 participants at 7/8 months. One hundred percent (15/15) of the participants seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at 7/8 months was 1758.1 mIU/ml (all vaccinees and responders by either cutoff).

Among the participants who had serology data at 12 months, 100% (12/12) were positive for anti-HBs (mIU/ml $\geq$10). The GMT for these vaccinees was 402.3 mIU/ml.

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for fifteen participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	80(12/15)	73(11/15)	73(11/15)
Systemic	33(5/15)	20(3/15)	7(1/15)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming reactions attributable to vaccine.

HBV Markers (Anti-HBc)

One subject had serum samples that tested transiently positive for anti-HBc. The 2, 3, and 4 month post-vaccination sera were positive for anti-HBc. His prevaccination blood sample and his 1, 5, 6, 7, 9 and 12 month blood samples were negative for anti-HBc. None of his sera were positive for HBsAg. All samples were normal with respect to AST and ALT.

PUBLICATIONS:

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:315-17.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
POPULATION : HEALTHY ADULTS
DOSE : 10 MCG
LOT : CJ625
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	45%	(5/11)	9.1%	(1/11)	1.7	6.1	55.5
2 MONTHS	93%	(14/15)	73%	(11/15)	32.0	44.7	88.0
3 MONTHS	100%	(14/14)	86%	(12/14)	60.5	60.5	83.5
6 MONTHS	100%	(15/15)	100%	(15/15)	68.0	68.0	68.0
7/8 MONTHS	100%	(15/15)	100%	(15/15)	1758.1	1758.1	1758.1
9 MONTHS	100%	(14/14)	100%	(14/14)	1319.9	1319.9	1319.9
12 MONTHS	100%	(14/14)	100%	(14/14)	402.3	402.3	402.3

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	11 (73.3%)	5 (33.3%)	3 (20.0%)	1 (6.7%)	0 (0.0%)	1 (7.1%)		12 (80.0%)
SORENESS	10 (66.7%)	5 (33.3%)	3 (20.0%)	1 (6.7%)	0 (0.0%)	1 (7.1%)		11 (73.3%)
TENDERNESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
ERYTHEMA (REDNESS)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
STIFFNESS/TIGHTNESS	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
ECCHYMOSIS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
SYSTEMIC	4 (26.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (7.1%)		5 (33.3%)
WHOLE BODY/GENERAL	3 (20.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (7.1%)		4 (26.7%)
FATIGUE/WEAKNESS	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (7.1%)		2 (13.3%)
HEADACHE	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
RESPIRATORY	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
SINUSITIS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PHARYNGITIS (SORE THROAT)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
DIGESTIVE SYSTEM	1 (6.7%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		2 (13.3%)
DYSPEPSIA/HEARTBURN	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
NAUSEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
PERSONS WITH COMPLAINTS	11 (73.3%)	6 (40.0%)	4 (26.7%)	2 (13.3%)	1 (6.7%)	2 (14.3%)		12 (80.0%)
PERSONS WITH NO COMPLAINTS	4 (26.7%)	9 (60.0%)	11 (73.3%)	13 (86.7%)	14 (93.3%)	12 (85.7%)		3 (20.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	9 (60.0%)	6 (40.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (73.3%)
SORENESS	9 (60.0%)	6 (40.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (73.3%)
STIFFNESS/TIGHTNESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
SYSTEMIC	1 (6.7%)	1 (6.7%)	1 (6.7%)	2 (13.3%)	1 (6.7%)	1 (6.7%)	3 (20.0%)
WHOLE BODY/GENERAL	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
FATIGUE/WEAKNESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
RESPIRATORY	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
PERSONS WITH COMPLAINTS	9 (60.0%)	6 (40.0%)	3 (20.0%)	2 (13.3%)	1 (6.7%)	1 (6.7%)	11 (73.3%)

69000

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	6 (40.0%)	9 (60.0%)	12 (80.0%)	13 (86.7%)	14 (93.3%)	14 (93.3%)	4 (26.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (15 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	9 (60.0%)	3 (20.0%)	4 (26.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	11 (73.3%)
PAIN	0 (0.0%)	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
SORENESS	9 (60.0%)	2 (13.3%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (60.0%)
TENDERNESS	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
STIFFNESS/TIGHTNESS	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)	1 (6.7%)
PERSONS WITH COMPLAINTS	9 (60.0%)	3 (20.0%)	4 (26.7%)	2 (13.3%)	2 (13.3%)	2 (13.3%)	11 (73.3%)
PERSONS WITH NO COMPLAINTS	6 (40.0%)	12 (80.0%)	11 (73.3%)	13 (86.7%)	13 (86.7%)	13 (86.7%)	4 (26.7%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

00073

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
< 99	10 (66.7%)	13 (86.7%)	14 (93.3%)	13 (86.7%)	14 (100.0%)	12 (85.7%)			10 (66.7%)
99 - 99.9	3 (20.0%)	1 (6.7%)	1 (6.7%)	2 (13.3%)	0 (0.0%)	2 (14.3%)			2 (13.3%)
100 - 100.9	1 (6.7%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			2 (13.3%)
101 - 101.9	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (6.7%)
TEMPERATURE TAKEN	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	14 (93.3%)	14 (93.3%)			15 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (6.7%)			0 (0.0%)

00072

Table 3 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	13 (86.7%)	15 (100.0%)	14 (93.3%)	12 (92.3%)	13 (92.9%)	12 (92.3%)		11 (73.3%)
99 - 99.9	2 (13.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (7.1%)	1 (7.7%)		3 (20.0%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)		1 (6.7%)
TEMPERATURE TAKEN	15 (100.0%)	15 (100.0%)	15 (100.0%)	13 (86.7%)	14 (93.3%)	13 (86.7%)		15 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	1 (6.7%)	2 (13.3%)		0 (0.0%)

Table 3 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (15 PATIENTS) - DOSE 3 — DAYS POST VACCINATION 0	1	2	3	4	5			NUMBER WITH MAX TEMP
NORMAL	2 (13.3%)	2 (13.3%)	2 (13.3%)	2 (13.3%)	2 (15.4%)	2 (13.3%)			2 (13.3%)
< 99	13 (86.7%)	13 (86.7%)	13 (86.7%)	13 (86.7%)	9 (69.2%)	12 (80.0%)			11 (73.3%)
99 - 99.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	1 (6.7%)			1 (6.7%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)	0 (0.0%)			1 (6.7%)
TEMPERATURE TAKEN	15 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	13 (86.7%)	15 (100.0%)			15 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)			0 (0.0%)

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23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

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Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

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Original Contributions

Clinical Evaluation in Healthy Adults of a Hepatitis B Vaccine Made by Recombinant DNA

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• A vaccine formulated from hepatitis B surface antigen (HBsAg) produced by a recombinant strain of the yeast *Saccharomyces cerevisiae* was administered to two groups of human volunteers composed of 37 healthy, low-risk adults. Each subject received a 10-μg dose of HBsAg at 0, 1, and 6 months. By one month, 27% to 40% of the vaccinees had antibody to HBsAg, and by three months 80% to 100% were antibody positive. Large boosts in titer followed the third dose at six months. The antibody formed is predominantly specific for the *a* determinant of HBsAg. There have been no serious reactions attributable to the vaccine. The most frequent complaint has been transient soreness at the injection site. As far as we know, this is the first reported use in man of a vaccine prepared by recombinant DNA technology.

(*JAMA* 1984;251:2812-2815)

WORLDWIDE, human hepatitis B infection constitutes a major public health problem. In addition to the disability associated with acute clinical disease, chronic liver disease, cirrhosis, and primary hepatocellular carcinoma are now recognized sequelae of unresolved hepatitis B infection. Indeed, in some areas of Asia and sub-Saharan Africa, primary hepatocellular carcinoma ostensibly attributable to hepatitis B infection ranks as a leading cause of cancer deaths among males.[1]

See also p 2765.

The reservoir of hepatitis B virus resides mainly in a population of chronic carriers now estimated to number more than 200 million.[1] Infection is transmitted to susceptible persons through contact with the blood, semen, or saliva of chronic carriers or persons suffering acute infection. In low-incidence countries, such as the United States, the risk of hepatitis B infection is still high among certain groups of health care personnel, patients receiving dialysis treatments or blood products made from large pools, children born to Alaskan Eskimos or to Indochinese or Haitian refugees, residents of institutions for the mentally handicapped, prisoners, users of illicit injectable drugs, and persons who are sexually very promiscuous.[1] In high-incidence areas such as Southeast Asia, transmission from mother to child in the perinatal period is the major mode of infection supplemented by horizontal transmission between other family contacts.[2]

Since there is no effective treatment for hepatitis B infection, prevention is essential. A safe, effective human hepatitis B vaccine is now available. However, it utilizes hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of hepatitis B virus infection. Consequently, the supply of vaccine is potentially limited by available sources of suitable plasma. In addition, extensive processing and safety testing have been necessary to ensure production of a vaccine antigen that is pure and free of any extraneous living agent that might have been present in the starting plasma. Even though multiple inactivation treatments used in the antigen purification process have been shown to inactivate representatives of all major groups of animal viruses,[3] concern over the theoretical possibility of a living organism such as the etiologic agent of acquired immune deficiency syndrome being present in plasma and surviving the purification and inactivation procedures has slowed acceptance of hepatitis B vaccine.

A promising alternative to infected human plasma as a source of HBsAg for vaccine is the use of recombinant DNA technology to effect synthesis of the surface antigen by a culture of microorganisms. The hepatitis B virus gene coding for HBsAg has been cloned both in *Escherichia coli* and in yeast[4-7]; however, expression of the gene in yeast has been much better than in *E coli*. Furthermore, HBsAg

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produced by recombinant yeast cells has been shown to aggregate into particles closely resembling those isolated from human plasma, and this material was shown to include antibodies in mice and guinea pigs.[9]

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for HBsAg has been formulated into a vaccine through adsorption on alum adjuvant. Electron microscopy reveals that the purified HBsAg used for this vaccine exists as aggregate particles 20 to 22 nm in diameter, a morphology also characteristic of free surface antigen in infected plasma and of the purified antigen now used in plasma-derived hepatitis B vaccine. In contrast to HBsAg from human plasma, the antigen produced by recombinant yeast is not glycosylated. Under reducing conditions, sodium dodecyl sulfate electrophoresis of the antigen purified from yeast reveals a single band of molecular weight 23,000, which corresponds to the nonglycosylated polypeptide that is the major component of the hepatitis B virus envelope. The vaccine formulated using this material has now been shown to be immunogenic for mice and for monkeys with a potency equal to or superior to that of vaccine made from plasma-derived antigen. In addition, chimpanzees immunized with this yeast recombinant hepatitis B vaccine (HBsAg subtype *adw*) were fully protected when challenged with virus of either type *adr* or *ayr*, while unimmunized animals all showed evidence of infection when challenged.[10]

In this article we describe results of the first human immunogenicity-safety trial of the yeast recombinant hepatitis B vaccine. To the best of our knowledge, this is the first time that a vaccine prepared by recombinant DNA technology has been used in man.

MATERIALS AND METHODS

Population

Participants in this study were healthy, nonpregnant adult employees of Merck and Co, Inc. Subjects had to be negative for hepatitis B serological markers and have a normal level of alanine aminotransferase and must not have received any other hepatitis B vaccine. Written consent was obtained after providing each participant with information on the source of the investigational yeast recombinant hepatitis B vaccine, animal test results obtained with the vaccine, vaccination and bleeding schedules, and the potential risks and benefits of participation in the study.

Vaccine

Hepatitis B surface antigen for the vaccine was produced in fermentation cultures of a recombinant strain of the yeast *S cerevisiae* containing a plasmid carrying the gene for the *adw* subtype of HBsAg, as described previously.[7,8]

Two methods were employed for the purification of HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends on selection of water-immiscible molecules followed by separation by molecular size. Details of the expression of HBsAg in yeast and the purification of the surface antigen will be published elsewhere. Purified HBsAg was treated with formaldehyde to stabilize the material and to kill any extraneous living agents that might be present. The antigen was then formulated into a vaccine through adsorption on alum adjuvant to give 10 μg of HBsAg and 0.5 mg of aluminum (hydroxide) per 1-mL dose. The final formulation also contained 1:20,000 thimerosal as a preservative. Vaccine was maintained at 2 to 8 °C until used.

Procedures

A blood sample was obtained from each subject approximately two weeks prior to the first vaccination and was tested for HBsAg, antibody to HBsAg (anti-HBs), antibody to core antigen (anti-HBc), alanine aminotransferase (ALT), and yeast antibody. Subjects found eligible on the basis of these assays were scheduled to receive a 1.0-mL (10-μg HBsAg) intramuscular injection of the yeast recombinant vaccine at 0, 1, and 6 months. Postvaccination blood samples for the determination of hepatitis B serological markers, ALT, and yeast antibody were scheduled monthly for seven months and at 9, 12, and 24 months following the first injection.

Vaccinees were asked to take their temperature daily for five days after each injection of vaccine and to report any local or systemic reactions that might occur during this period.

Assays

Standard radioimmunoassay test kits were used for the determination of HBsAg, anti-HBs, and anti-HBc. Titers of anti-HBs were expressed in international milliunits per milliliter using the formulation described by Hollinger et al.[11] A serum sample was considered positive for anti-HBs if the ratio of the sample counts per minute to the negative control serum counts per minute was 2.1 or greater.

Estimates of the proportion of anti-HBs in postvaccination sera specific for the *a* or *d* determinants of HBsAg were based on an assay described by Hoofnagle et al.[12] Briefly, aliquots of each serum sample are incubated with a subtype *ad* HBsAg-positive serum, with a subtype *ay* HBsAg-positive serum, and with normal human serum for two hours at room temperature, and then each mixture is carried through a standard radioimmunoassay to measure residual anti-HBs. Based on the percent of neutralization with the two HBsAg subtype sera when compared with the unneutralized normal human serum, an estimate can be made of the relative amounts of anti-*a* and anti-*d* antibodies present. Since the vaccine is a monovalent-type *adw* preparation, sera will contain either anti-*d* antibodies, anti-*a* antibodies, or a combination of both types, and the amount of neutralization with the HBsAg-*ay* serum is therefore a direct assay for the amount of anti-*a* present. Subtracting the amount of neutralization with the HBsAg-*ay* serum from that found for the HBsAg-*ad* serum then gives an estimate of the amount of anti-*d* present.

A radioimmunoassay was developed to detect yeast antibodies in the sera of vaccine recipients. For this assay, an extract of the parent strain of *S cerevisiae* lacking the plasmid containing the gene for HBsAg was prepared by disrupting a 50% suspension of the cells in a homogenizer and then clarified by centrifugation at 9,000 *g* followed by passage through a 0.45-mμm membrane filter. The clarified, filtered extract was diluted to a final protein concentration of 80 μg/mL with 0.1 M carbonate buffer and pH 9.6 and adsorbed to ¼-in polystyrene beads overnight at 4 °C. Washed, dried beads were maintained at −20 °C. Two hundred-microliter volumes of sera diluted 1:100, 1:1,000, and 1:10,000 in phosphate-buffered saline containing 0.5% bovine serum albumin and 0.5% Tween 20 were incubated with coated beads for three hours at 37 °C. Following three washes with water, the beads were incubated with 200 μL of iodine 125 protein A (specific activity, 100,000 cpm) for 1.5 hours at 37 °C. The protein A binds and labels any antiyeast antibody on the bead that is of the IgG class. After three additional water washes, the beads were counted and titers of yeast antibody were determined by interpolation from a standard curve derived using dilutions of a hyperimmune guinea pig serum having an antibody titer to parent yeast extract of 1 million.

The serum samples of vaccinees were also measured for changes in preexisting specific yeast antibodies or the appearance of new yeast antibodies using a sodium dodecyl sulfate polyacrylamide gel electrophoresis (reducing), Western blot technique. In this procedure, parent yeast extract is separated on a 12.5% polyacrylamide gel. After transfer to a nitrocellulose sheet, polypeptides from the gel are detected by incubation with a 1:50 dilution of the vaccinee's serum, followed by incubation with ^{125}I protein A and exposure to x-ray film (T. Mason, PhD, oral communication, 1982).

RESULTS

The vaccine has been well tolerated. None of the 37 subjects studied to date has experienced a serious adverse effect attributable to vaccine. There has been no evidence of hepatitis B infection among vaccinees, ie, no elevation of ALT values and no antigenemia. Mild soreness at the injection site generally lasting one to two days was reported by 73% to 80% of vaccinees who received vaccine purified by immune affinity chromatography (lot 934) but by a substantially smaller proportion—20% to 24%—of subjects who received vaccine prepared by hydrophobic interaction chromatography (lot 972) (Table 1). Infrequent systemic complaints occurring within a five-day period following vaccination have included elevated temperature (38.3 to 38.8 °C [101 to 102 °F], oral), fatigue, headache, gastrointestinal disturbance, symptoms of upper respiratory tract infection, and nosebleed.

Table 2 summarizes our observations to date on the human immunogenicity of yeast recombinant hepatitis B vaccine. Fifteen persons (ten men, five women; age range, 23 to 53 years; median age, 33 years) have received all three doses of lot 934 vaccine prepared by the immune affinity chromatography method. Forty percent had a detectable titer of anti-HBs within one month of receiving the first dose. By two months, the proportion of seroconverters rose to 93%, and at three months, all recipients of this vaccine were antibody positive. The geometric mean titer following primary immunization reached a plateau at four months, then increased more than 25-fold following the booster dose at six months.

Table 1.—Proportion (%) of Vaccinees With Clinical Complaints During a Five-Day Period Following Injection of Yeast Recombinant Hepatitis B Vaccine

Nature of Complaint	Vaccine Lot No.	Dose 1	Dose 2	Dose 3
Soreness at injection site	934	12/15 (80)	11/15 (73)	11/15 (73)
	972	5/21 (24)	3/15 (20)	...
Systemic* complaints	934	5/15 (33)	3/15 (20)	1/15 (7)
	972	1/21 (5)	2/15 (13)	...

*Includes persons with one or more episodes of the following: temperature, 38.3 to 38.8 °C (101 to 102 °F) (two), fatigue (three), gastrointestinal disturbance (four), headache (five), symptoms of upper respiratory tract infection (three), and nosebleed (one).

Table 2.—Seroconversion Frequencies and Geometric Mean Titers (GMTs)* for Anti-HBs Among Initially Seronegative Healthy Adults Receiving 10-µg Doses of Yeast Recombinant Hepatitis B Vaccine†

Vaccine Lot No. (Method of Preparation)	No. of Subjects Vaccinated	Time, mo	Seroconversion Proportion (%)	GMT: All Vaccinees‡	GMT: Responders Only
934 (Immune affinity chromatography)	15	1	6/15 (40)	1.6	8.0
		2	14/15 (93)	31.7	44.2
		3	15/15 (100)	56.5	56.5
		4	15/15 (100)	78.2	78.2
		5	14/14 (100)	77.2	77.2
		6	15/15 (100)	87.9	87.9
		7	12/12 (100)	1,906.1	1,906.1
972 (Hydrophobic interaction chromatography)	22	1	4/15 (27)	1.4	39.6
		2	8/12 (67)	17.8	103.7
		3	6/6 (100)	59.5	218.5

*In international milliunits per milliliter.
†At 0, 1, and 6 months.
‡All serum samples with titers of less than 0.6 mIU/mL were assigned a value of 0.3 mIU/mL for calculating GMTs.

Table 3.—Percentages of Anti-HBs Specific for *a* and *d* Determinants of HBsAg in Postvaccination Sera*

Vaccine Lot No.	Time, mo	No. of Samples	% Anti-*a*: Range	% Anti-*a*: Mean	% Anti-*d*: Range	% Anti-*d*: Mean
934	1	1	...	47	...	53
	2	7	87-98	93	2-10	6
	3	10	83-98	89	2-37	13
	4	13	88-98	89	2-35	11
	5	12	80-97	92	2-20	8
	6	8	92-97	94	2-8	5
	7	12	89-100	98	0-11	2
972	1	2	56-91	74	9-44	26
	2	8	87-100	94	0-13	6

*Assay done only on serum samples having an anti-HBs titer of 25 mIU/mL or greater.

Twenty-two subjects have received vaccine from lot 972 made from HBsAg purified by the hydrophobic intraction chromatography method. These vaccinees have not been followed up for as long as the lot 934 recipients, and none has yet received a third dose. Preliminary serological results are shown in Table 2 for 15 of these volunteers (12 men, three women; age range, 24 to 63 years; median age, 40 years). The percentage of seroconverters was 27% at one month, 67% at two months, and 80% at three months. Geometric mean titers within the first three months of follow-up were similar to those observed among recipients of lot 934 vaccine.

Postvaccination serum samples with anti-HBs titers of 25 ImU/mL or greater were assayed to determine the percentage of antibody specific for the *a* and *d* determinants of HBsAg. Table 3 shows the results of these assays. Antibody specific for the *a* determinant predominates. In the interval from two to seven

months following the first dose of vaccine, anti-*a* antibody accounted for approximately 90% of the total anti-HBs.

Earlier studies (unpublished) showed that the yeast recombinant hepatitis B vaccine induced a predominantly anti-*a* form of anti-HBs in African green monkeys and that these antibodies have persisted through two years of follow-up.

Analysis of serum samples from participants in this study has revealed no significant postvaccination increases in yeast antibody titers as measured by radioimmunoassay. By Western blot analysis, each human serum sample shows a unique "fingerprint" spectrum of antibodies to yeast components. There may be only a few or as many as 20 different bands present. Analysis of monthly postvaccination serum samples from participants in this study has shown no change in the yeast antibody pattern for any person as compared with his prevaccination pattern. There has been no appearance of new antibodies in postvaccination sera and no significant increases in the intensity of existing antibody bands.

CONCLUSIONS

The results of this study indicate that an alum-adsorbed hepatitis B vaccine formulated using HBsAg of subtype *adw* synthesized by recombinant yeast cells is safe and immunogenic for man. Seroconversion rates and titers of anti-HBs obtained with the yeast recombinant vaccine in this study are comparable with those observed in earlier studies of healthy adults using vaccine derived from human plasma.[4,5,7]

Previous studies with hepatitis B vaccine of human plasma origin showed that protection from infection is associated with vaccine-induced anti-HBs.[10-12] Furthermore, one of these trials demonstrated that antibody formed in response to vaccine of HBsAg subtype *ad* provided cross-protection against infection caused by heterologous virus of subtype *ay*.[12] Since the antibody formed by recipients of the yeast recombinant hepatitis B vaccine is predominantly anti-*a*, this vaccine should be protective against all hepatitis B virus subtypes. The efficacy of the yeast vaccine against both homologous *ad* and heterologous *ay* virus challenge in chimpanzees has been demonstrated.[10]

Studies are under way to assess antibody persistence and to determine optimal doses of the yeast recombinant hepatitis B vaccine for both healthy and immunocompromised adults and children.

References

1. Francis DP: Selective primary health care: Strategies for control of disease in the developing world: III. Hepatitis B virus and its related diseases. *Rev Infect Dis* 1983;5:322-329.
2. Gust I: Comparison of the epidemiology of hepatitis A and B, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 129-143.
3. Immunization Practices Advisory Committee: Inactivated hepatitis B virus vaccine. *Ann Intern Med* 1982;97:379-383.
4. Hilleman MR, McAleer WJ, Buynak EB, et al: Quality and safety of human hepatitis B vaccine. *Dev Biol Stand* 1983;54:3-12.
5. Burrell CJ, Mackay P, Greenaway PJ, et al: Expression in *Escherichia coli* of hepatitis B virus DNA sequences cloned in plasmid pBR322. *Nature* 1979;279:43-47.
6. Valenzuela P, Gray P, Quiroga M, et al: Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen. *Nature* 1979;280:815-819.
7. Valenzuela P, Medina A, Rutter WJ, et al: Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298:347-350.
8. Hitzeman RA, Chen CY, Hagie FE, et al: Expression of hepatitis B virus surface antigen in yeast. *Nucleic Acids Res* 1983;11:2745-2763.
9. Miyanohara A, Toh-e A, Nozaki C, et al: Expression of hepatitis B surface antigen gene in yeast. *Proc Natl Acad Sci USA* 1983;80:1-5.
10. McAleer WJ, Buynak EB, Maigetter RZ, et al: Human hepatitis B vaccine from recombinant yeast. *Nature* 1984;307:178-180.
11. Hilleman FB, Adam E, Hoiberg D, et al: Response to hepatitis B vaccine in a young adult population, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 451-466.
12. Hoofnagle JH, Gerety RJ, Smallwood LA, et al: Subtyping of hepatitis B surface antigen and antibody by radioimmunoassay. *Gastroenterology* 1977;72:280-286.
13. Deinhardt F, Zachoval R, Fresser H, et al: Passive-active immunization against hepatitis B, in Krugman S, Sherlock S (eds): *Proceedings of the European Symposium on Hepatitis*. New York, KPR Inter/Media Corporation, 1981, pp 140-150.
14. Szmuness W, Stevens CE, Harley EJ, et al: The immune response of healthy adults to a reduced dose of hepatitis B vaccine. *J Med Virol* 1981;8:123-129.
15. Krugman S, Holley HP Jr, Davidson M, et al: Immunogenic effect of inactivated hepatitis B vaccine: Comparison of 20 microgram and 40 microgram doses. *J Med Virol* 1981;8:119-121.
16. Hilleman MR, Buynak EB, McAleer WJ, et al: Hepatitis A and hepatitis B vaccines, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 335-397.
17. Desmyter J, Colaert J, Verstraete M, et al: Hepatitis B vaccination of hemophiliacs. *Scand J Infect Dis* 1983;38(suppl):42-45.
18. Szmuness W, Stevens EC, Zang EA, et al: A controlled trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981;1:377-385.
19. Francis DP, Hadler SC, Thompson SE, et al: The prevention of hepatitis B with vaccine: Report of the Centers for Disease Control multicenter efficacy trial among homosexual men. *Ann Intern Med* 1982;97:362-366.
20. Szmuness W, Stevens CE, Harley EJ, et al: Hepatitis B vaccine in medical staff of hemodialysis units: Efficacy and subtype cross-protection. *N Engl J Med* 1982;307:1481-1486.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

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PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 792
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Recombinant Hepatitis B Vaccine Lot #934/C-J625 (10 mcg HBsAg/ml) Lot #979/C-K564 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Jules L. Dienstag, M.D. Associate Professor of Medicine Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114
SECONDARY INVESTIGATOR:	Eloise Watkins, R.N., M.P.H. Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114 Lynn F. Butterly, M.D. Clinical & Research Fellow Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114
STUDY LOCATION:	Massachusetts General Hospital Fruit Street Boston, MA 02114
DATE STUDY INITIATED:	November 10, 1983.
DATE STUDY COMPLETED:	In progress.

Study 792

STUDY POPULATION: The study population consists of 65 health care personnel of either sex (excluding pregnant women), who were negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

PROCEDURE: Eligible participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine produced by the immune affinity or the (b) (4) procedure at 0, 1, and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination and on the day of the first vaccination. Post-vaccination blood samples are obtained monthly for seven months and at 9, 12, and 24 months from subjects vaccinated with lot #934/C-J625. Post-vaccination blood samples are taken at 1, 2, 3, 6, 8, 12, and 24 months from persons injected with vaccine lot #979/C-K564. The samples are assayed for HBsAg, anti-HBc, anti-HBs, yeast antibody and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml are tested for the proportions of anti-a and anti-d activity.

STUDY RESULTS: HEALTH CARE PERSONNEL (Immune Affinity Vaccine):

10 mcg lot #934/C-J625 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
30	30	27

Study 792

RESULTS: (Cont.)

2. Serologic Results:

Serologic data are available for 26 study participants at 7/8 months. One hundred percent of the participants seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months was 1400.1 mIU/ml (for all vaccinees and for responders by either cutoff).

Among subjects with serology data at 12 months, 96% (25/26) were positive for anti-HBs (mIU/ml ≥10). The GMT at that time was 329.8 mIU/ml for all vaccinees and 436.4 mIU/ml for responders with a titer of mIU/ml ≥10..

See Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for 27 participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	78(21/27)	43(13/30)	59(16/27)
Systemic	18(5/27)	13(4/30)	11(3/27)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no alarming or serious reactions attributable to vaccine.

ALT Elevations

A 30-year old male subject was noted to have a serum ALT 3-4 times the upper limit of normal 3 months after receiving the third injection of vaccine (Lot C-J625). All sera remained negative for anti-HBc and HBsAg.

Study 792

RESULTS: (Cont.)

The subject had been taking two antimalarial drugs for two months prior to the observed ALT. The reaction was not felt to be related to the vaccine.

PUBLICATIONS:

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

Dienstag JL, Watkins E, Hinkle CA. Safety and immunogenicity of a recombinant hepatitis B vaccine (Abstract). In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:710.

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:315-17.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CJ625
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	40%	(12/30)	6.7%	(2/30)	1.0	6.6	20.0
2 MONTHS	79%	(23/29)	62%	(18/29)	16.7	35.8	61.2
3 MONTHS	93%	(26/28)	75%	(21/28)	29.8	41.0	65.3
6 MONTHS	96%	(26/27)	85%	(23/27)	50.5	64.2	93.4
7/8 MONTHS	100%	(26/26)	100%	(26/26)	1400.1	1400.1	1400.1
9 MONTHS	100%	(24/24)	96%	(23/24)	911.3	911.3	1145.9
12 MONTHS	96%	(25/26)	96%	(25/26)	329.8	436.4	436.4

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	19 (70.4%)	2 (7.4%)	4 (14.8%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	21 (77.8%)
SORENESS	15 (55.6%)	1 (3.7%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (59.3%)
TENDERNESS	3 (11.1%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (14.8%)
SLOUGH/TISSUE NECROSIS	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
NUMBNESS	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
PIGMENT CHANGE	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
SYSTEMIC	0 (0.0%)	3 (11.1%)	1 (3.7%)	2 (7.4%)	3 (11.1%)	2 (7.4%)	5 (18.5%)
WHOLE BODY/GENERAL	0 (0.0%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	3 (11.1%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)
MALAISE	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	2 (7.4%)
HEADACHE	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
RESPIRATORY	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	2 (7.4%)	2 (7.4%)	2 (7.4%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)
HEMIC AND LYMPHATIC	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
LYMPHADENOPATHY, CERVICAL	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
MYALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
PERSONS WITH COMPLAINTS	19 (70.4%)	5 (18.5%)	5 (18.5%)	3 (11.1%)	3 (11.1%)	2 (7.4%)	22 (81.5%)
PERSONS WITH NO COMPLAINTS	8 (29.6%)	22 (81.5%)	22 (81.5%)	24 (88.9%)	24 (88.9%)	25 (92.6%)	5 (18.5%)
PERSONS WITH NO DATA	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)	3 (10.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	12 (40.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	13 (43.3%)
SORENESS	10 (33.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	11 (36.7%)
TENDERNESS	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
SYSTEMIC	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	2 (6.7%)	1 (3.3%)	4 (13.3%)
WHOLE BODY/GENERAL	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	1 (3.3%)	3 (10.0%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
MALAISE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)	1 (3.3%)	2 (6.7%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (3.3%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	2 (6.7%)
PERSONS WITH COMPLAINTS	12 (40.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	2. (6.7%)	1 (3.3%)	14 (46.7%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	18 (60.0%)	29 (96.7%)	29 (96.7%)	29 (96.7%)	28 (93.3%)	29 (96.7%)	16 (53.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

06000

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (27 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	14 (51.9%)	5 (18.5%)	5 (18.5%)	1 (3.7%)	2 (7.4%)	1 (3.7%)	16 (59.3%)
PAIN	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
SORENESS	12 (44.4%)	5 (18.5%)	5 (18.5%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	13 (48.1%)
TENDERNESS	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
SWELLING	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.7%)
PAPULE(S)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	1 (3.7%)
SYSTEMIC	0 (0.0%)	3 (11.1%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	3 (11.1%)
WHOLE BODY/GENERAL	0 (0.0%)	2 (7.4%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	2 (7.4%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
HEADACHE	0 (0.0%)	1 (3.7%)	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
RESPIRATORY	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.7%)

16000

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (27 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	14 (51.9%)	8 (29.6%)	5 (18.5%)	2 (7.4%)	2 (7.4%)	1 (3.7%)	17 (63.0%)
PERSONS WITH NO COMPLAINTS	13 (48.1%)	19 (70.4%)	22 (81.5%)	25 (92.6%)	25 (92.6%)	26 (96.3%)	10 (37.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	25 (83.3%)	25 (86.2%)	25 (83.3%)	23 (85.2%)	22 (78.6%)	25 (89.3%)		17 (56.7%)
99 - 99.9	5 (16.7%)	4 (13.8%)	5 (16.7%)	4 (14.8%)	6 (21.4%)	3 (10.7%)		13 (43.3%)
TEMPERATURE TAKEN	30 (100.0%)	29 (96.7%)	30 (100.0%)	27 (90.0%)	28 (93.3%)	28 (93.3%)		30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (3.3%)	0 (0.0%)	3 (10.0%)	2 (6.7%)	2 (6.7%)		0 (0.0%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 2												NUMBER WITH MAX TEMP
	DAYS POST VACCINATION												
	0	1	2	3	4	5							
< 99	25 (83.3%)	25 (83.3%)	28 (93.3%)	25 (86.2%)	25 (83.3%)	25 (86.2%)							20 (66.7%)
99 - 99.9	5 (16.7%)	5 (16.7%)	2 (6.7%)	4 (13.8%)	5 (16.7%)	4 (13.8%)							10 (33.3%)
TEMPERATURE TAKEN	30 (100.0%)	30 (100.0%)	30 (100.0%)	29 (96.7%)	30 (100.0%)	29 (96.7%)							30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	1 (3.3%)							0 (0.0%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (27 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	22 (81.5%)	21 (80.8%)	21 (84.0%)	19 (76.0%)	20 (80.0%)	20 (80.0%)		15 (55.6%)
99 - 99.9	5 (18.5%)	5 (19.2%)	4 (16.0%)	6 (24.0%)	5 (20.0%)	5 (20.0%)		12 (44.4%)
TEMPERATURE TAKEN	27 (100.0%)	26 (96.3%)	25 (92.6%)	25 (92.6%)	25 (92.6%)	25 (92.6%)		27 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (3.7%)	2 (7.4%)	2 (7.4%)	2 (7.4%)	2 (7.4%)		0 (0.0%)

56000

RECOMBINANT YEAST HEPATITIS B VACCINE: IMMUNOGENICITY AND SAFETY. JL Dienstag, E Watkins, and CA Winkle. Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

Cumbersome to produce, expensive, and limited in supply, currently available human plasma-derived hepatitis B vaccines are likely to be replaced in the future by "genetically engineered" vaccines. Recently, a recombinant DNA vaccine was prepared in recombinant yeast Saccharomyces cerevisiae strain 2150-2-3 cells transformed with the plasmid pHBS 56-CAP347/33, containing the gene for hepatitis B surface antigen (HBsAg/ad) (Valenzuela et al. Nature 1982; 298:347-50). Purified by biochemical and biophysical methods from the yeast extract, the HBsAg particles synthesized by these yeast cells are not glycosylated but otherwise are indistinguishable from native 22 nm HBsAg particles. Treated with formalin and adsorbed to alum, the recombinant vaccine is immunogenic and protective in experimental animals. We administered three 10 µg doses of the recombinant hepatitis B vaccine (Merck Sharp & Dohme Research Laboratories) at time 0, 1, and 6 months to 60 seronegative adult health workers. The frequency and geometric mean titer (mIU/ml) of anti-HBs responses were as follows:

Month	1	2	3	4	5	6
Number	37	29	30	29	25	16
anti-HBs+	41%	83%	93%	97%	96%	94%
GMT ± SD	7 ± 2	33 ± 5	36 ± 6	66 ± 6	55 ± 6	79 ± 4

94 ± 9 (mean ±.SD) % of the anti-HBs was specific for the a determinant of HBsAg. Changes in antibodies to yeast antigens were negligible. The most frequent adverse reaction was transient soreness at the injection site, occurring after 52% of first, 37% of second, and 55% of third injections. No serious adverse effects were encountered, and neither type B nor non-B hepatitis has occurred in any vaccinee. These preliminary results demonstrate that the recombinant yeast hepatitis B vaccine is safe and that 10 µg of the recombinant vaccine is equivalent in immunogenicity to 20 µg of the plasma-derived vaccine.

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

SAT-LA.50

SAFETY AND IMMUNOGENICITY OF A RECOMBINANT HEPATITIS B VACCINE

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Currently available, licensed hepatitis B vaccines are prepared from plasma obtained from hepatitis B surface antigen (HBsAg) carriers. Cumbersome to produce, expensive, and available in limited supply, the plasma vaccine is likely to be replaced in the future by one of a number of later generation vaccines. Recently, a recombinant DNA vaccine was prepared in recombinant yeast Saccharomyces cerevisiae strain 2150-2-3 cells transformed with plasmid pHBS56-GAP347/33, which contains the gene for HBsAg (Valenzuela et al, Nature 1982; 298:347-50). The HBsAg synthesized by these yeast cells was purified from the yeast extract by physical and chemical methods and was found to be indistinguishable from native 22 nm HBsAg particles, except that the HBsAg is not glycosylated. Treated with formalin and adsorbed to alum, the recombinant vaccine is comparable in purity to the plasma vaccine and is immunogenic and protective in experimental animals.

We studied the immunogenicity and safety of recombinant hepatitis B vaccine Lot 934, formulated to contain 10 micrograms of HBsAg per 1.0 ml dose (Merck Sharp & Dohme Research Laboratories). Thirty seronegative adult health care workers received three 1.0 ml doses of the recombinant vaccine at time 0, 1 and 6 months. Adverse effects were limited to soreness at the injection site, and immunogenicity was excellent, approximating 50% at one month. Three months of follow-up will be complete by the time of the International Meeting.

Dienstag JL, Watkins E, Hinkle CA. Safety and immunogenicity of a recombinant hepatitis B vaccine (Abstract). In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984:710.

Edward M. Scolnick, Arlene A. McLean,
David J. West, Jules L. Dienstag,
Eloise Watkins, Friedrich Deinhardt and Wolfgang Jilg

23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

VIRAL HEPATITIS and LIVER DISEASE
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Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 795
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine by health care personnel and other healthy adults negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625 (10mcg HBsAg/ml) Lot #979/C-K564 (10mcg HBsAg/ml) Lot #81990 D/18066/C-L215 (10 mcg HBsAg/0.5 ml)
PRINCIPAL INVESTIGATOR:	Prof. Dr. Friedrich Deinhardt Max v. Pettenkofer Institut Pettenkoferstrasse 9a 8000 Muenchen 2 WEST GERMANY
SECONDARY INVESTIGATORS:	Dr. W. Jilg Dr. R. Zachoval Dr. G. Zoulek Dr. M. Kroner Dr. J. Abb Dr. B. Lorbeer The above secondary investigators have the same address as the principal investigator. Dr. U. Bienzle Landesinstitut fuer Tropenmedizin Ansbacherstr. 5 D-1000 Berlin 30 WEST GERMANY
STUDY LOCATIONS:	Max V. Pettenkofer Institut Pettenkoferstrasse 9a 8000 Muenchen 9a WEST GERMANY Landesinstitut fuer Tropenmedizin Ansbacherstr. 5 D-1000 Berlin 30 WEST GERMANY

Study 795

DATE INITIATED: November 21, 1983.

DATE COMPLETED: In progress.

STUDY POPULATION: The study population consists of approximately 300 health care personnel and other healthy adults of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

PROCEDURE: Eligible participants receive a 10 mcg injection intramuscular injection of vaccine produced by the immune affinity or (b) (4) procedure at 0, 1, and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination and on the day of the first vaccination. Post-vaccination blood samples are obtained monthly for seven months and at 9, 12, and 24 months from recipients of lot #934/C-J625 vaccine. Recipients of lots #979/C-K564 and #81990D/18066/C-L215 are bled at 1, 2, 3, 6, 8, 12, and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml are tested for the proportions of anti-a and anti-d activity. Samples may also be assayed for yeast antibody.

Study 795

RESULTS:

HEALTH CARE PERSONNEL (Immune Affinity Vaccine):

10 mcg Lot #934/C-J625 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
30	30	30

2. Serologic Results:

Serologic data are available for 29 participants at 7/8 months. One hundred percent (29/29) of the subjects seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months was 1735.7 mIU/ml (all vaccinees and responders by either cutoff).

Among participants with serology data available at 12 months, 93% (25/27) were positive for anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 271.5 mIU/ml, while it was 419.2 mIU/ml for subjects with titers of mIU/ml ≥10.

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for at least 23 participants after each injection. The overall frequencies of complaints are presented below:

Type of Complaint	Frequency in % by Injection No.		
	1	2	3
Injection Site	21(6/29)	28(7/25)	26(6/23)
Systemic	21(6/29)	8(2/25)	9(2/23)

Study 795

RESULTS (CONT.):

Refer to Table 2 for listings of specific complaints after each injection. Maximum temperature data are presented in Table 3.

There were no serious or alarming reactions attributable to vaccine.

PUBLICATIONS:

Deinhardt F, Jilg W, Zoulek G, Lorbeer B, Wilske B. Clinical evaluation of a recombinant hepatitis B vaccine. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:699.

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Dienhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2:1174-5.

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Dienhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984:315-17.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CJ625
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	28%	(8/29)	10%	(3/29)	0.8	8.6	25.0
2 MONTHS	72%	(21/29)	59%	(17/29)	10.8	37.5	55.7
3 MONTHS	96%	(27/28)	71%	(20/28)	22.8	26.8	50.5
6 MONTHS	97%	(28/29)	86%	(25/29)	48.5	58.2	75.7
7/8 MONTHS	100%	(29/29)	100%	(29/29)	1735.7	1735.7	1735.7
9 MONTHS	100%	(22/22)	95%	(21/22)	990.8	990.8	1263.5
12 MONTHS	96%	(26/27)	93%	(25/27)	271.5	352.7	419.2

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1 DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	5 (17.2%)	2 (6.9%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		6 (20.7%)
PAIN	4 (13.8%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (13.8%)
TENDERNESS	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.4%)
ERYTHEMA (REDNESS)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.4%)
ECCHYMOSIS	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.4%)
SYSTEMIC	3 (10.3%)	2 (6.9%)	4 (13.8%)	2 (6.9%)	1 (3.4%)	1 (3.4%)		6 (20.7%)
WHOLE BODY/GENERAL	1 (3.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.9%)
FATIGUE/WEAKNESS	1 (3.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.9%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.4%)
HERPES LABIALIS, RECURRENT	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.4%)
RESPIRATORY	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)		1 (3.4%)
RHINITIS	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	0 (0.0%)	0 (0.0%)		1 (3.4%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
NAUSEA	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
ORGANS OF SPECIAL SENSE	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)
CONJUNCTIVITIS	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)	1 (3.4%)
PERSONS WITH COMPLAINTS	8 (27.6%)	3 (10.3%)	5 (17.2%)	2 (6.9%)	1 (3.4%)	1 (3.4%)	11 (37.9%)
PERSONS WITH NO COMPLAINTS	21 (72.4%)	26 (89.7%)	24 (82.8%)	27 (93.1%)	28 (96.6%)	28 (96.6%)	18 (62.1%)
PERSONS WITH NO DATA	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	4 (16.0%)	3 (12.0%)	3 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (28.0%)
PAIN	4 (16.0%)	2 (8.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (20.0%)
SWELLING	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
PARESTHESIA	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
SYSTEMIC	1 (4.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.0%)
WHOLE BODY/GENERAL	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
FATIGUE/WEAKNESS	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
RESPIRATORY	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
RHINITIS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
LARYNGITIS	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)
COUGH	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
DIGESTIVE SYSTEM	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
NAUSEA	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
PERSONS WITH COMPLAINTS	5 (20.0%)	4 (16.0%)	3 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		8 (32.0%)
PERSONS WITH NO COMPLAINTS	20 (80.0%)	21 (84.0%)	22 (88.0%)	25 (100.0%)	25 (100.0%)	25 (100.0%)		17 (68.0%)
PERSONS WITH NO DATA	5 (16.7%)	5 (16.7%)	5 (16.7%)	5 (16.7%)	5 (16.7%)	5 (16.7%)		5 (16.7%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	5 (21.7%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		6 (26.1%)
PAIN	4 (17.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (17.4%)
TENDERNESS	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
WARMTH	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
SWELLING	1 (4.3%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (8.7%)
PRURITIS (ITCHING)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
SYSTEMIC	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		2 (8.7%)
WHOLE BODY/GENERAL	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
FATIGUE/WEAKNESS	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.3%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		1 (4.3%)
VIRAL INFECTION, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		1 (4.3%)
PERSONS WITH COMPLAINTS	6 (26.1%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.5%)		7 (30.4%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH NO COMPLAINTS	17 (73.9%)	22 (95.7%)	23 (100.0%)	23 (100.0%)	23 (100.0%)	21 (95.5%)		16 (69.6%)
PERSONS WITH NO DATA	3 (11.5%)	3 (11.5%)	3 (11.5%)	3 (11.5%)	3 (11.5%)	3 (12.0%)		3 (11.5%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	18 (78.3%)	21 (87.5%)	20 (80.0%)	21 (84.0%)	20 (87.0%)	20 (83.3%)		16 (64.0%)
99 - 99.9	5 (21.7%)	3 (12.5%)	5 (20.0%)	4 (16.0%)	3 (13.0%)	4 (16.7%)		9 (36.0%)
TEMPERATURE TAKEN	23 (76.7%)	24 (80.0%)	25 (83.3%)	25 (83.3%)	23 (76.7%)	24 (80.0%)		25 (83.3%)
TEMPERATURE NOT TAKEN	7 (23.3%)	6 (20.0%)	5 (16.7%)	5 (16.7%)	7 (23.3%)	6 (20.0%)		5 (16.7%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	11 (64.7%)	12 (66.7%)	13 (76.5%)	11 (61.1%)	11 (64.7%)	12 (66.7%)			10 (55.6%)
99 - 99.9	6 (35.3%)	6 (33.3%)	4 (23.5%)	7 (38.9%)	6 (35.3%)	6 (33.3%)			8 (44.4%)
TEMPERATURE TAKEN	17 (56.7%)	18 (60.0%)	17 (56.7%)	18 (60.0%)	17 (56.7%)	18 (60.0%)			18 (60.0%)
TEMPERATURE NOT TAKEN	13 (43.3%)	12 (40.0%)	13 (43.3%)	12 (40.0%)	13 (43.3%)	12 (40.0%)			12 (40.0%)

Table 3 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CJ625
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 3								DAYS POST VACCINATION	NUMBER WITH MAX TEMP
	0	1	2	3	4	5				
< 99	10 (71.4%)	11 (78.6%)	12 (85.7%)	13 (92.9%)	12 (85.7%)	10 (76.9%)				10 (66.7%)
99 - 99.9	4 (28.6%)	3 (21.4%)	2 (14.3%)	1 (7.1%)	2 (14.3%)	2 (15.4%)				4 (26.7%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)				1 (6.7%)
TEMPERATURE TAKEN	14 (46.7%)	14 (46.7%)	14 (46.7%)	14 (46.7%)	14 (46.7%)	13 (43.3%)				15 (50.0%)
TEMPERATURE NOT TAKEN	16 (53.3%)	16 (53.3%)	16 (53.3%)	16 (53.3%)	16 (53.3%)	17 (56.7%)				15 (50.0%)

SAT-LA.10

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

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Thirty healthy, young volunteers free of any HBV markers were vaccinated with a recombinant hepatitis B vaccine prepared by Merck, Sharp & Dohme, West Point, PA. Ten µg HBsAg were administered intramuscularly at time 0, and one month later. Seroconversion rates and geometric mean concentrations after 1, 2 and 3 months were compared with an age- and sex-matched control group vaccinated with 20 µg of plasma derived vaccine (Merck Sharp & Dohme) (Table 1).

Table 1: Comparison of immune response after recombinant vaccine and plasma derived vaccine.

month	seroconversion %		anti-HBs (geom. mean) mIU	
	recombinant vaccine	plasma vaccine	recombinant vaccine	plasma vaccine
1	27	44	8.6	15.2
2	70	95	37.8	52.9
3	97	95	27.4	164.4

In the recombinant vaccine group, 38% of the total anti-HBs at month 3 was directed against the determinant a of HBsAg, compared to 30% in the control group. No increase in antibody titers against candida albicans was found in recipients of the recombinant vaccine 4 weeks after the second injection as compared to prevaccination levels. No serious side effects were observed in any of the vaccinated individuals.

Deinhardt F, Jilg W, Zoulek G, Lorbeer B, Wilske B. Clinical evaluation of a recombinant hepatitis B vaccine. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Straton, 1984:699.

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

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Summary Recombinant hepatitis B vaccine prepared from antigen expressed in yeast was given to 30 healthy young volunteers. Seroconversion rates and anti-HBs levels were compared with those in a control group matched for age and sex who had received plasma-derived hepatitis B vaccine. 4 weeks after the third immunisation results were similar in the two groups. In the recombinant vaccine group the immune response developed more slowly during the early phase and seroconversion rates and mean anti-HBs levels were slightly lower in males; this probably reflects use of a lower dose of recombinant vaccine (10 μg compared with 20 μg of the plasma vaccine). Side-effects were slight and antibody titres against *Candida albicans* were not increased in recipients of the recombinant vaccine.

Introduction

CURRENT hepatitis B vaccines are effective and safe.[1] However, because they are prepared from plasma of human hepatitis B virus carriers, supply is restricted by the amount of plasma available and by the cost of purifying the hepatitis B surface antigen (HBsAg) to render it free from hepatitis B virus and other possible infectious agents. Thus, to meet the worldwide need for hepatitis B vaccine, new means of preparation are required. Lately, vectors carrying the DNA sequence for HBsAg were prepared[2] and the antigen was expressed in the yeast *Saccharomyces cerevisiae*.[3] Yeast cells assemble the HBsAg polypeptides into particles similar to the 22 nm particles found in human plasma; yeast HBsAg, however, unlike human HBsAg is not glycosylated. A vaccine developed from yeast HBsAg stimulated antibody production in mice, grivet monkeys, and chimpanzees; and when vaccinated chimpanzees were challenged with human hepatitis B virus of different subtypes, they were completely protected.[4] We now report the immunisation of 30 healthy young volunteers with the first hepatitis B vaccine produced by recombinant DNA technology.

Subjects, Materials, and Methods

Subjects

30 healthy medical students and laboratory workers were studied (17 female, 13 male; mean age 25±3 yr, range 21–34). Subjects in the control group had been immunised with plasma-derived vaccine in an earlier study;[5] they were matched by age and sex to the study group (table I). Before vaccination, all subjects were negative for HBsAg, anti-HBs, and antibodies against hepatitis B core antigen (anti-HBc), and their aminotransferase levels were normal (alanine and aspartate aminotransferases ≤17 and ≤19 IU/l, respectively).

TABLE I—SEX AND AGE DISTRIBUTION OF THE TWO VACCINATION GROUPS*

	Total		Female		Male	
	No	Age (yr)	No	Age (yr)	No	Age (yr)
Recombinant vaccine	30	26·0±3·1 (21–34)	17	26·0±3·5 (21–34)	13	25·3±2·6 (23–32)
Plasma-derived vaccine	41	25·0±2·7 (21–32)	23	24·7±3·0 (21–32)	18	25·4±2·3 (23–32)

*Means and standard deviations (range).

Vaccines

The recombinant hepatitis B vaccine was prepared by Merck Sharp & Dohme research laboratories (lot 934/C-J 625). It consists of purified HBsAg, subtype *adw*, produced in recombinant *S cerevisiae* and absorbed on aluminium hydroxide. 1 ml of vaccine contained 10 μg of HBsAg. Plasma vaccine was also subtype *adw* (lot 773/001-2/ C-F 732-2 Merck Sharp & Dohme). Subjects in the study group received 10 μg of recombinant vaccine intramuscularly at 0, 1, and 6 months; subjects in the control group received 20 μg of plasma-derived vaccine at the same intervals. (Since the recombinant vaccine was treated with formalin only, and not with pepsin and urea, it was initially thought to be more immunogenic than the plasma vaccine.) Blood samples were taken on the day of the first vaccination and then monthly. Subjects were asked to keep daily records of body temperature and side-effects for 5 days after each injection.

Serology

HBsAg, anti-HBs, and anti-HBc were tested by radioimmunoassay with commercially available kits ('AUSRIA II', 'AUSAB', 'CORAB', Abbott Laboratories). Anti-HBs concentrations in IU/l were calculated by the method of Hollinger *et al*,[6] the first WHO reference preparation 1977 being used in a dilution of 1:400.[7] Because *S cerevisiae* and *C albicans* have common antigenic determinants,[8] antibodies against *C albicans* were determined by passive haemagglutination in 26 subjects on day 0 and 4 weeks after the second and third injections of recombinant vaccine. Sera were examined for antibodies against the determinant *a* of HBsAg as previously described.[9]

Results

Seroconversion rates and mean anti-HBs levels during the course of immunisation are shown in table II. The immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels. These differences became non-significant after the booster dose at month 6 when 29 out of 30 subjects (97%) were anti-HBs positive (control, 41 out of 41) with a geometric mean anti-HBs level of 2135 IU/l (control, 4299 IU/l). All anti-HBs-positive individuals in the recombinant vaccine group had anti-HBs values above 10 IU/l; 2 (6·7%) were low responders (anti-HBs below 100 IU/l), 3 (10%) were intermediate responders (anti-HBs 101–1000 IU/l), and 22 (73·3%) were normal to high responders (anti-HBs greater than 1000 IU/l). Similar values

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2:1174-5.

TABLE II—IMMUNE RESPONSES AFTER VACCINATION

Month	Seroconversion (%)		Anti-HBs (IU/l)*		p†
	Recombinant vaccine (n = 30)	Plasma-derived vaccine (n = 41)	Recombinant vaccine	Plasma-derived vaccine	
1	0 (27)	10 (44)	9	15	<0·05
2	21 (70)	39 (95)	38	93	<0·05
3	28 (93)	39 (95)	89	164	<0·05
4	28 (93)	39 (95)	63	226	<0·05
5	28 (93)	39 (95)	79	273	<0·05
6	28 (93)	39 (95)	68	363	<0·05
7	29 (97)	41 (100)	2135	4200	>0·05

*Anti-HBs is given as the geometric mean in responders only.
†Wilcoxon's rank-sum test.

TABLE III—IMMUNE RESPONSES IN MALES AND FEMALES (AFTER THREE INOCULATIONS)

—	Recombinant vaccine	Plasma-derived vaccine	p*
Males:			
Seroconversion (%)†	12/13 (92)	18/18 (100)	
Anti-HBs (IU/l)‡	911	3894	<0·05
Females:			
Seroconversion (%)†	17/17 (100)	23/23 (100)	
Anti-HBs (IU/l)‡	3282	4640	>0·05

*Wilcoxon's rank-sum test.
†Number of anti-HBs-positive subjects divided by the total number.
‡Geometric mean.

were obtained in the control group. Although the immune responses to the two vaccines were similar after the full course of immunisation, responses of male and female subjects differed. In both groups all the women seroconverted and the geometric mean anti-HBs levels did not differ significantly (3282 IU/l vs 4640 IU/l). However, in males receiving recombinant vaccine the seroconversion rate was 92% vs 100%, and the geometric mean anti-HBs was 911 vs 3894 IU/l (table III).

Preliminary tests indicate that recombinant vaccine, like the plasma-derived vaccine, induces antibodies against both the *a* and the *d* components of HBs antigen. After month 3, about 38% of the total anti-HBs was directed against determinant *a*.

No important side-effects were observed after immunisation with the recombinant vaccine. Minor local symptoms such as transient pain, itching, burning, and slight swelling at the injection site were reported after 24 of the 90 injections. On no occasion did body temperature rise above 37·9°C.

Of 26 subjects tested, all had antibodies against *C albicans* on day 0 (titres from 1:80 to 1:320) and titres did not increase after immunisation.

Discussion

Three doses of 10 μg recombinant hepatitis B vaccine gave seroconversion rates and geometric mean anti-HBs levels similar to those induced by three doses of 20 μg plasma-derived vaccine. The results were also comparable with those obtained in large trials of conventional vaccines.[10,11]

The immune response to the recombinant vaccine, however, was less strong during the early phase (1–6 months) in all subjects, and in males mean anti-HBs values were lower in the recombinant group even after the complete course of immunisation. These results are comparable with findings in subjects immunised with a smaller dose (5 μg) of conventional vaccine (Jilg W, Zachoval R, Schmidt M, Deinhardt F, unpublished), and may reflect the use of smaller amounts of antigen. Antigen content of both recombinant vaccine and plasma-derived vaccine is determined as HBsAg protein. The vaccines are produced and treated differently, however;[4,12] therefore similar protein content does not necessarily mean similar immunogenicity. The yeast and plasma derived HBsAg differed in reactivity in radioimmunoassay tests; the reactivity of the HBsAg produced in yeast was only 20–50% of the reactivity of plasma-derived HBsAg.[4] Thus, weight-for-weight the immunogenicity of the recombinant vaccine seems to be less than that of the plasma-derived vaccine. Another explanation for the lower immune response may be that 10 μg of recombinant vaccine was given per single dose compared with 20 μg of plasma-derived vaccine. A higher dose (20 or 40 μg) of the recombinant vaccine would probably give the same results as the plasma-derived vaccine.

Despite the slightly lower immunity achieved with the recombinant vaccine, protection will probably be as good as with the conventional vaccine, in that all 29 subjects with detectable anti-HBs had values above the protection level of 10 IU/l.[13] In 73%, anti-HBs levels after the third vaccination were more than 1000 IU/l; this has been shown to guarantee persistence of anti-HBs above the protective limit for at least 3 years.[14] In addition, all subjects who seroconverted had antibodies against the common determinant *a* of HBsAg, indicating cross-protection against infections with other subtypes of HBsAg. Side-effects after the recombinant vaccine were negligible and did not differ from those observed after plasma-derived vaccine. The absence of a rise in antibodies against *C albicans* indicates that no cross-reacting yeast antigens were present in the vaccine.

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REFERENCES

1. Deinhardt F. Control of hepatitis A and B with vaccines. *Ann Clin Res* 1982; 14: 230–44.
2. Valenzuela P, Gray P, Quiroga M, Zaldivar J, Goodman HM, Rutter WJ. Nucleotide sequence of the gene coding for the major protein of hepatitis B surface antigen. *Nature* 1979; 280: 815–19.
3. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298: 347–50.
4. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984; 307: 178–80.
5. Zachoval R, Jilg W, Lorbeer B, Schmidt M, Deinhardt F. Passive-active immunization against hepatitis B. *J Infect Dis* 1984; 150: 112–17.
6. Hollinger FB, Adler E, Hadsell D, Melnick JL. Response to hepatitis B vaccine in a young adult population. In: Szmuness W, Alter HJ, Maynard JE, eds. Viral hepatitis: 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 491–96.
7. World Health Organization. *WHO Tech Rep Ser* no 630; 1979: 39
8. Tsuchiya T, Fukazawa Y, Kuroshima S. Serologic classification of the genus *Candida*. In: Tokyo Research Committee of Candidiasis. Studies of candidiasis in Japan. Tokyo: Educational Ministry of Japan, 1981: 30–36.
9. Jilg W, Deinhardt C, Deinhardt F, Konstantinou-Koryopoulou AJ, Papavangelou GJ, Mandalenakis EK, Crowley LB. Hepatitis B surface antigen (HBsAg) subtype-specific antibodies in persons vaccinated against hepatitis B. *J Med Virol* 1984; 13: 171–78.
10. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981; 1: 377–85.
11. Crumpton J, Jungson P, Courouce AM, et al. Randomized placebo-controlled trial of hepatitis B surface antigen vaccine in French hemodialysis units. *J Medical staff Lancet* 1981; 1: 459–60.
12. Hilleman MR, Buynak EB, McAleer WJ, McLean AA. Human hepatitis B vaccine. In: Krugman S, Gershon S, eds. Proceedings of the European Symposium on Hepatitis B. Rahway: Merck Sharp & Dohme International, 1981: 179–90.
13. Goudeau A, Courouce P, Barin F, et al. Prevention of hepatitis B by active and passive immunization. In: Szmuness W, Alter HJ, Maynard JE, eds. Viral hepatitis 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 589–95.
14. Jilg W, Schmidt M, Zachoval R, Deinhardt F. Persistenz von Antikörpern gegen Hepatitis B-Oberflächenantigen nach Impfung gegen Hepatitis B. *Dtsch Med Wochenschr* (in press).

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23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

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Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

(b) (4)

[redacted]

TEST FOR
NONINFECTIVITY

TEST FOR NONINFECTIVITY
STUDY 839

In clinical trials of the hepatitis B vaccine derived from infected human plasma, one study was specifically designated as a safety study to ascertain that hepatitis B was not transmitted via the purified vaccine. The yeast recombinant hepatitis B vaccine is not made from plasma, and intact hepatitis B virus should not be present at any stage of its formulation. However, in early discussions with the OoBRR, it was suggested that one study be conducted as a true human "safety" test.

In Study 839, a single 10 mcg dose of vaccine was administered to five healthy adult volunteers. The subjects were followed serologically for six months. During that time period, none of the participants developed any marker of hepatitis B infection (HBsAg, anti-HBc, or elevated ALT). One subject developed a low titer (6.0 mIU/ml) of anti-HBs four months after receiving the single 10 mcg injection of vaccine. There were no reports of serious or alarming adverse experiences.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 839.
PURPOSE:	To assess the lack of infectivity of the vaccine among healthy adults who are negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #972/C-K444 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Robert Bishop, M.D. Health Services WP 38-4 Merck Sharp and Dohme West Point, PA 19486
SECONDARY INVESTIGATOR:	E. P. Avancena, M.D. Health Services WP 38-4 Merck Sharp and Dohme West Point, PA 19486
STUDY LOCATION:	Merck Sharp and Dohme West Point, PA 19486
DATE INITIATED:	July 31, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 5 healthy adults of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level, have not previously received any hepatitis B vaccine and have no known risk factors for hepatitis B.
PROCEDURE:	Participants receive a single 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine. Vaccine recipients are asked to record their temperature daily for 5 days after vaccination and also to record any local or systemic complaints that they may have during this period. Unexpected or serious adverse reactions will be reported immediately to the study physician.

Study 839

PROCEDURE: (CONT.)

A blood specimen (10-15 ml) is obtained from each participant 1-2 weeks before vaccination. Post-vaccination blood samples are taken at 2, 4, and 6 months. All samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT at MSDRL. Samples may also be assayed for yeast antibody.

RESULTS:

HEALTHY ADULTS:

10 mcg Lot #972/C-K444 at time zero.

1. Number Vaccinated: 5

2. Serologic Results:

One subject developed a low titer (6.0 mIU/ml) of anti-HBs 4 months after receiving the vaccine. Refer to Table 1 for anti-HBs responses for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for all 5 participants. The overall frequencies of complaints are presented below.

Type	Frequency in %
Injection Site	20 (1/5)
Systemic	40 (2/5)

Refer to Table 2 for listings of specific clinical complaints. Maximum temperature data are provided in Table 3.

There were no serious or alarming adverse reactions attributable to vaccination.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0839
POPULATION : HEALTHY ADULTS
DOSE : 10 MCG
LOT : CK444
REGIMEN : Day 0
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
2 MONTHS	0%	(0/5)	0%	(0/5)	0.3		
4 MONTHS	25%	(1/4)	0%	(0/4)	1.2	6.0	
6 MONTHS	25%	(1/4)	0%	(0/4)	0.9	6.2	

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0839
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (5 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
SORENESS	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
SYSTEMIC	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
WHOLE BODY/GENERAL	2 (40.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
SWEATING	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
FATIGUE/WEAKNESS	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
INTEGUMENTARY SYSTEM	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
URTICARIA/HIVES	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
PRURITIS/ITCHING	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
NERVOUS SYSTEM	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
VERTIGO/DIZZINESS	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)
PERSONS WITH COMPLAINTS	3 (60.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (60.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0839
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (5 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO COMPLAINTS	2 (40.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	2 (40.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0839
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (5 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
< 99	4 (80.0%)	5 (100.0%)	4 (80.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)		3 (60.0%)
99 - 99.9	0 (0.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (20.0%)
101 - 101.9	1 (20.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (20.0%)
TEMPERATURE TAKEN	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)	5 (100.0%)		5 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

IMMUNOGENICITY/
SAFETY

HEALTH CARE PERSONNEL
/HEALTHY ADULTS

SUMMARY - HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS

Persons employed in a variety of health care occupations are known to be at above-average risk for hepatitis B infection and therefore constitute a sizeable candidate population for vaccination with hepatitis B vaccine. Initially seronegative health care personnel and other healthy adults were selected as a major group in which to evaluate the immunogenicity and reactogenicity of the yeast recombinant hepatitis B vaccine. To date, 2414 individuals in 36 studies have received at least one injection of vaccine, and 1442 of these have completed a 3 dose regimen of vaccination. Anti-HBs titers following the third injection have been measured in 1048 vaccinees, while clinical reports are available for 990 of these individuals. Titers currently available in units of mIU/ml for 829 subjects show that the vaccine is highly immunogenic, with protective levels of anti-HBs (mIU/ml $\geq$10) developed by 96%. The vaccine has been well tolerated with approximately one-fourth of the vaccinees reporting minor transient complaints such as injection site soreness, fatigue, and headache.

IMMUNOGENICITY

Dose:

Table 1 summarizes the antibody responses of 1123 health care personnel and other healthy adults (excludes data from study #880 which compares consistency lots), who received injections containing 2.5, 5, 10, or 20 mcg doses of yeast recombinant hepatitis B vaccine at 0, 1, and 6 months, and for whom post-vaccination test data are currently available in units of mIU/ml. Anti-HBs responses following the third injection of vaccine are shown for 736 subjects, while responses after only one or two injections of vaccine are included for an additional 387 subjects. At 3 months (2 months following the second injection of vaccine), 80-89% of the vaccine recipients had anti-HBs based on a cutoff of S/N $\geq$2.1. By 7/8 months (1-2 months after the third injection of vaccine), the proportion of vaccinees with antibody rose to 97-100%. Slightly lower seroconversion rates were observed using a cutoff of mIU/ml $\geq$10. With this cutoff, 57-75% of the vaccine recipients had anti-HBs by 3 months, while 89-97% were antibody positive by 7-8 months.

The effect of log dose level on seroconversion for anti-HBs was analyzed statistically. The analysis was done using only data from four studies that each involved more than one dose level, although seroconversion rates in these studies (Tables 2, 3) were very similar to those observed across all studies (Table 1). Over the four studies, seroconversion rate was found to increase significantly with log dose level at 1, 3, and 6 months based on a cutoff of S/N $\geq$2.1 ($p < 0.001$ to 0.002). There was no significant trend at 7/8 months, with 95% or more of the vaccinees positive for antibody regardless of dose level. (See Appendix 1 for a description of statistical methods used.)

Using data from three of the four studies (titers not available in units of mIU/ml for study #794) seroconversion rates based on a cutoff of mIU/ml ≥10 showed a significant upward trend with increasing log dose level at 3 and 6 months ($p < 0.001$). Again, at 7/8 months there was no significant trend, with 89% or more of the vaccinees having titers of mIU/ml ≥10 at all dose levels.

A regression of log anti-HBs titers on log dose level, sex, and age, for all vaccinees with mIU/ml data (study #859 excluded because of missing sex and age data), showed all three factors to be statistically significant at each time point with the exception of log dose level at 1 month ($p = 0.001$ for sex at 1 month and $p < 0.001$ for all else). Larger doses produced higher titers.

Overall geometric mean titers (GMTs) of anti-HBs by dose level are shown in Table 1. At 7/8 months, the GMTs for responders with a titer of S/N ≥2.1 were 255.8 mIU/ml (2.5 mcg dose), 245.1 mIU/ml (5 mcg dose), 1264.3 mIU/ml (10 mcg dose), and 539.0 mIU/ml (20 mcg dose). Among responders with a titer of mIU/ml ≥10, the GMTs at 7/8 months were 295.3 mIU/ml (2.5 mcg dose), 348.7 mIU/ml (5 mcg dose), 1321.9 mIU/ml (10 mcg dose) and 1021.5 mIU/ml (20 mcg dose).

Sex:

Table 4 shows antibody responses of health care personnel and other healthy adults by sex (does not include data from the consistency lots study, #880) who received 2.5, 5, or 10 mcg doses of yeast recombinant hepatitis B vaccine, and for whom test data are currently available in units of mIU/ml. Responses for the 20 mcg dose are not shown as recipients of this dose were exclusively male. Seroconversion rates tended to be somewhat lower among males as compared to females at early post-vaccination times. By 7/8 months, 97-100% of the vaccinees had anti-HBs (S/N ≥2.1) regardless of sex, while 87-100% had titers of mIU/ml ≥10.

As noted in the earlier discussion on dose level, multiple regression analysis showed that log anti-HBs titer was also significantly related to sex at all time points ($p = 0.001$ for sex at 1 month and $p < 0.001$ at other times). Females tended to have higher titers than males when adjusted for age and dose level.

Age:

Table 5 shows antibody responses of health care personnel and other healthy adults ≥40 years of age and <40 years of age, who received 10 mcg doses of the yeast recombinant hepatitis B vaccine, and for whom test data are available in units of mIU/ml (excludes data from study #880 which compares consistency lots). The summary of antibody response by age is limited to the 10 mcg dose of vaccine since few adults ≥40 years have yet received other dosages. In general, older individuals responded less rapidly and developed lower anti-HBs titers than younger subjects. However, by 7/8 months, 91% of even the older vaccinees had titers of mIU/ml ≥10.

first and second injection of vaccine as scheduled, while the third injection was not administered until 11 months after the first injection. The individual does have a history of allergies.

2. A 26-year old female became aware that she was pregnant after receiving one injection of vaccine. The vaccine was administered approximately one month after conception. She experienced a spontaneous abortion at 18 weeks after fetal death in utero. No microscopic examination was completed on the fetus. The subject previously delivered two healthy infants without complication of pregnancy. She had no known allergies.

3. A 37 year-old female noted facial warmth and flushing 14 hours after receiving her first injection of vaccine. Within the next 3 hours she developed facial urticaria. She was treated with cold packs. The symptoms subsided and she recovered in 12 hours. The subject was treated with Benedryl prior to the second and third injection, and had no post-vaccination reactions.

4. A 23 year-old female developed hives within 24 hours of receiving the first injection of vaccine. The hives were described as one large 3-4 inch lesion, pruritic, with several satellite lesions on the back, and several small lesions on the legs. All symptoms resolved by day 4 post vaccination. Within 24 hours of receiving the second injection of vaccine, the subject developed small hives on the back, arms. and left hand. All symptoms resolved by day 4 post vaccination. The individual received her third injection of vaccine with no evidence of hives. In the past, the subject developed hives during administration of contrast dye (for CAT scan). There is no other allergic history.

5. A 40 year-old female developed a few ecchymotic flat lesions on the lateral aspect of her breasts, bilaterally, 4 days after the first injection of vaccine. Over the following 2 days the lesions increased. Vomiting occurred on the third day. All symptoms disappeared over the next 36 hours, and the subject has remained well. There was no fever, and WBC, Hgb, platelets, and coagulation profile were normal. The patient has no history of allergies to exogenous substances. No further vaccine was administered to this patient.

Mild transient injection site reactions and systemic complaints were reported following injection of vaccine at frequencies of 17% and 15%, respectively (Table 8). The frequency of complaints after the first injection was higher than after the second or third injections. Table 9 lists specific injection site reactions that occurred with a frequency of $\geq$0.1%, while Tables 10 and 11 show specific systemic complaints that occurred at frequencies of $\geq$0.1%. The most frequent injection site reactions were soreness (8%), pain (5%), tenderness (3%) and pruritis (1%). Systemic complaints that occurred at a frequency of $\geq$1% include fatigue/weakness (4%), headache (4%), nausea (2%), pharyngitis (1%), malaise (1%), diarrhea (1%) and upper respiratory infection (not otherwise specified) (1%) (Table 11). A temperature of $\geq$100°F (oral) was reported following 3% of all injections (Table 12).

A statistical analysis of seroconversion rates as a function of age was done for recipients of 10 mcg doses of vaccine using only data from studies that involved subjects <40 years of age and ≥40 years of age. These data are summarized in Table 6. Based on a cutoff of S/N ≥2.1, the seroconversion rate over studies was significantly higher in the <40 year age group than in the ≥40 year age group at 1 ($p < 0.001$), 3 ($p = 0.021$), and 6 months ($p = 0.032$). Similar differences were seen when the seroconversion rates were based on a cutoff of mIU/ml ≥10, with significance achieved at 1 ($p = 0.021$), 3 ($p = 0.022$), and 6 months ($p = 0.047$).

The multiple regression analysis mentioned previously showed that log anti-HBs titer was also significantly related to age at each time point ($p < 0.001$). The level of response was shown to decrease with age.

Persistence of Antibody:

In most of the clinical studies now in progress, antibody titers will be monitored for a period of 2 years following the initial injection of vaccine. At present, limited data are available through 12 months of follow-up. Table 1 summarizes available data at this time point for 415 health care personnel and other healthy adults whose titers have been measured in units of mIU/ml. The GMTs of responders with titers of mIU/ml ≥10 at 7/8 months declined 2 to 4-fold by 12 months. Similar declines in antibody titer over this time interval were characteristic of the subset of vaccinees consisting of all those with serologic data at both 7/8 and 12 months. Table 7 shows the distribution of titers at 7/8 months and 12 months, respectively, for health care personnel and other healthy adults who received 10 mcg doses of vaccine. Minimal evidence of antibody (S/N ≥2.1) was present in 98% of the vaccinees at 7/8 months and 95% at 12 months, while fully protective levels (mIU/ml ≥10) were present in 97% and 90% at 7/8 and 12 months, respectively. Higher titers (mIU/ml ≥100) were characteristic of 89% of the vaccinees at 7/8 months and of 65% at 12 months, while 58% and 25% of the vaccine recipients were in the highest titer category (mIU/ml ≥1000) at 7/8 and 12 months, respectively.

SAFETY

In general, the yeast recombinant hepatitis B vaccine has been well tolerated. There have been no reports of serious or alarming reactions attributable to vaccination. Tables 8-12 summarize clinical complaints and elevated temperatures reported by health care personnel and other healthy adults following injection with the yeast recombinant hepatitis B vaccine (exclude data from study #880 which compares consistency lots).

Five subjects have had reactions that possibly were related to vaccination. These reactions are summarized below:

1. A forty-one year old female developed headache, swollen face and rash within several hours after receiving the third injection of vaccine. The headache and swollen face resolved in one day, while the rash faded over 4 days. No clinical complaints were reported by this individual following the first and second injections of vaccine. She received her

COMPARISON OF CONSISTENCY LOTS

Five lots of the yeast recombinant hepatitis B vaccine were manufactured in a production setting to demonstrate consistency. Study 880 was conducted to evaluate the safety and immunogenicity of these consistency lots in seronegative health care personnel. Subjects in this study receive 10 mcg doses of vaccine from one of the consistency lots at 0, 1, and 6 months. Data from this study were excluded from the preceding across studies summary for health care personnel and other healthy adults.

A total of 233 persons have received one or more doses of vaccine in Study 880. Postvaccination clinical data are currently available for all subjects, while serologic data have been obtained for 227 of the vaccinees. These include data on clinical complaints for 99 subjects and anti-HBs response data for 139 subjects who have received all three injections of vaccine.

Table 13 shows the age and sex characteristics by lot of the subjects vaccinated in Study 880. Recipients of each lot were fairly similar except for a preponderance of males among recipients of lot C-L220.

Table 14 summarizes the antibody responses of persons who received vaccine from the 5 consistency lots. At 3 months (2 months following the second injection of vaccine), 84% (range 66-97%) of the vaccine recipients had at least minimal levels of anti-HBs (S/N $\geq$2.1), while 72% (range 59-83%) had protective levels of antibody (mIU/ml $\geq$10). By 7/8 months (1-2 months after the third injection of vaccine), 98% (range 92-100%) of the vaccinees had antibody titers of S/N $\geq$2.1, and 96% (range 91-100%) had titers of mIU/ml $\geq$10. Geometric mean titers of antibody by 7/8 months were 627.6 mIU/ml (range 332.6-1187.6 mIU/ml) for all vaccinees, 742.9 mIU/ml (range 476.4-1187.6 mIU/ml) for responders with a titer of S/N $\geq$2.1, and 830.8 mIU/ml (range 593.6-1187.6 mIU/ml) for responders with a titer of mIU/ml $\geq$10.

Clinical complaints occurring during a five-day period following injections with vaccine from the consistency lots are summarized in Table 15. There were no serious adverse experiences attributed to vaccination. All reactions were mild and transient. Local (injection site) reactions were reported following 5-12% of injections with the various consistency lots. The frequency of systemic complaints following injection from these lots ranged from 3-9%. Ten to 15% of the injections from each lot of vaccine involved some complaint. A temperature of $\geq$100°F (oral) was reported following 0-3% of injections.

This study and a second of similar design continue in progress.

A statistical analysis is now being done to evaluate differences between the 5 consistency lots of vaccine with respect to seroconversion rates and geometric mean titers of anti-HBs as well as the reported frequencies of clinical reactions. The results of the analysis will be submitted to the OoBRR as a supplement to this report by the end of March, 1986.

SUMMARY OF ADULT STUDIES

The yeast recombinant hepatitis B vaccine has been well tolerated by healthy adult recipients. A vaccination regimen consisting of three 10 mcg doses is sufficient to induce fully protective titers of antibody in 97% of the vaccinees.

Table 1

Antibody Responses Among Health Care Personnel and Other Healthy Adults Receiving
Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months

Time (Months)	2.5 mcg					5 mcg *					10 mcg *					20 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders					Responders	
	S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10	S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10	S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10	S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10
1	27 (16/60)	15 (9/60)	1.0	23.6	65.9	27 (45/167)	15 (25/167)	0.9	15.7	50.7	30 (258/851)	16 (140/851)	1.0	15.1	43.0	29 (10/35)	11 (4/35)	0.7	8.7	72.9
3	85 (48/56)	62 (35/56)	17.0	33.0	63.2	80 (128/161)	62 (100/161)	12.4	31.6	56.9	88 (512/583)	75 (437/583)	31.2	55.1	89.7	89 (31/35)	57 (20/35)	10.3	16.4	38.1
6	85 (49/57)	70 (40/57)	17.7	32.1	47.0	84 (133/158)	68 (107/158)	18.7	39.9	67.8	94 (581/618)	87 (535/618)	60.2	89.2	101.0	91 (31/34)	79 (27/34)	26.2	40.3	57.6
7/8 †	100 (58/58)	97 (56/58)	255.8	255.8	295.3	97 (111/114)	90 (102/114)	205.7	245.1	348.7	98 (518/529)	97 (514/529)	1072.3	1264.3	1321.9	100 (35/35)	89 (31/35)	539.0	539.0	1021.5
12	95 (45/47)	87 (41/47)	98.1	127.0	172.3	92 (85/93)	74 (69/93	63.3	96.7	210.1	95 (228/240)	90 (216/240)	198.5	275.1	343.8	97 (34/35)	86 (30/35)	184.5	217.4	370.9

* Table does not include results for 11 subjects in Study P94 whose anti-HBs responses are available only in units of S/N.

† Table includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

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1/3/95

Table 2

Seroconversion Rates for Anti-HBs (Based on a Cutoff of S/N ≥2.1)
Among Health Care Personnel and Other Healthy Adults Receiving
Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months
(Studies Involving More Than One Dose Level)

Time (Months)	% (Proportion) with Anti-HBs			
	2.5 mcg	5 mcg	10 mcg	20 mcg
1	27 (16/60)	28 (54/196)	36 (74/205)	29 (10/35)
3	86 (48/56)	80 (151/190)	87 (167/191)	89 (31/35)
6	86 (49/57)	84 (154/184)	93 (177/190)	91 (31/34)
7/8*	100 (58/58)	95 (133/140)	98 (148/151)	100 (35/35)

* Includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

Studies: 794, 798, 813, 883

wva/3124I/5
1/9/86

Table 3

Seroconversion Rates for Anti-HBs (Based on a Cutoff of mIU ≥10)
Among Health Care Personnel and Other Healthy Adults Receiving
Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months
(Studies Involving More Than One Dose Level)

Time (Months)	% (Proportion) with Anti-HBs			
	2.5 mcg	5 mcg	10 mcg	20 mcg
1	15 (9/60)	15 (25/167)	19 (31/167)	11 (4/35)
3	62 (35/56)	62 (100/161)	72 (113/158)	57 (20/35)
6	70 (40/57)	68 (107/158)	84 (130/154)	79 (27/34)
7/8*	97 (56/58)	90 (102/114)	96 (110/114)	89 (31/35)

* Includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

Studies: 798, 813, 883

wva/3124I/6
1/9/86

Table 4

Antibody Responses by Sex Among Health Care Personnel and Other Healthy Adults Receiving Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months

Time (Months)	Sex	2.5 mcg					5 mcg ☆					10 mcg ☆				
		% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
					Responders					Responders					Responders	
		S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10	S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10	S/N≥2.1	mIU/ml ≥10	All Vaccinees	S/N≥2.1	mIU/ml ≥10
1	F	33 (7/21)	19 (4/21)	1.3	22.3	54.0	37 (16/43)	16 (7/43)	1.2	10.6	52.8	34 (140/418)	19 (78/418)	1.2	15.6	41.8
	M	23 (9/39)	13 (5/39)	0.8	24.6	77.3	23 (29/124)	14 (18/124)	0.8	19.5	49.9	26 (108/412)	14 (59/412)	0.9	15.1	45.4
3	F	90 (18/20)	60 (12/20)	18.4	29.0	61.8	93 (38/41)	80 (33/41)	35.2	49.2	69.2	88 (213/241)	81 (196/241)	44.8	80.1	100.6
	M	83 (30/36)	64 (23/36)	16.3	36.2	64.0	75 (90/120)	56 (67/120)	8.6	26.2	51.6	88 (274/311)	72 (224/311)	25.7	43.5	72.7
6	F	90 (17/19)	74 (14/19)	23.1	34.6	48.9	95 (38/40)	88 (35/40)	54.1	71.1	87.8	95 (256/269)	91 (244/269)	90.2	117.2	135.5
	M	84 (32/38)	68 (26/38)	14.8	30.9	45.9	80 (95/118)	61 (72/118)	13.1	31.7	59.8	93 (324/348)	84 (291/348)	43.8	59.2	78.6
7/8 †	F	100 (19/19)	100 (19/19)	301.5	301.5	301.5	100 (30/30)	97 (29/30)	560.3	560.3	646.1	99 (225/228)	97 (222/228)	1502.6	1675.1	1816.9
	M	100 (39/39)	95 (37/39)	236.2	236.2	292.2	96 (81/84)	87 (73/84)	144.8	180.5	272.9	97 (292/300)	97 (291/300)	829.0	1017.5	1036.9
12	F	100 (16/16)	88 (14/16)	94.9	94.9	144.4	100 (23/23)	91 (21/23)	238.5	238.5	357.3	94 (104/110)	91 (100/110)	264.9	374.5	448.6
	M	94 (29/31)	87 (27/31)	99.9	149.0	188.7	90 (63/70)	69 (48/70)	40.9	69.1	167.3	95 (124/130)	89 (116/130)	155.5	212.3	273.3

☆ Table does not include results for 71 subjects in Study 794 whose anti-HBs responses are available only in units of S/N.

† Table includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

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Table 5

Antibody Responses by Age Group Among Health Care Personnel and Other Healthy Adults Receiving 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine at 0, 1, and 6 Months*+

Time (Months)	Age Group (Years)	% with Anti-HBs		GMT (mIU/ml)		
				All Vaccinees	Responders	
		S/N ≥ 2.1	mIU/ml ≥ 10		S/N ≥ 2.1	mIU/ml ≥ 10
1	<40	32(227/699)	18(129/699)	1.1	15.7	42.7
	≥40	16(21/130)	6(9/130)	0.6	11.9	54.5
3	<40	89(449/503)	78(394/503)	36.7	60.4	86.2
	≥40	78(38/49)	55(27/49)	11.0	30.3	67.4
6	<40	95(534/564)	88(498/564)	66.4	85.4	104.4
	≥40	87(46/53)	70(37/53)	21.6	40.6	68.4
7/8**	<40	98(464/472)	98(462/472)	1225.9	1409.4	1446.0
	≥40	95(53/56)	91(51/56)	345.7	487.8	586.5
12	<40	96(190/198)	90(179/198	225.7	293.6	375.7
	≥40	90(38/42)	88(37/42)	108.4	198.7	223.7

*Table does not include results for 71 subjects in Study 794 whose anti-HBs responses were available only in units of S/N.

+Table does not include results for 32 subjects whose ages are not presently known.

**Table includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

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Table 6

Seroconversion Rates for Anti-HBs by Age Group
(Based on a Cutoff of S/N ≥2.1)
Among Health Care Personnel and Other Healthy Adults Receiving
10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine
at 0, 1, and 6 Months †

Time (Months)	Age Group (Years)	% (Proportion) with Titer	
		S/N ≥2.1 *	mIU/ml ≥10 **
1	<40	35 (131/378)	16 (57/350)
	≥40	16 (22/139)	6 (8/129)
3	<40	89 (224/253)	79 (181/230)
	≥40	73 (43/59)	55 (27/49)
6	<40	94 (250/266)	89 (212/239)
	≥40	84 (51/61)	69 (36/52)
7/8†	<40	98 (221/225)	97 (192/198)
	≥40	94 (61/65)	91 (50/55)

† Includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

* Studies: 779, 792, 794, 801, 803, 807, 809, 813, 835, 838, 869, 883, 889
** Studies: As above, but excluding study 794.

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1/9/86

Table 7

Distribution of Anti-HBs Titers at 7/8 and 12 Months
Among Health Care Personnel and Other Healthy Adults
Receiving 10 mcg Doses of Yeast Recombinant Hepatitis B Vaccine
at 0, 1, and 6 Months

Anti-HBs Titer	% (Proportion) with Titer	
	7/8 Months *	12 Months
S/N ≥2.1	98 (498/509)	95 (225/237)
mIU/ml ≥10	97 (494/509)	90 (213/237)
mIU/ml ≥100	89 (451/509)	65 (155/237)
mIU/ml ≥1000	58 (294/509)	25 (60/237)

* Includes a number of responses measured at 9 months when that was the first blood sample obtained following the third injection of vaccine.

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1/9/86

Table 8

Percentages of Health Care Personnel and Other Healthy
Adults with Clinical Complaints During a Five-Day Period
Following 3255 Injections of Yeast Recombinant Hepatitis B Vaccine

Type of Complaint	First Injection	Second Injection	Third Injection	All Injections
Local (Injection Site)	20 (248/1252)	14 (157/1162)	17 (139/841)	17 (544/3255)
Systemic	19 (244/1252)	13 (148/1162)	11 (90/841)	15 (482/3255)
Any Complaint	34 (426/1252)	23 (263/1162)	23 (196/841)	27 (885/3255)

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835, 838, 839, 860, 869, 883, 889

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Table 9

Frequency of Local (Injection Site) Complaints Occurring within 5 Days Among Health Care Personnel and Other Healthy Adults Following 3255 Injections of Yeast Recombinant Hepatitis B Vaccine

Number of Vaccine Recipients: 1252

Complaint	Number	Frequency as %
Soreness	259	8
Pain	149	5
Tenderness	98	3
Pruritis	36	1
Stiffness/Tightness	14	0.4
Erythema	14	0.4
Ecchymosis	10	0.3
Swelling	10	0.3
Pain on Injection	6	0.2
Warmth	6	0.2
Lymphadenopathy, Regional	5	0.2
Arm Feels Heavy	5	0.2
Nodule	4	0.1
Paresthesia	4	0.1
Papule	3	0.1
Inflammation	3	0.1
Numbness	3	0.1

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835, 838, 839, 860, 869, 883, 889

Table 10

Percentage (Number) of Health Care Personnel and Other Healthy Adults with Specific Systemic Complaints During a Five-Day Period Following 3255 Injections of Yeast Recombinant Hepatitis B Vaccine

Number of Vaccine Recipients: 1252

Complaint Frequency 1-4%	
Fatigue/Weakness	4 (138)
Headache	4 (135)
Nausea	2 (58)
Pharyngitis	1 (40)
Malaise	1 (38)
Diarrhea	1 (35)
Upper Respiratory Infection, NOS	1 (32)

Complaint Frequency 0.4-0.9%	
Rhinitis	0.8 (26)
Dizziness	0.5 (16)
Sweating	0.5 (15)
Achiness	0.4 (14)
Myalgia	0.4 (13)
Sensation of Warmth, General	0.4 (13)
Illness, NOS	0.4 (12)

Complaint Frequency 0.1-0.3%	
Arthralgia, Other	0.3 (11)
Influenza, NOS	0.3 (10)
Abdominal Pains/Cramps	0.3 (10)
Lightheaded	0.3 (10)
Vomiting	0.3 (10)
Pruritis/Itching	0.3 (10)
Rash	0.3 (10)
Chills	0.2 (8)
Flush	0.2 (8)
Shoulder Pain	0.2 (7)
Cough	0.2 (7)
Back Pain	0.2 (6)
Neck Pain	0.2 (6)
Dyspepsia/Heartburn	0.2 (6)
Neck Stiffness	0.2 (5)
Earache	0.2 (5)
Lymphadenopathy, Cervical	0.2 (5)
Lymphadenopathy, General	0.1 (4)
Arthralgia, Monoarticular	0.1 (4)
Diminished Appetite	0.1 (4)
Paresthesia	0.1 (4)
Urticaria/Hives	0.1 (4)
Clay Colored Stools	0.1 (3)
Insomnia/Disturbed Sleep	0.1 (3)
Sinusitis	0.1 (3)
Laryngitis	0.1 (3)

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835, 838, 839, 860, 869, 883, 889

Table 11

Frequency of Systemic Complaints by Body System Occurring Within Five Days Among Health Care Personnel and Other Healthy Adults Following 3255 Injections of Yeast Recombinant Hepatitis B Vaccine

Number of Vaccine Recipients: 1252

Body System/Complaint	Frequency as % (Number)
Whole Body/General	**10 (315)**
Fatigue/Weakness	4 (138)
Headache	4 (135)
Malaise	1 (38)
Sweating	0.5 (15)
Achiness	0.4 (14)
Sensation of Warmth, General	0.4 (13)
Illness, NOS	0.4 (12)
Lightheaded	0.3 (10)
Chills	0.2 (8)
Flush	0.2 (8)
Digestive	**3 (103)**
Nausea	2 (58)
Diarrhea	1 (35)
Abdominal Pains/ Cramps	0.3 (10)
Vomiting	0.3 (10)
Dyspepsia/ Heartburn	0.2 (6)
Diminished Appetite	0.1 (4)
Clay-colored Stools	0.1 (3)
Respiratory	**3 (87)**
Pharyngitis	1 (40)
Upper Respiratory Infection, NOS	1 (32)
Rhinitis	0.8 (26)
Cough	0.2 (7)
Sinusitis	0.1 (3)
Laryngitis	0.1 (3)

Body System/Complaint	Frequency as % (Number)
Musculoskeletal	**2 (52)**
Myalgia	0.4 (13)
Arthralgia, Other	0.3 (11)
Shoulder Pain	0.2 (7)
Back Pain	0.2 (6)
Neck Pain	0.2 (6)
Neck Stiffness	0.2 (5)
Arthralgia, Monoarticular	0.1 (4)
Nervous System	**0.8 (27)**
Dizziness	0.5 (16)
Paresthesias	0.1 (4)
Integumentary	**0.7 (24)**
Pruritis/Itching	0.3 (10)
Rash	0.3 (10)
Urticaria/Hives	0.1 (4)
Infections Syndromes	**0.4 (12)**
Influenza, NOS	0.3 (10)
Organs of Special Sense	**0.3 (11)**
Earache	0.2 (5)
Hemic/Lymphatic	**0.2 (8)**
Lymphadenopathy, Cervical	0.2 (5)
Lymphadenopathy, General	0.1 (4)
Urogenital	**0.2 (6)**
Psychiatric/Behavioral	**0.2 (6)**
Insomnia/Disturbed Sleep	0.1 (3)
Cardiovascular	**0.2 (5)**

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835, 838, 839, 860, 869, 883, 889

Table 12

Percentages of Health Care Personnel and Other Healthy Adults with Elevated Temperatures During a Five-Day Period Following 3097 Injections of Yeast Recombinant Hepatitis B Vaccine*

(Oral) Temperature	First Injection	Second Injection	Third Injection	All Injections
≥100°F	4 (45/1217)	3 (28/1111)	4 (27/769)	3 (100/3097)
≥101°F	0.7 (9/1217)	0.5 (6/1111)	1 (7/769)	0.7 (22/3097)
≥102°F	0.1 (1/1217)	0.1 (1/1111)	0.4 (3/769)	0.2 (5/3097)
≥103°F	0 (0/1217)	0.1 (1/1111)	0 (0/769)	0.03 (1/3097)

Studies: 779, 792, 794, 795, 798, 801, 803, 807, 808, 809, 813, 816, 835 838, 839, 860, 869, 883, 889

* Fever, temperature not recorded, was reported in 14 cases.

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1/2/86

Table 13

Age and Sex Characteristics of Health Care Personnel
Receiving Injections of Yeast Recombinant Hepatitis B Vaccine
from Five Consistency Lots in Study 880

Lot Number	Age (Years)		Sex (%)	
	Mean	S.D.	Male	Female
C-L215	25.6	3.6	54.2	45.8
C-L216	30.8	6.9	58.1	41.9
C-L217	32.0	10.0	56.6	43.4
C-L219	30.6	9.5	54.4	45.6
C-L220	25.6	4.3	74.4	25.6

Table 14

Antibody Responses Among Health Care Personnel Receiving 10 mcg Doses of
Yeast Recombinant Hepatitis B Vaccine (5 Consistency Lots) at 0, 1, and 6 Months in Study 880

	All Lots Combined					Lot C-L215					Lot C-L216				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Months)	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10
1	25 (56/227)	11 (26/227)	0.9	12.5	49.8	24 (11/46)	13 (64/64)	0.9	12.5	33.0	20 (8/41)	7 (3/41)	0.7	9.3	39.6
3	84 (144/171)	72 (123/171)	23.9	49.7	73.2	86 (32/37)	73 (27/37)	31.9	58.7	95.4	86 (25/29)	76 (22/29)	18.7	34.2	45.7
6	92 (143/156)	79 (124/156)	32.0	45.5	62.8	86 (31/36)	64 (23/36)	23.0	36.8	71.8	100 (22/22)	100 (22/22)	51.5	51.5	51.5
7/8	98 (136/139)	96 (133/139)	627.6	742.9	830.8	100 (33/33)	94 (31/33)	591.2	591.2	799.3	100 (24/24)	100 (24/24)	1187.6	1187.6	1187.6

	Lot C-L217					Lot C-L219					Lot C-L220				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Months)	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10	S/N ≥2.1	mIU/ml ≥10	All Vaccinees	S/N ≥2.1	mIU/ml ≥10
1	19 (10/52)	8 (4/52)	0.8	14.5	91.2	22 (10/45)	9 (4/45)	0.7	10.7	36.7	40 (17/43)	21 (9/43)	1.7	14.6	63.8
3	84 (32/38)	68 (26/38)	23.6	48.7	77.4	66 (21/32)	59 (19/32)	9.5	51.7	63.9	97 (34/35)	83 (29/35)	50.5	55.6	84.8
6	87 (26/30)	77 (23/30)	27.5	53.5	69.7	90 (27/30)	73 (22/30)	29.7	48.0	77.2	97 (37/38)	89 (34/38)	39.5	43.2	53.1
7/8	96 (22/23)	91 (21/23)	345.8	476.4	593.6	92 (23/25)	92 (23/25)	332.6	612.6	612.0	100 (34/34)	100 (34/34)	1012.0	1012.0	1012.0

Table 15

Percent (Proportion) of Health Care Personnel With Clinical Complaints During a 5-Day Period Following Vaccination With Yeast Recombinant Hepatitis B Vaccine From Five Consistency Lots in Study 880*

Lot #	Type of Complaint	First Injection	Second Injection	Third Injection	Total
C-L215	Local (Injection Site)	8 (4/48)	12 (6/46)	4 (1/24)	9 (11/118)
	Systemic	2 (1/48)	2 (1/46)	4 (1/24)	3 (3/118)
	Any Local or Systemic	10 (5/48)	13 (6/46)	4 (1/24)	10 (12/118)
	Temperature ≥100°F (Oral)	2 (1/45)	0 (0/38)	0 (0/4)	1 (1/97)
C-L216	Local (Injection Site)	9 (4/43)	5 (2/43)	9 (1/11)	7 (7/97)
	Systemic	19 (8/43)	2 (1/43)	0 (0/11)	9 (9/97)
	Any Local or Systemic	21 (9/43)	5 (2/43)	9 (1/11)	12 (12/97)
	Temperature ≥100°F (Oral)	0 (0/35)	0 (0/25)	0 (0/6)	0 (0/66)
C-L217	Local (Injection Site)	11 (6/53)	4 (2/53)	0 (0/17)	7 (8/123)
	Systemic	13 (7/53)	4 (2/53)	0 (0/17)	7 (9/123)
	Any Local or Systemic	23 (12/53)	4 (2/53)	0 (0/17)	11 (14/123)
	Temperature ≥100°F (Oral)	3 (1/38)	3 (1/32)	0 (0/5)	3 (2/75)
C-L219	Local (Injection Site)	17 (8/46)	9 (4/46)	6 (1/17)	12 (13/109)
	Systemic	9 (4/46)	0 (0/46)	6 (1/17)	5 (5/109)
	Any Local or Systemic	22 (10/46)	9 (4/46)	12 (2/17)	15 (16/109)
	Temperature ≥100°F (Oral)	0 (0/38)	0 (0/26)	0 (0/12)	0 (0/76)
C-L220	Local (Injection Site)	0 (0/43)	9 (4/43)	7 (2/30)	5 (6/116)
	Systemic	7 (3/43)	5 (2/43)	3 (1/30)	5 (6/116)
	Any Local or Systemic	7 (3/43)	14 (6/43)	10 (3/30)	10 (12/116)
	Temperature ≥100°F (Oral)	0 (0/42)	0 (0/40)	0 (0/20)	0 (0/102)

*A complaint or an elevated temperature is recorded here if it occurred during any portion of a 5-day follow-up period.

APPENDIX 1

STATISTICAL METHODS

All tests of significance were two-sided at 0.05 significance level.

A. Clinical Complaints

1. The incidence of the various clinical complaints in dialysis patients on the three dose regimen, healthy teenagers and healthy children were evaluated as a function of log dose level using the Mantel-Haenszel Test[1] for trend.

2. All other differences in the incidences of the various clinical complaints in dialysis patients due to dose level or regimen and in health care personnel receiving vaccine from consistency lots were assessed by the Likelihood Ratio Chi-Square.

B. Seroconversion Rates

1. The effect of dose level on seroconversion rates in healthy adults, healthy teenagers and healthy children was analyzed over studies using the Mantel Haenszel Test[1] for trend.

2. Differences in seroconversion rates in healthy adults due to age or sex were evaluated over studies using the Mantel Haenszel Test[1] for heterogeneity.

3. Differences in seroconversion rates due to age in healthy children, dose level in dialysis patients, and vaccine lot in health care personnel were assessed by the Likelihood Ratio Chi-Square.

C. Level of Response (Titers)

The effect of age, sex, lot (consistency lots only in Study 880), or dose level (all other studies) in health care personnel and other healthy adults, of dose level in healthy teenagers, of dose level and age in healthy children, and of dose level and regimen in dialysis patients were analyzed by fitting these variables to a regression model. Subjects who were negative for antibody to hepatitis B surface antigen were assigned a titer of 0.3 mIU/ml in the analysis.

REFERENCE

1. Tarone RE, Ware J: On Distribution-Free Tests for Equality of Survival Distributions. Biometrika 64: 156-160, 1977.

HEALTH CARE PERSONNEL AND OTHER HEALTHY ADULTS

Study 779 - West Point, PA - Dr. R. Bishop

Healthy adults are receiving 10 mcg injections of vaccine from one of two lots at 0, 1, and 6 months.

Twenty-six adults received two injections of vaccine from lot C-K444, and 21 of these received the third injections. Seroconversion for anti-HBs (S/N $\geq$ 2.1) at 7/8 months was 100% (17/17). Ninety-four percent (16/17) developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at 7/8 months for all vaccinees was 808.5 mIU/ml and 1124.9 for responders (mIU/ml $\geq$10). Subjects continue to be followed for persistence of antibody.

One person who received vaccine from lot C-K444 developed a frontal headache and erythematous papular rash several hours after the third injection was administered. This individual has a history of multiple allergies. The reaction was considered vaccine-related.

Refer to the summary on immune affinity vaccine for responses of subjects vaccinated in this study using vaccine produced by that method.

Study 792 - Boston, MA - Dr. J. Dienstag

Initially seronegative health care personnel are receiving 10 mcg injections of vaccine from one of two lots at 0, 1, and 6 months.

Thirty-five subjects have received two injections of vaccine from lot C-K564 and 32 of these have received the third injection. Seroconversion for anti-HBs (S/N $\geq$ 2.1) was 96% (27/28) at 9 months. Ninety-three percent (26/28) of the participants developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at 7/8 months for all vaccinees was 531.1 mIU/ml and 826.3 for responders (mIU/ml $\geq$10).

There have been no reports of serious or alarming reactions attributable to vaccine. Subjects continue to be followed for persistence of antibody.

Refer to the summary on immune affinity vaccine for responses of subjects vaccinated in this study using vaccine produced by that method.

Study 794 - Bethesda, MD - Dr. H. Alter

Health care personnel and nonresponders to plasma-derived vaccine, who are negative for hepatitis B serologic markers, are enrolled in study 794. Health care workers receive 5 mcg or 10 mcg injections and nonresponders receive 10 mcg injections of yeast recombinant vaccine from lot C-K444 vaccine at 0, 1, and 6 months. Forty-one health care workers received the initial 10 mcg injection of vaccine and forty of these participants have also received the

Study 794 - Bethesda, MD - Dr. H. Alter (Contd)

second and third injections. At seven months, 97% (35/36) of the vaccinees seroconverted for anti-HBs (S/N ≥2.1). Ninety-four percent (34/36) developed levels of anti-HBs ≥10 S/N. The GMT at seven months for all vaccinees was 160.8 S/N and 209.3 for responders (S/N ≥10).

Thirty subjects received two 5 mcg injections of vaccine. Twenty-eight of these participants received the third injection. Eighty-four percent (21/25) of the vaccinees seroconverted (S/N ≥2.1) for anti-HBs at seven months. Seventy-six percent (19/25) developed anti-HBs titers ≥10 S/N at that time. The GMT for all vaccinees was 54.0 S/N and 152.9 for responders (S/N ≥10).

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 795 - West Germany - Dr. F. Deinhardt

The study population consists of health care personnel and other healthy adults who are negative for hepatitis B serologic markers. Participants are scheduled to receive 10 mcg injections of vaccine at 0, 1, and 6 months from one of 3 vaccine lots.

One hundred forty-eight persons have received vaccine from lot C-K564. One hundred twenty-six of these participants have received all three injections. Seroconversion for anti-HBs (S/N ≥2.1) at 7/8 months was 100% (76/76). All of these vaccinees developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months for all vaccinees was 2143.1 mIU/ml.

Ninety-seven persons have received lot C-L215 vaccine. Ninety-four of those participants have received all three injections. At 7/8 months, 99% (79/80) of the vaccinees seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 7/8 months for all vaccinees was 2436.1 mIU/ml and 2655.2 for responders (mIU/ml ≥10).

No serious or alarming reactions attributable to vaccine have been reported. The study continues in progress.

Refer to the summary on immune affinity vaccine for responses of subjects vaccinated in this study using vaccine produced by that method.

Study 798 - Houston, TX - Dr. F. B. Hollinger

The study population consists of male paramedical personnel who are initially negative for hepatitis B serologic markers. Participants are assigned to receive vaccine at one of three dose levels (5 mcg, 10 mcg or 20 mcg) from lot C-K446 at 0, 1, and 6 months.

Thirty-six persons have received the initial 20 mcg injection of vaccine, and all but one of these have received the second and third injections. Sero-

Study 798 - Houston, TX - Dr. F. B. Hollinger (Cont.)

conversion for anti-HBs at 7/8 months (S/N ≥2.1) was 100% (35/35). Ninety-one percent (32/35) of the vaccine recipients had an anti-HBs titer ≥10 mIU/ml with a GMT for the responders of 1193.3 mIU/ml.

Thirty-seven participants received three 10 mcg injections of vaccine. Seroconversion (S/N ≥ 2.1) at 7/8 months was 97% (34/35). Ninety-seven percent (35/36) of the vaccine recipients had anti-HBs titers of mIU/ml ≥ 10 with a GMT for responders of 601.6 mIU/ml.

Thirty-six persons have received three 5 mcg injections of vaccine. Ninety-seven percent (35/36) of the vaccine recipients seroconverted for anti-HBs (S/N ≥ 2.1) at 7/8 months. Eighty-three percent (30/36) of the participants developed titers of mIU/ml ≥ 10. The GMT at 7/8 months was 72.9 mIU/ml for all vaccinees and 136.9 for responders (mIU/ml ≥10). Subjects continue to be followed for persistence of antibody.

No serious or alarming adverse experiences attributable to vaccine have been reported. Subjects continue to be followed for persistence of antibody.

Study 801 - Houston, TX - Dr. E. Septimus

Initially seronegative health care workers in this study are receiving 10 mcg injections of vaccine from lot C-K444 at 0, 1, and 6 months.

Twenty-two subjects have received the first injection of vaccine and twenty-one of these have also received the second and third injections. Seroconversion for anti-HBs (S/N ≥2.1) at 7 to 8 months was 100% (21/21). All of these participants developed protective levels (mIU/ml ≥10) of anti-HBs at that time. The GMT at 7/8 months for all vaccinees was 280.8 mIU/ml. Subjects continue to be followed for persistence of antibody.

One subject (26-year old female) became aware that she was pregnant after receiving one injection of vaccine. The vaccine was administered approximately one month after conception. She experienced a spontaneous abortion at 18 weeks after fetal death in utero. No microscopic examination was completed on the fetus. The subject previously delivered two healthy infants without complication of pregnancy. She had no known allergies. The experience was considered possibly related to vaccine.

Study 803 - Denver, CO - Dr. G. Judson

Health care personnel, negative for hepatitis B serologic markers, are receiving 10 mcg injections of vaccine from lot C-K444 at 0, 1, and 6 months.

Study 803 - Denver, CO - Dr. G. Judson (Cont.)

Thirty-one persons have received the initial injection. Thirty of these have also received the second and third injections. At 7/8 months, 85% (22/26) of the participants seroconverted (S/N ≥2.1) and developed protective levels (mIU/ml ≥10) of anti-HBs. The GMT at that time for all vaccinees was 584.6 mIU/ml and 2136.0 for responders (mIU/ml ≥10).

No serious or alarming reactions attributable to vaccine have been reported. Subjects continue to be followed for persistence of antibody.

Study 807 - The Netherlands - Dr. S. Schalm

Health care personnel who are negative for hepatitis B virus serologic markers, are receiving 10 mcg injections of yeast recombinant hepatitis B vaccine lot C-K444 or 20 mcg injections of licensed plasma-derived vaccine lot 1510J (HEPTAVAX-B) at 0, 1, and 6 months.

Thirty-one participants have received three 10 mcg injections of yeast recombinant vaccine. Seroconversion for anti-HBs (S/N ≥ 2.1 and mIU/ml ≥ 10) at 7/8 months was 100% (31/31) with a GMT of 885.1 mIU/ml for all vaccinees.

Twenty-five subjects have received three 20 mcg injections of licensed plasma-derived vaccine. At 7/8 months, seroconversion for anti-HBs (S/N ≥ 2.1 and mIU/ml ≥ 10) was 100% (22/22) with a GMT of 6164.4 mIU/ml for all vaccinees.

No study participant reported a serious or alarming reaction attributable to vaccine. Serologic testing continues in progress.

Study 808 - Tucson, Arizona - Dr. R. Sampliner

Health care personnel who are negative for hepatitis B virus serologic markers, are receiving 10 mcg injections of vaccine from lot C-K444 at 0, 1, and 6 months.

Twenty-five subjects have received three injections of vaccine. At 7/8 months, 96% (22/23) of the participants seroconverted (S/N ≥2.1) and developed protective levels (mIU/ml ≥10) of anti-HBs. The GMT at that time for all vaccinees was 1711.5 mIU/ml and 2535.7 for responders (mIU/ml ≥10).

The vaccine has been well tolerated with no reports of serious adverse events related to vaccine. The study continues in progress.

Study 809 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

In study 809 healthy adults and healthy children (1-11 years), initially negative for hepatitis B serologic markers, are scheduled to receive vaccine at 0, 1, and 6 months.

Study 809 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr (Cont.)

Eighteen healthy adults have received the initial 10 mcg injection of vaccine from lot C-K444. All but one of these participants received the second and third injections. At 7/8 months, 100% (11/11) of the vaccinees seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at that time for all vaccinees was 955.7 mIU/ml.

There have no reports of alarming or serious adverse experiences attributable to vaccine. Subjects continue to be followed up for persistence of anti-HBs. Refer to the summary on infants and children for responses of other subjects vaccinated in this study.

Study 811 - Switzerland - Dr. P. Grob

Health care personnel and predialysis patients, initially negative for hepatitis B virus serologic markers, are enrolled in study 811. Health care personnel receive 10 mcg injections of vaccine lot C-K446 at 0, 1, and 6 months.

Eleven health care personnel have received an initial 10 mcg injection of yeast recombinant vaccine. Eight of these have received the second and third injections. At 7/8 months, 86% (6/7) of the participants seroconverted for anti-HBs (S/N ≥2.1). Eighty-three percent (5/6) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 7/8 months for all vaccinees was 275.1 mIU/ml and 1076.6 mIU/ml for five of the responders. Among subjects with serology data available at 12 months, 83% (5/6) were positive for anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 44.1 mIU/ml.

There have been no reports of serious or alarming reactions attributable to vaccine. Subjects continue to be followed for persistence of antibody. Refer to the summary on dialysis and predialysis patients for responses of other subjects vaccinated in this study.

Study 813 - New York, NY - Dr. M. Davidson

The study enrolls health care personnel, some of whom are seronegative for hepatitis B virus markers and have never been vaccinated, and others (preimmune) who have previously been vaccinated with either yeast recombinant hepatitis B vaccine or plasma-derived hepatitis B vaccine (HEPTAVAX-B). There are five groups of initially seronegative adults, not randomized by age, who are scheduled to receive vaccine from lots C-K444 or C-L220 at 0, 1, and 6 months. These participants receive either 2.5 mcg, 5 mcg or 10 mcg injections. There is an additional group of seronegative adults, ≥40 years of age, who are scheduled to receive either 10 mcg injections of lot C-M126 or 20 mcg injections of lot C-M125 at 0, 1, and 6 months.

Sixty-one health care personnel have received two 2.5 mcg injections of vaccine and sixty of these have received the third injection. At 7/8 months,

Study 813 - New York, NY - Dr. M. Davidson (Cont.)

100% (40/40) of the subjects seroconverted for anti-HBs (S/N ≥2.1) and 97% (39/40) developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees at that time was 291.5 mIU/ml and 321.5 for responders (mIU/ml ≥10).

One-hundred-twenty-one seronegative adults have received one 5 mcg injection of vaccine. One-hundred-twenty and 115 of these have received the second and third injections, respectively. Ninety-eight percent (42/43) of the participants seroconverted for anti-HBs (S/N ≥2.1) at 7/8 months. Ninety-five percent (41/43) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at 7/8 months was 523.8 mIU/ml and 693.9 for responders (mIU/ml ≥10).

In the 10 mcg dose group, 131 health care personnel have received the first injection of vaccine. One-hundred-twenty-four and 109 of these have received the second and third injections, respectively. At 7/8 months, 100% (36/36) of the vaccinees seroconverted (S/N ≥2.1) and developed protective levels of anti-HBs (mIU/ml ≥10). The GMT for all vaccinees at that time was 1509.3 mIU/ml.

Seven adults have received one 20 mcg injection of vaccine and four of these have received the second injection. Serologic data are not yet available for these participants.

To date, recipients of 10 mcg injections have developed higher anti-HBs titers than those receiving 2.5 mcg or 5 mcg injections of vaccine.

A 23 year-old female developed pruritic hives on her back and extremities after the first and second 10 mcg injections of lot C-L220 vaccine. All symptoms resolved within four days after each injection. The reaction is considered vaccine related. The subject has a history of allergy to contrast dye. She received the third injection of vaccine without development of hives.

No serious adverse experiences attributable to vaccine have been reported. The study continues in progress. Refer to the summary on preimmune adults for data regarding other subjects vaccinated in this study.

Study 815 - Holland - Dr. S. Schalm

The study population consists of institutionalized mentally retarded individuals and health care personnel who are seronegative for hepatitis B markers. The health care personnel will serve as controls in this study. Participants will be paired (mentally retarded and controls) and randomized to receive either 10 mcg or 20 mcg injections of yeast recombinant vaccine or 20 mcg injections of plasma-derived vaccine. All injections will be administered at 0, 1, and 6 months.

Serologic and clinical follow-up data for the health care personnel are not presently available. No serious or alarming adverse reactions attributable to vaccine have been reported. Vaccination and follow-up of all participants continues in progress.

Study 816 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

The population consists of three groups of initially seronegative adults: dialysis patients, dialysis patients who were previously vaccinated with plasma-derived hepatitis B vaccine and failed to respond, and health care personnel. All participants are receiving vaccine from lot C-K446 at 0, 1, and 6 months. Dialysis patients receive 40 mcg injections of vaccine, while health care personnel are administered 10 mcg injections.

Eight health care personnel have received two 10 mcg injections and 6 of these have received the third injection. At 7/8 months, anti-HBs (S/N $\geq$ 2.1 or mIU/ml $\geq$ 10) was present in 80% (4/5) of the subjects tested. The GMT for all vaccinees and responders (mIU/ml $\geq$10) at 7/8 months was 37.9 mIU/ml and 127.2 mIU/ml, respectively.

Refer to the summary on dialysis/predialysis patients for responses of other subjects vaccinated in this study.

Study 834 - Italy - Dr. M. Rizzetto

Initially seronegative healthy adults are receiving 10 mcg (1.0 ml) injections of vaccine lot C-K564 at 0, 1, and 6 months.

Twenty-five subjects have been enrolled in the study and have received one injection of vaccine. Serologic and clinical follow-up data are not presently available.

There has been one report of an adverse experience considered possibly related to vaccine. A 40 year-old female developed a few ecchymotic flat lesions on the lateral aspect of her breast, bilaterally, 4 days after the first injection of vaccine. Over the following 2 days the lesions increased. Vomiting occurred on the third day. All symptoms disappeared over the next 36 hours, and the subject has remained well. There was no fever, and WBC, Hgb, platelets, and coagulation profile were normal. The patient has no history of allergies to exogenous substances. No further vaccine was administered to this patient.

The study continues in progress.

Study 835 - Chapel Hill, NC - Dr. S. Lemon

Health care personnel, who are negative for hepatitis B virus serologic markers, are receiving 10 mcg injections of vaccine from lot C-K564 at 0, 1, and 6 months.

Twenty-nine subjects have received the first two injections of vaccine, and 23 of these have received the third injection. At 7/9 months, 100% (19/19) of the participants seroconverted (S/N 2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT at that time for all vaccinees was 560.9 mIU/ml.

Study participants have not reported any alarming or serious adverse events related to vaccine. The study continues in progress.

Study 838 - West Germany - Dr. F. Deinhardt

Populations vaccinated in this study include health care personnel and adult dialysis and predialysis patients. Health care personnel are receiving 10 mcg injections of vaccine from lot C-K733 at 0, 1, and 6 months.

Twenty-two health care personnel have received the first 10 mcg injection. Nineteen and 17 of these have received the second and third injections, respectively. At 7/8 months, 94% (16/17) of the participants seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT at that time for all vaccinees and responders was 284.8 mIU/ml and 437.1 mIU/ml, respectively.

There have been no reports of alarming or serious adverse experiences attributable to vaccine. The study continues in progress. Refer to the summary on dialysis and predialysis patients for responses of the other subjects vaccinated in this study.

Study 841 - London, UK - Dr. A. Zuckerman and Dr. I. Murray-Lyon

Initially seronegative health care personnel are receiving 10 mcg (1.0 ml) injections of vaccine lot C-K563 at 0, 1, and 6 months.

Serologic and clinical follow-up data are not presently available. No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress.

Study 859 - Belgium - Dr. N. Clumeck

Health care personnel are receiving 10 mcg injections of yeast recombinant vaccine from lot C-K563 at 0, 1, and 6 months.

Thirty-one persons have received the first two injections. One month after the second injection, 80% (24/30) of the vaccine recipients were positive for anti-HBs (S/N $\geq$ 2.1). Fifty-three percent (16/30) of the subjects developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at three months for all vaccinees was 11.8 mIU/ml and 60.0 for responders (mIU/ml $\geq$10).

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 860 - Hamburg, West Germany - Dr. R. Laufs

Health care personnel, initially seronegative for hepatitis B serologic markers, are receiving 10 mcg injections of vaccine from lot C-K564 at 0, 1, and 6 months.

Sixty persons have received the initial injection, and 59 of these have received the second and third injections. At 7/8 months, 100% (56/56) of the participants seroconverted (S/N $\geq$2.1) and developed protective levels (mIU/ml $\geq$10) of anti-HBs. The GMT for all vaccinees was 2421.1 mIU/ml.

Study 860 - Hamburg, West Germany - Dr. R. Laufs (Cont.)

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 869 - Toronto, Ontario - Dr. J. Rankin

The study population consists of seronegative health care personnel who are receiving 10 mcg injections of vaccine from lot C-L217 at 0, 1, and 6 months.

Seventy-one participants have received the first two injections of vaccine. At one month, 32% (22/68) of the subjects seroconverted (S/N $\geq$2.1) for anti-HBs. Twelve percent (8/68) developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT at one month for all vaccinees was 1.2 mIU/ml and 44.8 for responders (mIU/ml $\geq$10).

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 877 - Republic of Singapore - Prof. Oon Chong Jin

Healthy adults, who are negative for hepatitis B virus serologic markers, are receiving 10 mcg injections of vaccine from lot C-K564 at 0, 1, and 6 months.

Thirty-one subjects have received all three injections of vaccine. At 7/8 months, 97% (28/29) of the participants seroconverted (S/N $\geq$2.1) and developed protective levels (mIU/ml $\geq$10) of anti-HBs. The GMT at that time was 508.9 mIU/ml for all vaccinees and 663.7 for responders (mIU/ml $\geq$10).

There have been no reports of serious or alarming reactions attributable to vaccine. The study continues in progress.

Study 880 - Valhalla, NY - Dr. G. Wormser

Initially seronegative health care personnel are receiving 10 mcg injections (0.5 ml) of vaccine at 0, 1, and 6 months from one of the following consistency lots: C-L215, C-L216, C-L217, C-L219, C-L220.

Forty-eight subjects have received two injections of vaccine lot C-L215 and forty of these have received the third injection. At 7/8 months, 100% (29/29) seroconverted (S/N $\geq$2.1) for anti-HBs and 93% (27/29) developed protective levels of antibody (mIU/ml $\geq$10). The GMT for all vaccinees at that time was 602.9 mIU/ml and 853.6 for responders (mIU/ml $\geq$10).

Forty-three subjects have received two injections of vaccine lot C-L216 and eighteen of these have received the third injection. At 7/8 months, 100% (10/10) seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT for all vaccinees was 986.9 mIU/ml.

Study 880 - Valhalla, NY - Dr. G. Wormser (Cont.)

Fifty-three participants have received two injections of vaccine lot C-L217. Twenty-six of these were administered the third injection. Ninety-one percent (10/11) seroconverted for anti-HBs (S/N ≥2.1) at 7/8 months. Eighty-two percent (9/11) developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees at 7/8 months was 331.1 mIU/ml and 1157.1 for responders (mIU/ml ≥10).

Forty-six adults have received two injections of vaccine lot C-L219 and twenty-one of these have received the third injection. At 7/8 months, 100% (11/11) seroconverted (S/N ≥2.1) and developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees at that time was 583.4 mIU/ml.

Forty-three participants have received two injections of vaccine lot C-L220. Thirty-eight of these have been administered the third injection. At 7/8 months, 100% (29/29) seroconverted for anti-HBs (S/N ≥ 2.1) and developed protective levels of antibody (mIU/ml ≥10). The GMT for all vaccinees at that time was 1009.9 mIU/ml.

No serious or alarming adverse experiences related to vaccine have been reported. Clinical and serologic follow-up continues in progress.

Study 882 - Tokyo, Japan - Dr. S. Iino

Healthy adults, initially negative for hepatitis B serologic markers, are receiving 10 mcg injections of vaccine from lot C-L215 at 0, 1, and 6 months.

Forty adults have received all three injections of vaccine. At 7 months, 100% (40/40) of the vaccine recipients seroconverted for anti-HBs (S/N ≥ 2.1).

No serious or alarming reactions related to vaccine have been reported. This study continues in progress.

Study 883 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr

Initially seronegative health care personnel are receiving 5 mcg or 10 mcg injections of vaccine from lot C-L220 at 0, 1, and 6 months.

Twenty-five subjects have received two 5 mcg injections of vaccine, and 24 of these have received the third injection. At 7/8 months, 100% (20/20) of the participants seroconverted (S/N ≥2.1) for anti-HBs. Ninety-five percent (19/20) developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months for all vaccinees was 215.3 mIU/ml and 259.0 for responders (mIU/ml ≥10).

Twenty-eight subjects have received two 10 mcg injections of vaccine, and 27 of these have received the third injection. One hundred percent (24/24) of the participants seroconverted (S/N ≥ 2.1) for anti-HBs at 7/8 months.

Study 883 - Philadelphia, PA - Dr. S. Plotkin and Dr. S. Starr (Cont.)

Ninety-six percent (23/24) developed protective levels of anti-HBs (mIU/ml ≥10). The GMT at 7/8 months for all vaccinees was 863.2 mIU/ml and 1084.9 for responders (mIU/ml ≥10).

There have been no reports of serious or alarming reactions to vaccine. The study continues in progress.

Study 885 - Tampa, FL - Dr. A. Leibowitz

Initially seronegative healthy adults are receiving 10 mcg doses of vaccine at 0, 1, and 6 months from one of the following consistency lots: C-L215, C-L216, C-L217, C-L219, C-L220.

One hundred fifty persons have received the first injection of vaccine. One hundred of these participants have received the second injection. No serologic results are currently available. There have been no reports of serious or alarming adverse experiences attributable to vaccine. The study continues in progress.

Study 889 - St. Louis, MO - Dr. R. Perrillo

The study population consists of two initially seronegative groups: institutionalized mentally retarded individuals and health care personnel. Mentally retarded individuals receive either 10 mcg injections or 20 mcg injections of vaccine. Health care personnel receive 10 mcg injections. All participants are receiving vaccine from lot C-K937 at 0, 1, and 6 months.

Eighty-eight health care personnel have received the first injection of vaccine and 82 of these have received the second injection. At one month, 17% (14/82) of the participants seroconverted (S/N ≥2.1) for anti-HBs with a GMT for all vaccinees of 0.5 mIU/ml.

One female subject developed facial urticaria approximately one hour after receiving the first injection of vaccine. All symptoms subsided within 12 hours after onset. The reaction was considered probably related to vaccine. The subject received Benadryl prior to the second and third injections and had no post-vaccination reactions.

There were no serious adverse experiences attributable to vaccine. The study continues in progress.

Study 894 - Baltimore, MS - Dr. B. F. Polk

The study population consists of homosexual males who are negative for all hepatitis B markers and have not previously received any hepatitis B vaccine. Participants are randomized to receive either 20 mcg infections of plasma-derived vaccine (lot C-M252) or 10 mcg injections of yeast recombinant vaccine (lot C-K563) at 0, 1, and 6 months.

Study 894 - Baltimore, MS - Dr. B. F. Polk (Cont.)

Eighty-seven participants have received one 10 mcg injection of yeast recombinant vaccine and sixty-three of these have received the second injection. One subject only has received the third injection. Serologic data are not presently available.

Eighty-eight participants have received one 20 mcg injection of plasma-derived vaccine and seventy of these have received the second injection. None have yet received the third injection. Serologic data are not presently available.

No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress.

Study 898 - West Point, PA - Dr. R. Bishop

Initially seronegative healthy adults, 40 years of age or older, are receiving either 10 mcg (1.0 ml) injections of vaccine lot C-M126 or 20 mcg (1.0 ml) injections of vaccine lot C-M125. All injections are administered at 0, 1, and 6 months.

To date, one participant has received the initial 10 mcg injection of vaccine, while two subjects have received single 20 mcg injections of vaccine. Post-vaccination serologic results are not presently available. No serious or alarming adverse reactions attributable to vaccine have been reported. The study continues in progress.

Study 900 - London, UK - Dr. A. Zuckerman and Dr. I. Murray-Lyon

Initially seronegative healthy male homosexuals are receiving 10 mcg (1.0 ml) injections of vaccine lot C-M126 at 0, 1, and 6 months.

Serologic and clinical follow-up data are currently not available. No serious or alarming adverse experiences attributable to vaccine have been reported. The study continues in progress.

Study 904 - Chicago, IL - Dr. H. A. Kessler

Initially seronegative healthy adults are scheduled to receive 10 mcg (0.5 ml) injections of vaccine from lot C-M178 or from lot C-L217 at 0, 1, and 6 months.

One hundred participants (50 for each lot) have received the first and second injections of vaccine. Serologic and clinical follow-up data are not presently available. No serious or alarming adverse experiences have been reported. The study continues in progress.

Study 907 - Tokyo and Osaka, Japan - Dr. S. Iino and Dr. T. Kuroki

Healthy adults are receiving 10 mcg (0.5 ml) intramuscular or subcutaneous injections of vaccine lot C-L215 at 0, 1, and 6 months.
Sixty-two participants have received the first and second injections of vaccine by the intramuscular route. Sixty-two subjects have also received the first and second injections of vaccine by the subcutaneous route. One hundred twenty-one of the participants (both routes) have received the third injection. At one month after the third injection, 98% (54/55) of the vaccinees who received intramuscular injections seroconverted for anti-HBs (S/N $\geq$2.1). Ninety-seven percent (56/58) of the participants who received subcutaneous injections seroconverted for anti-HBs (S/N $\geq$2.1) at that time.

There have been no reports of alarming or serious adverse reactions attributable to vaccine. The frequency of systemic complaints was higher in the subcutaneous injection group after the first injection and higher in the intramuscular injection group after the second injection. The frequency of injection site complaints are similar between both groups after the first and second injections. The study continues in progress.

Study 912 - Japan - Dr. T. Shimizu, Dr. M. Nakao, Dr. T. Marimo, et al

Health care personnel are receiving 10 mcg (0.5 ml) intramuscular or subcutaneous injections of vaccine lot C-L220 at 0, 1, and 6 months.

Eighty-seven participants have received the first injection of vaccine by the intramuscular route. Eighty-five of these subjects received the second injection. At one month after the second injection, 75% (56/75) of the subjects seroconverted for anti-HBs (S/N $\geq$2.1).

Eighty-eight participants have received two injections of vaccine by the subcutaneous route. At one month after the second injection, 59% (43/73) of the subjects seroconverted for anti-HBs (S/N $\geq$2.1).

There have been no reports of alarming or serious adverse experiences attributable to vaccine. The frequencies of injection site and systemic complaints, after the first and second injections, were high for vaccinees in the subcutaneous injection group. The study continues in progress.

Study 914 - Bruxelles, Belgium - Dr. A. Burette and Dr. M. Deltenre

Initially seronegative health care personnel are scheduled to receive 10 mcg (1.0 ml) injections of vaccine lot C-M126 at 0, 1, and 6 months.

Twenty participants have received the first and second injections of vaccine. Serologic and clinical follow-up data are currently not available. There have been no reports of alarming or serious adverse experiences attributable to vaccine. The study continues in progress.

STUDY 779

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 779
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among healthy adults who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot 934/C-J625 (10 mcg HBsAg/ml) Lot 972/C-K444 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Robert P. Bishop, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486
SECONDARY INVESTIGATORS:	E. P. Avancena, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486 Joseph C. Rogers, M.D. Health Services Merck Sharp and Dohme West Point, PA 19486 Joseph P. Romano, M.D. Health Services Merck Sharp and Dohme Rahway, NJ 07065
STUDY LOCATION:	Merck Sharp and Dohme West Point, PA 19486
DATE INITIATED:	July 13, 1983
DATE COMPLETED:	In progress

Study 779

STUDY PROCEDURE:

The study population consists of 41 healthy adults of either sex (excluding pregnant women) employed at Merck and Co., Inc., who were initially negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

Eligible participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine produced by either the immune affinity or the (b)(4) procedure at 0, 1 and 6 months. Study participants are asked to take and record their temperatures for five days after each injection of vaccine and to record any local or systemic complaints that they may experience.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before vaccination. Post-vaccination blood samples (10-15 ml) are obtained monthly for seven months and at 9, 12 and 24 months following the first injection of vaccine. Samples are assayed for HBsAg, anti-HBc, anti-HBs and ALT, and these may be assayed for antibody to antigens in yeast extract. Samples with an anti-HBs titer $\geq$ 25 mIU/ml units are tested to determine the relative proportions of anti-a and anti-d activity.

STUDY RESULTS:

HEALTHY ADULTS (b)(4) Vaccine):

10 mcg Lot 972/C-K444 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
26	26	21

Study 779

RESULTS (CONT.):

2. Serologic Results:

Serologic data are available for 17 participants at 7/8 months. Seroconversion (S/N ≥2.1) for anti-HBs at 7/8 months was 100% (17/17). Ninety-four percent (16/17) of the vaccinees developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at 7/8 months for all vaccinees was 808.5 mIU/ml and 1124.9 mIU/ml for responders with a titer of mIU/ml ≥10.

Among participants with serology data at 12 months, 100% (12/12) were positive for anti-HBs (mIU/ml ≥10). The GMT at that time was 459.4 mIU/ml (all vaccinees and responders by either cutoff).

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for at least 20 participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	23(6/26)	15(4/26)	10(2/20)
Systemic	4(1/26)	15(4/26)	5(1/20)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming reactions attributable to vaccine.

Study 779

RESULTS (CONT.):

Reactions reported to the DoBRR

A 41-year old female subject, with a history of multiple allergies, received her first and second injections of vaccine without clinical complaints.

Several hours after receiving her third injection of vaccine, she developed a frontal headache and an erythematous papular rash. One 4 mg chlortrimeton tablet was administered. The headache resolved within 24 hours and the rash faded over the next four days. The clinical investigator considered the reaction to be vaccine related.

PUBLICATIONS:

Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoffnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando: Grune and Stratton, 1984: 315-17.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
POPULATION : HEALTHY ADULTS
DOSE : 10 MCG
LOT : CK444
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
						RESPONDERS	
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	S/N >= 2.1	MIU/ML >= 10
1 MONTH	29%	(7/24)	17%	(4/24)	1.3	24.0	98.7
2 MONTHS	65%	(15/23)	52%	(12/23)	10.4	58.4	110.4
3 MONTHS	76%	(16/21)	62%	(13/21)	16.1	52.6	107.2
6 MONTHS	89%	(17/19)	53%	(10/19)	19.3	31.6	122.6
7/8 MONTHS	100%	(17/17)	94%	(16/17)	808.5	808.5	1124.9
9 MONTHS	100%	(11/11)	91%	(10/11)	767.2	767.2	1274.3
12 MONTHS	100%	(12/12)	100%	(12/12)	459.4	459.4	459.4

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	4 (15.4%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (23.1%)
SORENESS	4 (15.4%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (23.1%)
SYSTEMIC	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
WHOLE BODY/GENERAL	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
HEADACHE	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
PERSONS WITH COMPLAINTS	5 (19.2%)	2 (7.7%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (26.9%)
PERSONS WITH NO COMPLAINTS	21 (80.8%)	24 (92.3%)	25 (96.2%)	26 (100.0%)	26 (100.0%)	26 (100.0%)	19 (73.1%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.8%)	2 (7.7%)	3 (11.5%)	2 (7.7%)	1 (3.8%)	0 (0.0%)	4 (15.4%)
SORENESS	1 (3.8%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)
TENDERNESS	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
STIFFNESS/TIGHTNESS	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (3.8%)
SYSTEMIC	0 (0.0%)	3 (11.5%)	0 (0.0%)	1 (3.8%)	3 (11.5%)	3 (11.5%)	4 (15.4%)
WHOLE BODY/GENERAL	0 (0.0%)	2 (7.7%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	3 (11.5%)
SWEATING	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)
HEADACHE	0 (0.0%)	1 (3.8%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	2 (7.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)
CARDIOVASCULAR	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (3.8%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (26 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
HYPERTENSION	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)	1 (3.8%)		1 (3.8%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)		2 (7.7%)
NAUSEA	0 (0.0%)	1 (3.8%)	0 (0.0%)	0 (0.0%)	1 (3.8%)	1 (3.8%)		2 (7.7%)
PERSONS WITH COMPLAINTS	1 (3.8%)	5 (19.2%)	3 (11.5%)	3 (11.5%)	4 (15.4%)	3 (11.5%)		8 (30.8%)
PERSONS WITH NO COMPLAINTS	25 (96.2%)	21 (80.8%)	23 (88.5%)	23 (88.5%)	22 (84.6%)	23 (88.5%)		18 (69.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 2 (Contd)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK464
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

CLINICAL COMPLAINTS	TOTAL VACCINEES (21 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	2 (10.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (10.0%)
SORENESS	2 (10.0%)	2 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (10.0%)
SYSTEMIC	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)		1 (5.0%)
WHOLE BODY/GENERAL	1 (5.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
EDEMA, FACE	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
HEADACHE	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)		1 (5.0%)
PRURITIS/ITCHING	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
RASH, NOS	0 (0.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)		1 (5.0%)
PERSONS WITH COMPLAINTS	3 (15.0%)	3 (15.0%)	1 (5.0%)	1 (5.0%)	1 (5.0%)	0 (0.0%)		3 (15.0%)
PERSONS WITH NO COMPLAINTS	17 (85.0%)	17 (85.0%)	19 (95.0%)	19 (95.0%)	19 (95.0%)	20 (100.0%)		17 (85.0%)
PERSONS WITH NO DATA	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)	1 (4.8%)		1 (4.8%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (26 PATIENTS) - DOSE 1							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	1 (3.8%)	1 (3.8%)	1 (3.8%)	1 (4.2%)	1 (4.2%)	1 (4.3%)		1 (3.8%)
< 99	24 (92.3%)	24 (92.3%)	24 (92.3%)	23 (95.8%)	22 (91.7%)	21 (91.3%)		21 (80.8%)
99 - 99.9	1 (3.8%)	1 (3.8%)	1 (3.8%)	0 (0.0%)	1 (4.2%)	1 (4.3%)		4 (15.4%)
TEMPERATURE TAKEN	26 (100.0%)	26 (100.0%)	26 (100.0%)	24 (92.3%)	24 (92.3%)	23 (88.5%)		26 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.7%)	2 (7.7%)	3 (11.5%)		0 (0.0%)

Table 3 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (26 PATIENTS) - DOSE 2							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	2 (8.0%)	2 (8.0%)	2 (8.0%)	2 (8.7%)	2 (8.7%)	2 (9.1%)		2 (8.0%)
< 99	22 (88.0%)	20 (80.0%)	23 (92.0%)	21 (91.3%)	21 (91.3%)	20 (90.9%)		19 (76.0%)
99 - 99.9	1 (4.0%)	2 (8.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (12.0%)
101 - 101.9	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (4.0%)
TEMPERATURE TAKEN	25 (96.2%)	25 (96.2%)	25 (96.2%)	23 (88.5%)	23 (88.5%)	22 (84.6%)		25 (96.2%)
TEMPERATURE NOT TAKEN	1 (3.8%)	1 (3.8%)	1 (3.8%)	3 (11.5%)	3 (11.5%)	4 (15.4%)		1 (3.8%)

Table 3 (Contd)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0779
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTHY ADULTS

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (21 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	5 (25.0%)	5 (25.0%)	5 (25.0%)	5 (27.8%)	5 (29.4%)	5 (27.8%)		5 (25.0%)
< 99	14 (70.0%)	14 (70.0%)	15 (75.0%)	12 (66.7%)	12 (70.6%)	13 (72.2%)		14 (70.0%)
99 - 99.9	1 (5.0%)	1 (5.0%)	0 (0.0%)	1 (5.6%)	0 (0.0%)	0 (0.0%)		1 (5.0%)
TEMPERATURE TAKEN	20 (95.2%)	20 (95.2%)	20 (95.2%)	18 (85.7%)	17 (81.0%)	18 (85.7%)		20 (95.2%)
TEMPERATURE NOT TAKEN	1 (4.8%)	1 (4.8%)	1 (4.8%)	3 (14.3%)	4 (19.0%)	3 (14.3%)		1 (4.8%)

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23

Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

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vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

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Original Contributions

Clinical Evaluation in Healthy Adults of a Hepatitis B Vaccine Made by Recombinant DNA

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• A vaccine formulated from hepatitis B surface antigen (HBsAg) produced by a recombinant strain of the yeast *Saccharomyces cerevisiae* was administered to two groups of human volunteers composed of 37 healthy, low-risk adults. Each subject received a 10-μg dose of HBsAg at 0, 1, and 6 months. By one month, 27% to 40% of the vaccinees had antibody to HBsAg, and by three months 80% to 100% were antibody positive. Large boosts in titer followed the third dose at six months. The antibody formed is predominantly specific for the *a* determinant of HBsAg. There have been no serious reactions attributable to the vaccine. The most frequent complaint has been transient soreness at the injection site. As far as we know, this is the first reported use in man of a vaccine prepared by recombinant DNA technology.

(*JAMA* 1984;251:2812-2815)

WORLDWIDE, human hepatitis B infection constitutes a major public health problem. In addition to the disability associated with acute clinical disease, chronic liver disease, cirrhosis, and primary hepatocellular carcinoma are now recognized sequelae of unresolved hepatitis B infection. Indeed, in some areas of Asia and sub-Saharan Africa, primary hepatocellular carcinoma ostensibly attributable to hepatitis B infection ranks as a leading cause of cancer deaths among males.[1]

See also p 2765.

The reservoir of hepatitis B virus resides mainly in a population of chronic carriers now estimated to number more than 200 million.[2] Infection is transmitted to susceptible persons through contact with the blood, semen, or saliva of chronic carriers or persons suffering acute infection. In low-incidence countries, such as the United States, the risk of hepatitis B infection is still high among certain groups of health care personnel, patients receiving dialysis treatments or blood products made from large pools, children born to Alaskan Eskimos or to Indochinese or Haitian refugees, residents of institutions for the mentally handicapped, prisoners, users of illicit injectable drugs, and persons who are sexually very promiscuous.[3] In high-incidence areas such as Southeast Asia, transmission from mother to child in the perinatal period is the major mode of infection supplemented by horizontal transmission between other family contacts.[3]

Since there is no effective treatment for hepatitis B infection, prevention is essential. A safe, effective human hepatitis B vaccine is now available. However, it utilizes hepatitis B surface antigen (HBsAg) purified from the plasma of human carriers of hepatitis B virus infection. Consequently, the supply of vaccine is potentially limited by available sources of suitable plasma. In addition, extensive processing and safety testing have been necessary to ensure production of a vaccine antigen that is pure and free of any extraneous living agent that might have been present in the starting plasma. Even though multiple inactivation treatments used in the antigen purification process have been shown to inactivate representatives of all major groups of animal viruses,[4] concern over the theoretical possibility of a living organism such as the etiologic agent of acquired immune deficiency syndrome being present in plasma and surviving the purification and inactivation procedures has slowed acceptance of hepatitis B vaccine.

A promising alternative to infected human plasma as a source of HBsAg for vaccine is the use of recombinant DNA technology to effect synthesis of the surface antigen by a culture of microorganisms. The hepatitis B virus gene coding for HBsAg has been cloned both in *Escherichia coli* and in yeast[5,6]; however, expression of the gene in yeast has been much better than in *E coli*. Furthermore, HBsAg

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produced by recombinant yeast cells has been shown to aggregate into particles closely resembling those isolated from human plasma, and this material was shown to include antibodies in mice and guinea pigs.[9]

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for HBsAg has been formulated into a vaccine through adsorption on alum adjuvant. Electron microscopy reveals that the purified HBsAg used for this vaccine exists as aggregate particles 20 to 22 nm in diameter, a morphology also characteristic of free surface antigen in infected plasma and of the purified antigen now used in plasma-derived hepatitis B vaccine. In contrast to HBsAg from human plasma, the antigen produced by recombinant yeast is not glycosylated. Under reducing conditions, sodium dodecyl sulfate electrophoresis of the antigen purified from yeast reveals a single band of molecular weight 23,000, which corresponds to the nonglycosylated polypeptide that is the major component of the hepatitis B virus envelope. The vaccine formulated using this material has now been shown to be immunogenic for mice and for monkeys with a potency equal to or superior to that of vaccine made from plasma-derived antigen. In addition, chimpanzees immunized with this yeast recombinant hepatitis B vaccine (HBsAg subtype *adw*) were fully protected when challenged with virus of either type *adr* or *ayr*, while unimmunized animals all showed evidence of infection when challenged.[10]

In this article we describe results of the first human immunogenicity-safety trial of the yeast recombinant hepatitis B vaccine. To the best of our knowledge, this is the first time that a vaccine prepared by recombinant DNA technology has been used in man.

MATERIALS AND METHODS

Population

Participants in this study were healthy, nonpregnant adult employees of Merck and Co, Inc. Subjects had to be negative for hepatitis B serological markers and have a normal level of alanine aminotransferase and must not have received any other hepatitis B vaccine. Written consent was obtained after providing each participant with information on the source of the investigational yeast recombinant hepatitis B vaccine, animal test results obtained with the vaccine, vaccination and bleeding schedules, and the potential risks and benefits of participation in the study.

Vaccine

Hepatitis B surface antigen for the vaccine was produced in fermentation cultures of a recombinant strain of the yeast *S cerevisiae* containing a plasmid carrying the gene for the *adw* subtype of HBsAg, as described previously.[10]

Two methods were employed for the purification of HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends on selection of water-immiscible molecules followed by separation by molecular size. Details of the expression of HBsAg in yeast and the purification of the surface antigen will be published elsewhere. Purified HBsAg was treated with formaldehyde to stabilize the material and to kill any extraneous living agents that might be present. The antigen was then formulated into a vaccine through adsorption on alum adjuvant to give 10 μg of HBsAg and 0.5 mg of aluminum (hydroxide) per 1-mL dose. The final formulation also contained 1:20,000 thimerosal as a preservative. Vaccine was maintained at 2 to 8 °C until used.

Procedures

A blood sample was obtained from each subject approximately two weeks prior to the first vaccination and was tested for HBsAg, antibody to HBsAg (anti-HBs), antibody to core antigen (anti-HBc), alanine aminotransferase (ALT), and yeast antibody. Subjects found eligible on the basis of these assays were scheduled to receive a 1.0-mL (10-μg HBsAg) intramuscular injection of the yeast recombinant vaccine at 0, 1, and 6 months. Postvaccination blood samples for the determination of hepatitis B serological markers, ALT, and yeast antibody were scheduled monthly for seven months and at 9, 12, and 24 months following the first injection.

Vaccinees were asked to take their temperature daily for five days after each injection of vaccine and to report any local or systemic reactions that might occur during this period.

Assays

Standard radioimmunoassay test kits were used for the determination of HBsAg, anti-HBs, and anti-HBc. Titers of anti-HBs were expressed in international milliunits per milliliter using the formulation described by Hollinger et al.[11] A serum sample was considered positive for anti-HBs if the ratio of the sample counts per minute to the negative control serum counts per minute was 2.1 or greater.

Estimates of the proportion of anti-HBs in postvaccination sera specific for the *a* or *d* determinants of HBsAg were based on an assay described by Hoofnagle et al.[12] Briefly, aliquots of each serum sample are incubated with a subtype *ad* HBsAg-positive serum, with a subtype *ay* HBsAg-positive serum, and with normal human serum for two hours at room temperature, and then each mixture is carried through a standard radioimmunoassay to measure residual anti-HBs. Based on the percent of neutralization with the two HBsAg subtype sera when compared with the unneutralized normal human serum, an estimate can be made of the relative amounts of anti-*a* and anti-*d* antibodies present. Since the vaccine is a monovalent-type *adw* preparation, sera will contain either anti-*d* antibodies, anti-*a* antibodies, or a combination of both types, and the amount of neutralization with the HBsAg-*ay* serum is therefore a direct assay for the amount of anti-*a* present. Subtracting the amount of neutralization with the HBsAg-*ay* serum from that found for the HBsAg-*ad* serum then gives an estimate of the amount of anti-*d* present.

A radioimmunoassay was developed to detect yeast antibodies in the sera of vaccine recipients. For this assay, an extract of the parent strain of *S cerevisiae* lacking the plasmid containing the gene for HBsAg was prepared by disrupting a 50% suspension of the cells in a homogenizer and then clarified by centrifugation at 9,000 g followed by passage through a 0.45-mμm membrane filter. The clarified, filtered extract was diluted to a final protein concentration of 80 μg/mL with 0.1 M carbonate buffer and pH 9.6 and adsorbed to ¼-in polystyrene beads overnight at 4 °C. Washed, dried beads were maintained at −20 °C. Two hundred-microliter volumes of sera diluted 1:100, 1:1,000, and 1:10,000 in phosphate-buffered saline containing 0.5% bovine serum albumin and 0.5% Tween 20 were incubated with coated beads for three hours at 37 °C. Following three washes with water, the beads were incubated with 200 μL of iodine 125 protein A (specific activity, 100,000 cpm) for 1.5 hours at 37 °C. The protein A binds and labels any antiyeast antibody on the bead that is of the IgG class. After three additional water washes, the beads were counted and titers of yeast antibody were determined by interpolation from a standard curve derived using dilutions of a hyperimmune guinea pig serum having an antibody titer to parent yeast extract of 1 million.

The serum samples of vaccinees were also measured for changes in preexisting specific yeast antibodies or the appearance of new yeast antibodies using a sodium dodecyl sulfate polyacrylamide gel electrophoresis (reducing), Western blot technique. In this procedure, parent yeast extract is separated on a 12.5% polyacrylamide gel. After transfer to a nitrocellulose sheet, polypeptides from the gel are detected by incubation with a 1:50 dilution of the vaccinee's serum, followed by incubation with ^{125}I protein A and exposure to x-ray film (T. Mason, PhD, oral communication, 1982).

RESULTS

The vaccine has been well tolerated. None of the 37 subjects studied to date has experienced a serious adverse effect attributable to vaccine. There has been no evidence of hepatitis B infection among vaccinees, ie, no elevation of ALT values and no antigenemia. Mild soreness at the injection site generally lasting one to two days was reported by 73% to 80% of vaccinees who received vaccine purified by immune affinity chromatography (lot 934) but by a substantially smaller proportion—20% to 24%—of subjects who received vaccine prepared by hydrophobic interaction chromatography (lot 972) (Table 1). Infrequent systemic complaints occurring within a five-day period following vaccination have included elevated temperature (38.3 to 38.8 °C [101 to 102 °F] oral), fatigue, headache, gastrointestinal disturbance, symptoms of upper respiratory tract infection, and nosebleed.

Table 2 summarizes our observations to date on the human immunogenicity of yeast recombinant hepatitis B vaccine. Fifteen persons (ten men, five women; age range, 23 to 53 years; median age, 33 years) have received all three doses of lot 934 vaccine prepared by the immune affinity chromatography method. Forty percent had a detectable titer of anti-HBs within one month of receiving the first dose. By two months, the proportion of seroconverters rose to 93%, and at three months, all recipients of this vaccine were antibody positive. The geometric mean titer following primary immunization reached a plateau at four months, then increased more than 25-fold following the booster dose at six months.

Table 1.—Proportion (%) of Vaccinees With Clinical Complaints During a Five-Day Period Following Injection of Yeast Recombinant Hepatitis B Vaccine

Nature of Complaint	Vaccine Lot No.	Dose 1	Dose 2	Dose 3
Soreness at injection site	934	12/15 (80)	11/15 (73)	11/15 (73)
	972	5/21 (24)	3/15 (20)	
Systemic* complaints	934	5/15 (33)	3/15 (20)	1/15 (7)
	972	1/21 (5)	2/15 (13)	

*Includes persons with one or more episodes of the following: temperature, 38.3 to 38.8 °C (101 to 102 °F) (two), fatigue (three), gastrointestinal disturbance (four), headache (five), symptoms of upper respiratory tract infection (three), and nosebleed (one).

Table 2.—Seroconversion Frequencies and Geometric Mean Titers (GMTs)* for Anti-HBs Among Initially Seronegative Healthy Adults Receiving 10-μg Doses of Yeast Recombinant Hepatitis B Vaccine†

Vaccine Lot No. (Method of Preparation)	No. of Subjects Vaccinated	Time, mo	Seroconversion Proportion (%)	GMT All Vaccinees‡	GMT Responders Only
934 (Immune affinity chromatography)	15	1	6/15 (40)	1.6	3.9
		2	14/15 (93)	31.7	44.2
		3	15/15 (100)	55.5	55.5
		4	15/15 (100)	78.2	78.2
		5	14/14 (100)	77.2	77.2
		6	15/15 (100)	97.9	97.9
		7	12/12 (100)	1,905.1	1,905.1
972 (Hydrophobic interaction chromatography)	22	1	4/15 (27)	1.4	39.9
		2	8/12 (67)	17.8	105.7
		3	4/5 (80)	56.5	218.5

*In international milliunits per milliliter.
†At 0, 1, and 6 months.
‡All serum samples with titers of less than 0.6 ImU/mL were assigned a value of 0.3 ImU/mL for calculating GMTs.

Table 3.—Percentages of Anti-HBs Specific for *a* and *d* Determinants of HBsAg in Postvaccination Sera*

Vaccine Lot No.	Time, mo	No. of Samples	% Anti-*a* Range	% Anti-*a* Mean	% Anti-*d* Range	% Anti-*d* Mean
934	1	1		47		53
	2	7	87-98	93	2-10	6
	3	10	83-98	88	2-37	13
	4	13	88-98	89	2-35	11
	5	12	89-97	92	2-20	8
	6	6	92-97	94	2-8	5
	7	12	89-100	98	0-11	2
972	1	8	56-91	74	9-44	26
	2	6	87-100	94	0-13	6

*Assay done only on serum samples having an anti-HBs titer of 25 ImU/mL or greater.

Twenty-two subjects have received vaccine from lot 972 made from HBsAg purified by the hydrophobic intraction chromatography method. These vaccinees have not been followed up for as long as the lot 934 recipients, and none has yet received a third dose. Preliminary serological results are shown in Table 2 for 15 of these volunteers (12 men, three women; age range, 24 to 63 years; median age, 40 years). The percentage of seroconverters was 27% at one month, 67% at two months, and 80% at three months. Geometric mean titers within the first three months of follow-up were similar to those observed among recipients of lot 934 vaccine.

Postvaccination serum samples with anti-HBs titers of 25 ImU/mL or greater were assayed to determine the percentage of antibody specific for the *a* and *d* determinants of HBsAg. Table 3 shows the results of these assays. Antibody specific for the *a* determinant predominates. In the interval from two to seven

months following the first dose of vaccine, anti-*a* antibody accounted for approximately 90% of the total anti-HBs.

Earlier studies (unpublished) showed that the yeast recombinant hepatitis B vaccine induced a predominantly anti-*a* form of anti-HBs in African green monkeys and that these antibodies have persisted through two years of follow-up.

Analysis of serum samples from participants in this study has revealed no significant postvaccination increases in yeast antibody titers as measured by radioimmunoassay. By Western blot analysis, each human serum sample shows a unique "fingerprint" spectrum of antibodies to yeast components. There may be only a few or as many as 20 different bands present. Analysis of monthly postvaccination serum samples from participants in this study has shown no change in the yeast antibody pattern for any person as compared with his prevaccination pattern. There has been no appearance of new antibodies in postvaccination sera and no significant increases in the intensity of existing antibody bands.

CONCLUSIONS

The results of this study indicate that an alum-adsorbed hepatitis B vaccine formulated using HBsAg of subtype *adw* synthesized by recombinant yeast cells is safe and immunogenic for man. Seroconversion rates and titers of anti-HBs obtained with the yeast recombinant vaccine in this study are comparable with those observed in earlier studies of healthy adults using vaccine derived from human plasma.[15-17]

Previous studies with hepatitis B vaccine of human plasma origin showed that protection from infection is associated with vaccine-induced anti-HBs.[18-20] Furthermore, one of these trials demonstrated that antibody formed in response to vaccine of HBsAg subtype *ad* provided cross-protection against infection caused by heterologous virus of subtype *ay*.[20] Since the antibody formed by recipients of the yeast recombinant hepatitis B vaccine is predominantly anti-*a*, this vaccine should be protective against all hepatitis B virus subtypes. The efficacy of the yeast vaccine against both homologous *ad* and heterologous *ay* virus challenge in chimpanzees has been demonstrated.[10]

Studies are under way to assess antibody persistence and to determine optimal doses of the yeast recombinant hepatitis B vaccine for both healthy and immunocompromised adults and children.

References

1. Francis DP: Selective primary health care: Strategies for control of disease in the developing world: III. Hepatitis B virus and its related diseases. *Rev Infect Dis* 1983;5:382-389.
2. Gust I: Comparison of the epidemiology of hepatitis A and B, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 129-143.
3. Immunization Practices Advisory Committee: Inactivated hepatitis B virus vaccine. *Ann Intern Med* 1982;97:379-383.
4. Hilleman MR, McAleer WJ, Buynak EB, et al: Quality and safety of human hepatitis B vaccine. *Dev Biol Stand* 1983;54:3-12.
5. Burrell CJ, Mackay P, Greenaway PJ, et al: Expression in *Escherichia coli* of hepatitis B virus DNA sequences cloned in plasmid pBR322. *Nature* 1979;279:43-47.
6. Valenzuela P, Gray P, Quiroga M, et al: Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen. *Nature* 1979;280:815-819.
7. Valenzuela P, Medina A, Rutter WJ, et al: Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298:347-350.
8. Hitzeman RA, Chen CY, Hagie FE, et al: Expression of hepatitis B virus surface antigen in yeast. *Nucleic Acids Res* 1983;11:2745-2763.
9. Miyanohara A, Toh-e A, Nozaki C, et al: Expression of hepatitis B surface antigen gene in yeast. *Proc Natl Acad Sci USA* 1983;80:1-5.
10. McAleer WJ, Buynak EB, Maigetter RZ, et al: Human hepatitis B vaccine from recombinant yeast. *Nature* 1984;307:178-180.
11. Hollinger FB, Adam E, Hoiberg D, et al: Response to hepatitis B vaccine in a young adult population, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 451-465.
12. Hollinger FB, Gerety RJ, Smallwood LA, et al: Subtyping of hepatitis B surface antigen and antibody by radioimmunoassay. *Gastroenterology* 1977;72:280-284.
13. Deinhardt F, Zacheval R, Fresser H, et al: Passive-active immunization against hepatitis B, in Krugman S, Shorlock S (eds): *Proceedings of the European Symposium on Hepatitis*. New York, KPR Infor/Media Corporation, 1981, pp 140-150.
14. Szmuness W, Stevens CE, Harley EJ, et al: The immune response of healthy adults to a reduced dose of hepatitis B vaccine. *J Med Virol* 1981;8:123-130.
15. Krugman S, Holley HP Jr, Davidson M, et al: Immunogenic effect of inactivated hepatitis B vaccine: Comparison of 20 microgram and 40 microgram doses. *J Med Virol* 1981;8:119-121.
16. Hilleman MR, Buynak EB, McAleer WJ, et al: Hepatitis A and hepatitis B vaccines, in Szmuness W, Alter HJ, Maynard JE (eds): *Viral Hepatitis*. Philadelphia, Franklin Institute Press, 1982, pp 385-397.
17. Desmyter J, Colaert J, Verstraete M, et al: Hepatitis B vaccination of hemophiliacs. *Scand J Infect Dis* 1983;38(suppl):42-45.
18. Szmuness W, Stevens EC, Zang EA, et al: A controlled trial of the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981;1:377-385.
19. Francis DP, Hadler SC, Thompson SE, et al: The prevention of hepatitis B with vaccine: Report of the Centers for Disease Control multicenter efficacy trial among homosexual men. *Ann Intern Med* 1982;97:362-366.
20. Szmuness W, Stevens CE, Harley EJ, et al: Hepatitis B vaccine in medical staff of hemodialysis units: Efficacy and subtype cross-protection. *N Engl J Med* 1982;307:1481-1486.

Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA 1984; 251:2812-15.

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STUDY 792

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 792
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine among health care personnel who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625 (10 mcg HBsAg/ml) Lot #979/C-K564 (10 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	Jules L. Dienstag, M.D. Associate Professor of Medicine Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114
SECONDARY INVESTIGATOR:	Eloise Watkins, R.N., M.P.H. Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114 Lynn F. Butterly, M.D. Clinical & Research Fellow Gastrointestinal Unit Massachusetts General Hospital Fruit Street Boston, MA 02114
STUDY LOCATION:	Massachusetts General Hospital Fruit Street Boston, MA 02114
DATE INITIATED:	November 10, 1983.
DATE COMPLETED:	In progress.

Study 792

STUDY POPULATION: The study population consists of 65 health care personnel of either sex (excluding pregnant women), who were negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

PROCEDURE: Eligible participants receive a 1.0 ml (10 mcg HBsAg) intramuscular injection of vaccine produced by the immune affinity or the (b)(4) procedure at 0, 1, and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination and on the day of the first vaccination. Post-vaccination blood samples are obtained monthly for seven months and at 9, 12, and 24 months from subjects vaccinated with lot #934/C-J625. Post-vaccination blood samples are taken at 1, 2, 3, 6, 8, 12, and 24 months from persons injected with vaccine lot #979/C-K564. The samples are assayed for HBsAg, anti-HBc, anti-HBs, yeast antibody and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml are tested for the proportions of anti-a and anti-d activity.

STUDY RESULTS: HEALTH CARE PERSONNEL (b)(4) Vaccine):

10 mcg lot #979/C-K564 at 0, 1, and 6 months

1. Number Vaccinated:

Injection No.		
1	2	3
35	35	32

Study 792

RESULTS: (Cont.)

2. Serologic Results:

Serologic data are available for 28 study participants at nine months. Seroconversion (S/N ≥2.1) for anti-HBs at 9 months was 96% (27/28). Ninety-three percent (26/28) of the participants developed protective levels of anti-HBs (mIU/ml ≥10) at that time. The GMT at nine months was 531.1 mIU/ml for all vaccinees and 826.3 mIU/ml for responders with a titer of mIU/ml ≥10.

Among participants with serology data at 12 months, 83% (20/24) were positive for anti-HBs (mIU/ml ≥10). The GMT at that time was 234.1 mIU/ml for all vaccinees and 403.0 mIU/ml for responders with a titer of mIU/ml ≥10.

See Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for all participants after each injection. The overall frequencies of complaints are presented below.

Type of Complaint	Frequency in % by Injection No. 1	2	3
Injection Site	20(7/35)	23(8/35)	25(8/32)
Systemic	14(5/35)	11(4/35)	9(3/32)

Refer to Table 2 for listings of specific clinical complaints by injection number. Maximum temperature data are provided in Table 3.

There were no serious or alarming reactions attributable to the vaccine.

PUBLICATION:

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

Table 1

ANTIBODY RESPONSES FOLLOWING VACCINATION WITH RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
POPULATION : HEALTH CARE PERSONNEL
DOSE : 10 MCG
LOT : CK564
REGIMEN : 0, 1, AND 6 MONTHS
INITIAL SEROLOGY: NEGATIVE

TIME (MONTHS)	% WITH ANTI-HBS				GMT (MIU/ML)		
	S/N >= 2.1		MIU/ML >= 10		ALL VACCINEES	RESPONDERS S/N >= 2.1	RESPONDERS MIU/ML >= 10
1 MONTH	29%	(10/34)	5.9%	(2/34)	1.1	7.2	78.6
2 MONTHS	88%	(28/32)	75%	(24/32)	24.5	43.4	65.9
3 MONTHS	91%	(29/32)	81%	(26/32)	45.1	63.4	83.3
6 MONTHS	97%	(29/30)	97%	(29/30)	72.4	84.0	84.0
9 MONTHS	96%	(27/28)	93%	(26/28)	531.1	672.7	826.3
12 MONTHS	92%	(22/24)	83%	(20/24)	234.1	403.0	403.0

Table 2
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 1 — DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	6 (17.1%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	7 (20.0%)
PAIN	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
SORENESS	5 (14.3%)	2 (5.7%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	6 (17.1%)
SYSTEMIC	2 (5.7%)	3 (8.6%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	1 (2.9%)	5 (14.3%)
WHOLE BODY/GENERAL	1 (2.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	4 (11.4%)
SWEATING	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
MALAISE	0 (0.0%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
HEADACHE	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	2 (5.7%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
MUSCULOSKELETAL	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
MYALGIA	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	0 (0.0%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NAUSEA	0 (0.0%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NERVOUS SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
VERTIGO/DIZZINESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	8 (22.9%)	5 (14.3%)	3 (8.6%)	2 (5.7%)	0 (0.0%)	1 (2.9%)	11 (31.4%)
PERSONS WITH NO COMPLAINTS	27 (77.1%)	30 (85.7%)	32 (91.4%)	33 (94.3%)	35 (100.0%)	34 (97.1%)	24 (68.6%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (35 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	7 (20.0%)	2 (5.7%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
SORENESS	7 (20.0%)	2 (5.7%)	2 (5.7%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
SYSTEMIC	2 (5.7%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	4 (11.4%)
WHOLE BODY/GENERAL	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
HEADACHE	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	2 (5.7%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NERVOUS SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
VERTIGO/DIZZINESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	7 (20.0%)	2 (5.7%)	3 (8.6%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	9 (25.7%)
PERSONS WITH NO COMPLAINTS	28 (80.0%)	33 (94.3%)	32 (91.4%)	34 (97.1%)	34 (97.1%)	35 (100.0%)	26 (74.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 3 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	6 (18.8%)	3 (9.4%)	3 (9.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (25.0%)
PAIN	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
SORENESS	5 (15.6%)	1 (3.1%)	2 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (18.8%)
TENDERNESS	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
PRURITIS (ITCHING)	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
SYSTEMIC	1 (3.1%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	3 (9.4%)
WHOLE BODY/GENERAL	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
HEADACHE	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	2 (6.3%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (3.1%)	1 (3.1%)
MUSCULOSKELETAL	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (32 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
MYALGIA	1 (3.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
PERSONS WITH COMPLAINTS	6 (18.8%)	3 (9.4%)	3 (9.4%)	1 (3.1%)	1 (3.1%)	1 (3.1%)	9 (28.1%)
PERSONS WITH NO COMPLAINTS	26 (81.3%)	29 (90.6%)	29 (90.6%)	31 (96.9%)	31 (96.9%)	31 (96.9%)	23 (71.9%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (35 PATIENTS) - DOSE 1 — DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0	1	2	3	4	5			
< 99	25 (71.4%)	28 (84.8%)	31 (88.6%)	31 (91.2%)	26 (76.5%)	25 (75.8%)			15 (42.9%)
99 - 99.9	10 (28.6%)	4 (12.1%)	3 (8.6%)	3 (8.8%)	8 (23.5%)	8 (24.2%)			18 (51.4%)
100 - 100.9	0 (0.0%)	1 (3.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			2 (5.7%)
TEMPERATURE TAKEN	35 (100.0%)	33 (94.3%)	35 (100.0%)	34 (97.1%)	34 (97.1%)	33 (94.3%)			35 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	2 (5.7%)	0 (0.0%)	1 (2.9%)	1 (2.9%)	2 (5.7%)			0 (0.0%)

Table 3 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (35 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	27 (79.4%)	30 (85.7%)	30 (85.7%)	31 (88.6%)	26 (76.5%)	31 (91.2%)			18 (51.4%)
99 - 99.9	7 (20.6%)	5 (14.3%)	5 (14.3%)	4 (11.4%)	7 (20.6%)	3 (8.8%)			16 (45.7%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)			1 (2.9%)
TEMPERATURE TAKEN	34 (97.1%)	35 (100.0%)	35 (100.0%)	35 (100.0%)	34 (97.1%)	34 (97.1%)			35 (100.0%)
TEMPERATURE NOT TAKEN	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (2.9%)			0 (0.0%)

Table 3 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0792
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (32 PATIENTS) - DOSE 3							
	DAYS POST VACCINATION							NUMBER WITH MAX TEMP
	0	1	2	3	4	5		
< 99	28 (90.3%)	28 (93.3%)	28 (93.3%)	28 (93.3%)	22 (81.5%)	27 (93.1%)		21 (65.6%)
99 - 99.9	2 (6.5%)	2 (6.7%)	2 (6.7%)	2 (6.7%)	5 (18.5%)	2 (6.9%)		10 (31.3%)
100 - 100.9	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.1%)
TEMPERATURE TAKEN	31 (96.9%)	30 (93.8%)	30 (93.8%)	30 (93.8%)	27 (84.4%)	29 (90.6%)		32 (100.0%)
TEMPERATURE NOT TAKEN	1 (3.1%)	2 (6.3%)	2 (6.3%)	2 (6.3%)	5 (15.6%)	3 (9.4%)		0 (0.0%)

RECOMBINANT YEAST HEPATITIS B VACCINE: IMMUNOGENICITY AND SAFETY. JL Dienstag, E Watkins, and CA Hinkle.
Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

Cumbersome to produce, expensive, and limited in supply, currently available human plasma-derived hepatitis B vaccines are likely to be replaced in the future by "genetically engineered" vaccines. Recently, a recombinant DNA vaccine was prepared in recombinant yeast Saccharomyces cerevisiae strain 2150-2-3 cells transformed with the plasmid pHBS 56-CAP347/33, containing the gene for hepatitis B surface antigen (HBsAg/ad) (Valenzuela et al. Nature 1982; 298:347-50). Purified by biochemical and biophysical methods from the yeast extract, the HBsAg particles synthesized by these yeast cells are not glycosylated but otherwise are indistinguishable from native 22 nm HBsAg particles. Treated with formalin and adsorbed to alum, the recombinant vaccine is immunogenic and protective in experimental animals. We administered three 10 µg doses of the recombinant hepatitis B vaccine (Merck Sharp & Dohme Research Laboratories) at time 0, 1, and 6 months to 60 seronegative adult health workers. The frequency and geometric mean titer (mIU/ml) of anti-HBs responses were as follows:

Month	1	2	3	4	5	6
Number	37	29	30	29	25	16
anti-HBs+	41%	83%	93%	97%	96%	94%
GMT ± SD	7 ± 2	33 ± 5	36 ± 6	46 ± 6	55 ± 6	79 ± 6

94 ± 9 (mean ± SD) % of the anti-HBs was specific for the a determinant of HBsAg. Changes in antibodies to yeast antigens were negligible. The most frequent adverse reaction was transient soreness at the injection site, occurring after 52% of first, 37% of second, and 55% of third injections. No serious adverse effects were encountered, and neither type B nor non-B hepatitis has occurred in any vaccinee. These preliminary results demonstrate that the recombinant yeast hepatitis B vaccine is safe and that 10 µg of the recombinant vaccine is equivalent in immunogenicity to 20 µg of the plasma-derived vaccine.

Dienstag JL, Watkins E, Hinkle CA. Recombinant yeast hepatitis B vaccine: immunogenicity and safety. Hepatology 1984; 4:1077 (Abstract).

STUDY 794

PROGRAM:	Yeast Recombinant Hepatitis B Vaccine, Study 794
PURPOSE:	To evaluate antibody and clinical responses to the vaccine among: 1. health care personnel who are negative for hepatitis B virus serologic markers. 2. health care personnel immunized with plasma derived vaccine who were nonresponders (anti-HBs negative)
VACCINE:	Yeast Recombinant Hepatitis B Vaccine: Lot #972/C-K444 (10 mcg/HBsAg ml)
PRIMARY INVESTIGATOR:	Harvey J. Alter, M.D. Chief, Immunology Section Clinical Center Blood Bank National Institutes of Health Bethesda, Maryland
SECONDARY INVESTIGATOR:	David Henderson, M.D. James Schmitt, M.D. Ms. Deloris Koziol Ms. Beverly Elder
STUDY LOCATION:	Clinical Center Blood Bank National Institute of Health Bethesda, Maryland 20205
DATE INITIATED:	April 12, 1984
DATE COMPLETED:	In progress
STUDY POPULATION:	The study population consists of 71 health care personnel of either sex (excluding pregnant women) who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine. It also includes 11 nonresponders to plasma-derived vaccine.

Study 794

PROCEDURE:

Health care workers receive either 5 mcg or 10 mcg doses of vaccine at 0, 1 and 6 months. Nonresponders receive 10 mcg doses at 0, 1 and 6 months. All injections are intramuscular. Participants are asked to record their temperature for 5 days after each injection and note any local or systemic reactions.

Blood specimens are obtained prior to vaccination, and monthly for 7 months and at 9, 12 and 24 months post initial injection. All samples are assayed for anti-HBs, anti-HBc, HBsAg and ALT by Dr. Alter. Samples with anti-HBs titers $\geq$ 25 mIU/ml may be tested for anti-a and anti-d activity at MSDRL.

RESULTS:

HEALTH CARE PERSONNEL:

10 mcg Lot #972/C-K444 at 0, 1 and 6 months
5 mcg Lot #972/C-K444 at 0, 1 and 6 months

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
10 mcg	41	40	40
5 mcg	30	30	28

2. Serologic Results:

Serologic data are available for 36 study participants who received 10 mcg injections and for 25 who received 5 mcg injections at 7/8 months. Seroconversion at 7/8 months was 94% (34/36) S/N $\geq$10 among those receiving 10 mcg doses, with a GMT of 160.8 and 209.3 for all vaccinees and responders, respectively.

Among the recipients of 5 mcg doses, 76% (19/25) had seroconverted, with GMT's of 54 and 152.9 respectively. Table 1 shows seroconversion rates and GMT's for up to 12 months of follow-up.

Study 794

RESULTS: (Cont.)

3. Clinical Complaints:

Clinical follow-up data are available for 41, 40, and 40 participants following the first, second and third injections of 10 mcg doses, and for 30, 30, and 28 participants following the first, second and third injections of 5 mcg doses. Specific complaints and maximum temperatures reported during the 5 days following each injection are provided in Tables 2 through 5.

Type of Complaint	Dose Level	Frequency in % by Injection 1	2	3
Injection Site	10 mcg	25(10/42)	8(3/40)	23(9/40)
	5 mcg	13(4/30)	10(3/30)	14(4/28)
Systemic	10 mcg	18(7/41)	18(7/40)	10(4/40)
	5 mcg	17(5/30)	13(4/30)	14(4/28)

There were no serious or alarming adverse reactions attributable to vaccine.

ALT Elevations:

Two subjects who received 10 mcg doses of vaccine had transient elevation of ALT (1.5 - 4.0 times the upper limit of normal) one to two months after the second dose. Within one to two months of the elevations, the ALT levels returned to normal. A reason for the ALT elevations has not been discovered. The subjects have not shown any clinical or serologic signs (HBsAg or anti-HBc) of hepatitis B.

Table 1

Antibody Responses Among Health Care Personnel Following Vaccination
with 10 or 5 mcg Doses of Yeast Recombinant Hepatitis B Vaccine
Lots #972/C-K444 at 0, 1, and 6 Months in Study #794

	10 mcg					5 mcg				
	% with Anti-HBs		GMT (S/N)			% with Anti-HBs		GMT (S/N)		
Time (Months)	S/N ≥ 2.1	S/N ≥ 10	All Vaccinees	S/N ≥ 2.1	S/N ≥ 10	S/N ≥ 2.1	S/N ≥ 10	All Vaccinees	S/N ≥ 2.1	S/N ≥ 10
1	29(11/38)	18(7/38)	2.3	15.2	35.7	31(9/29)	14(4/29)	2.1	8.9	33.3
2	83(29/35)	54(19/35)	16.4	28.7	75.5	74(20/27)	48(13/27)	8.4	17.2	37.9
3	79(26/33)	61(20/33)	17.7	36.8	73.6	79(23/29)	59(17/29)	12.6	23.8	40.5
6	89(32/36)	69(25/36)	27.5	41.2	78.8	81(21/26)	69(18/26)	14.2	26.2	35.3
7	97(35/36)	94(34/36)	160.8	185.4	209.3	84(21/25)	76(19/25)	54.0	113.4	152.9
9	97(34/35	94(33/35)	132.7	152.8	166.5	83(19/23)	78(18/23)	44.9	98.1	119.5
12	97(33/34)	97(33/34)	99.2	113.7	113.7	83(19/23)	78(18/23)	44.5	96.9	113.5

Table 2

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (41 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	7 (17.5%)	7 (17.5%)	4 (10.0%)	2 (5.0%)	2 (5.0%)	1 (2.5%)	10 (25.0%)
INFLAMMATION	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PAIN	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
SORENESS	6 (15.0%)	5 (12.5%)	3 (7.5%)	2 (5.0%)	2 (5.0%)	1 (2.5%)	8 (20.0%)
TENDERNESS	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PRURITIS (ITCHING)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
SYSTEMIC	3 (7.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	1 (2.5%)	2 (5.0%)	7 (17.5%)
WHOLE BODY/GENERAL	3 (7.5%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	5 (12.5%)
SWEATING	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
FATIGUE/WEAKNESS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
MALAISE	2 (5.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	4 (10.0%)
HEADACHE	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)

00200

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (41 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
MUSCULOSKELETAL	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	2 (5.0%)
MYALGIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (2.5%)
ARTHRITIS	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
CLAY-COLORED STOOLS	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PERSONS WITH COMPLAINTS	10 (25.0%)	9 (22.5%)	5 (12.5%)	2 (5.0%)	3 (7.5%)	3 (7.5%)	16 (40.0%)
PERSONS WITH NO COMPLAINTS	30 (75.0%)	31 (77.5%)	35 (87.5%)	38 (95.0%)	37 (92.5%)	37 (92.5%)	24 (60.0%)
PERSONS WITH NO DATA	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)	1 (2.4%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	3 (7.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.5%)
SORENESS	2 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
TENDERNESS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PRURITIS (ITCHING)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
SYSTEMIC	3 (7.5%)	2 (5.0%)	2 (5.0%)	1 (2.5%)	1 (2.6%)	2 (5.3%)	7 (17.5%)
WHOLE BODY/GENERAL	3 (7.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	1 (2.6%)	6 (15.0%)
SWEATING	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
FLUSH	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
FATIGUE/WEAKNESS	1 (2.5%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
MALAISE	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	2 (5.0%)
HEADACHE	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
ECCHYMOSES	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
DIGESTIVE SYSTEM	1 (2.5%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
ABDOMINAL PAINS/CRAMPS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
DIARRHEA	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
NAUSEA	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
CLAY-COLORED STOOLS	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
NERVOUS SYSTEM	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	2 (5.0%)
VERTIGO/DIZZINESS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
TREMOR	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.6%)	1 (2.5%)
PERSONS WITH COMPLAINTS	6 (15.0%)	2 (5.0%)	2 (5.0%)	1 (2.5%)	1 (2.6%)	2 (5.3%)	10 (25.0%)
PERSONS WITH NO COMPLAINTS	34 (85.0%)	38 (95.0%)	38 (95.0%)	39 (97.5%)	38 (97.4%)	36 (94.7%)	30 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (2.6%)	0 (0.0%)

00203

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	8 (20.0%)	3 (7.5%)	2 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (22.5%)
PAIN	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
SORENESS	5 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (12.5%)
TENDERNESS	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
PAPULE(S)	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PRURITIS (ITCHING)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
ECCHYMOSIS	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
SYSTEMIC	2 (5.0%)	1 (2.5%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	4 (10.0%)
WHOLE BODY/GENERAL	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
FATIGUE/WEAKNESS	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
MALAISE	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)

Table 2 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (40 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	2 (5.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
LOOSE STOOL	0 (0.0%)	0 (0.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
CLAY-COLORED STOOLS	0 (0.0%)	0 (0.0%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
PERSONS WITH COMPLAINTS	9 (22.5%)	3 (7.5%)	4 (10.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)	10 (25.0%)
PERSONS WITH NO COMPLAINTS	31 (77.5%)	37 (92.5%)	36 (90.0%)	39 (97.5%)	40 (100.0%)	40 (100.0%)	30 (75.0%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 3

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (41 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
NORMAL	5 (12.5%)	6 (16.7%)	6 (16.2%)	6 (16.2%)	6 (16.7%)	6 (18.2%)		5 (12.5%)
< 99	30 (75.0%)	29 (80.6%)	30 (81.1%)	30 (81.1%)	29 (80.6%)	27 (81.8%)		27 (67.5%)
99 - 99.9	5 (12.5%)	1 (2.8%)	1 (2.7%)	0 (0.0%)	1 (2.8%)	0 (0.0%)		7 (17.5%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)		1 (2.5%)
TEMPERATURE TAKEN	40 (97.6%)	36 (87.8%)	37 (90.2%)	37 (90.2%)	36 (87.8%)	33 (80.5%)		40 (97.6%)
TEMPERATURE NOT TAKEN	1 (2.4%)	5 (12.2%)	4 (9.8%)	4 (9.8%)	5 (12.2%)	8 (19.5%)		1 (2.4%)

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (40 PATIENTS) - DOSE 2								DAYS POST VACCINATION								NUMBER WITH MAX TEMP
	0		1		2		3		4		5						
NORMAL	5	(12.5%)	5	(13.5%)	5	(13.9%)	5	(13.5%)	5	(15.2%)	6	(17.6%)					5 (12.5%)
< 99	32	(80.0%)	31	(83.8%)	30	(83.3%)	31	(83.8%)	26	(78.8%)	26	(76.5%)					29 (72.5%)
99 - 99.9	3	(7.5%)	1	(2.7%)	1	(2.8%)	1	(2.7%)	2	(6.1%)	2	(5.9%)					6 (15.0%)
TEMPERATURE TAKEN	40	(100.0%)	37	(92.5%)	36	(90.0%)	37	(92.5%)	33	(82.5%)	34	(85.0%)					40 (100.0%)
TEMPERATURE NOT TAKEN	0	(0.0%)	3	(7.5%)	4	(10.0%)	3	(7.5%)	7	(17.5%)	6	(15.0%)					0 (0.0%)

00207

Table 3 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK464
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (40 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
NORMAL	8 (20.0%)	8 (20.5%)	8 (21.6%)	8 (21.1%)	8 (21.1%)	8 (20.5%)			8 (20.0%)
< 99	30 (75.0%)	29 (74.4%)	26 (70.3%)	29 (76.3%)	28 (73.7%)	30 (76.9%)			26 (65.0%)
99 - 99.9	2 (5.0%)	2 (5.1%)	3 (8.1%)	1 (2.6%)	2 (5.3%)	1 (2.6%)			6 (15.0%)
TEMPERATURE TAKEN	40 (100.0%)	39 (97.5%)	37 (92.5%)	38 (95.0%)	38 (95.0%)	39 (97.5%)			40 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	1 (2.5%)	3 (7.5%)	2 (5.0%)	2 (5.0%)	1 (2.5%)			0 (0.0%)

Table 4

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0796
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1 — DAYS POST VACCINATION 0	1	2	3	4	5	NUMBER WITH COMPLAINTS
REACTION, LOCAL (INJECT. SITE)	4 (13.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (13.3%)
PAIN	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
SORENESS	2 (6.7%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (10.0%)
ERYTHEMA (REDNESS)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
STIFFNESS/TIGHTNESS	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
SYSTEMIC	1 (3.3%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	3 (10.3%)	2 (6.9%)	5 (16.7%)
WHOLE BODY/GENERAL	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	3 (10.3%)	1 (3.4%)	4 (13.3%)
SENSATION OF WARMTH, GENERAL	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
FATIGUE/WEAKNESS	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
MALAISE	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	2 (6.9%)	0 (0.0%)	2 (6.7%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	0 (0.0%)	1 (3.3%)
SYSTEMIC INFECTION	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.4%)	1 (3.3%)

00209

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
RESPIRATORY	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
DIGESTIVE SYSTEM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.3%)
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)	1 (3.3%)
PERSONS WITH COMPLAINTS	5 (16.7%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	3 (10.3%)	2 (6.9%)	8 (26.7%)
PERSONS WITH NO COMPLAINTS	25 (83.3%)	27 (90.0%)	28 (93.3%)	29 (100.0%)	26 (89.7%)	27 (93.1%)	22 (73.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.3%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (10.0%)
PAIN	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
SORENESS	1 (3.3%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
SYSTEMIC	3 (10.0%)	1 (3.3%)	3 (10.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	4 (13.3%)
WHOLE BODY/GENERAL	3 (10.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	3 (10.0%)
CHILLS	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (3.3%)
MALAISE	1 (3.3%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
HEADACHE	2 (6.7%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
AXILLARY AREA SORE	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)
DIGESTIVE SYSTEM	0 (0.0%)	1 (3.3%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.3%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (30 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
NAUSEA	0 (0.0%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
PERSONS WITH COMPLAINTS	3 (10.0%)	2 (6.7%)	4 (13.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)		5 (16.7%)
PERSONS WITH NO COMPLAINTS	27 (90.0%)	28 (93.3%)	26 (86.7%)	30 (100.0%)	30 (100.0%)	29 (96.7%)		25 (83.3%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0796
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.6%)	3 (10.7%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (14.3%)
SORENESS	1 (3.6%)	3 (10.7%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (14.3%)
SYSTEMIC	2 (7.1%)	3 (10.7%)	1 (3.6%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	4 (14.3%)
WHOLE BODY/GENERAL	2 (7.1%)	3 (10.7%)	1 (3.6%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	4 (14.3%)
FATIGUE/WEAKNESS	0 (0.0%)	1 (3.6%)	1 (3.6%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	1 (3.6%)
MALAISE	0 (0.0%)	2 (7.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (7.1%)
HEADACHE	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
SWOLLEN ANKLES	1 (3.6%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
NERVOUS SYSTEM	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
VERTIGO/DIZZINESS	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)
PERSONS WITH COMPLAINTS	2 (7.1%)	6 (21.4%)	2 (7.1%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	7 (25.0%)
PERSONS WITH NO COMPLAINTS	26 (92.9%)	22 (78.6%)	26 (92.9%)	28 (100.0%)	27 (96.4%)	28 (100.0%)	21 (75.0%)

Table 4 (cont.)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK464
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (28 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE I: DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH MAX TEMP
NORMAL	1 (3.3%)	1 (3.3%)	1 (3.4%)	1 (3.6%)	1 (3.6%)	1 (3.4%)		1 (3.3%)
< 99	25 (83.3%)	24 (80.0%)	26 (89.7%)	24 (85.7%)	22 (78.6%)	24 (82.8%)		17 (56.7%)
99 - 99.9	4 (13.3%)	5 (16.7%)	2 (6.9%)	2 (7.1%)	5 (17.9%)	4 (13.8%)		11 (36.7%)
100 - 100.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)		1 (3.3%)
TEMPERATURE TAKEN	30 (100.0%)	30 (100.0%)	29 (96.7%)	28 (93.3%)	28 (93.3%)	29 (96.7%)		30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (3.3%)	2 (6.7%)	2 (6.7%)	1 (3.3%)		0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0794
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (30 PATIENTS) - DOSE 2												NUMBER WITH MAX TEMP
	DAYS POST VACCINATION												
	0	1	2	3	4	5							
NORMAL	2 (6.7%)	2 (6.7%)	2 (6.7%)	2 (7.1%)	2 (6.7%)	2 (6.7%)							2 (6.7%)
< 99	24 (80.0%)	24 (80.0%)	24 (80.0%)	24 (85.7%)	27 (90.0%)	26 (86.7%)							19 (63.3%)
99 - 99.9	4 (13.3%)	2 (6.7%)	4 (13.3%)	2 (7.1%)	1 (3.3%)	2 (6.7%)							7 (23.3%)
100 - 100.9	0 (0.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)							2 (6.7%)
TEMPERATURE TAKEN	30 (100.0%)	30 (100.0%)	30 (100.0%)	28 (93.3%)	30 (100.0%)	30 (100.0%)							30 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.7%)	0 (0.0%)	0 (0.0%)							0 (0.0%)

Table 5 (cont.)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0796
TREATMENT :
LOT NUMBER : CK444
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (28 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	4 (14.3%)	4 (14.3%)	4 (14.8%)	4 (14.3%)	4 (14.3%)	4 (14.3%)		4 (14.3%)
< 99	20 (71.4%)	21 (75.0%)	21 (77.8%)	21 (75.0%)	21 (75.0%)	22 (78.6%)		19 (67.9%)
99 - 99.9	4 (14.3%)	3 (10.7%)	2 (7.4%)	3 (10.7%)	3 (10.7%)	2 (7.1%)		5 (17.9%)
TEMPERATURE TAKEN	28 (100.0%)	28 (100.0%)	27 (96.4%)	28 (100.0%)	28 (100.0%)	28 (100.0%)		28 (100.0%)
TEMPERATURE NOT TAKEN	0 (0.0%)	0 (0.0%)	1 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 795
PURPOSE:	To evaluate antibody and clinical responses to yeast recombinant hepatitis B vaccine by health care personnel and other healthy adults negative for hepatitis B serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #934/C-J625 (10mcg HBsAg/ml) Lot #979/C-K564 (10mcg HBsAg/ml) Lot #81990 D/18066/C-L215 (10 mcg HBsAg/0.5 ml)
PRINCIPAL INVESTIGATOR:	Prof. Dr. Friedrich Deinhardt Max v. Pettenkofer Institut Pettenkoferstrasse 9a 8000 Muenchen 2 WEST GERMANY
SECONDARY INVESTIGATORS:	Dr. W. Jilg Dr. R. Zachoval Dr. G. Zoulek Dr. M. Kroner Dr. J. Abb Dr. B. Lorbeer The above secondary investigators have the same address as the principal investigator. Dr. U. Bienzle Landesinstitut fuer Tropenmedizin Ansbacherstr. 5 D-1000 Berlin 30 WEST GERMANY
STUDY LOCATIONS:	Max V. Pettenkofer Institut Pettenkoferstrasse 9a 8000 Muenchen 9a WEST GERMANY Landesinstitut fuer Tropenmedizin Ansbacherstr. 5 D-1000 Berlin 30 WEST GERMANY

Study 795

DATE INITIATED: November 21, 1983.

DATE COMPLETED: In progress.

STUDY POPULATION: The study population consists of approximately 300 health care personnel and other healthy adults of either sex (excluding pregnant women), who are negative for HBsAg, anti-HBc and anti-HBs, have a normal ALT level and have not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Eligible participants receive a 10 mcg intramuscular injection of vaccine produced by the immune affinity or (b)(4) procedure at 0, 1, and 6 months. Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (10-15 ml) was obtained from each participant approximately two weeks before the first vaccination and on the day of the first vaccination. Post-vaccination blood samples are obtained monthly for seven months and at 9, 12, and 24 months from recipients of lot #934/C-J625 vaccine. Recipients of lots #979/C-K564 and #81990D/18066/C-L215 are bled at 1, 2, 3, 6, 8, 12, and 24 months. The samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples with anti-HBs titers $\geq$ 25 mIU/ml may be tested for the proportions of anti-a and anti-d activity. Samples may also be assayed for yeast antibody.

RESULTS: HEALTH CARE PERSONNEL/OTHER HEALTHY ADULTS
(b)(4) Vaccine):

10 mcg Lot #979/C-K564 at 0, 1, and 6 months
10 mcg Lot #81990D/18066/C-L215 at 0, 1, and 6 months

Study 795

RESULTS: (Contd)

1. Number Vaccinated:

Vaccine Lot	Injection No. 1	2	3
Lot C-K564	148	146	126
Lot C-L215	97	97	94

2. Serologic Results:

Serologic data are available for 76 participants, who received vaccine from lot C-K564, at 7/8 months. At that time, 100% (76/76) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10). The GMT at 7/8 months for all vaccinees and for responders (either cutoff) it was 2143.1 mIU/ml.

Seven/eight month serologic data are available for 80 participants who received vaccine from lot C-L215. Ninety-nine percent (79/80) of the subjects seroconverted (S/N $\geq$2.1) and developed protective levels of anti-HBs (mIU/ml $\geq$10) at that time. The GMT was 2436.1 mIU/ml and 2655.2 mIU/ml for all vaccinees, while it was 2655.2 mIU/ml for responders (either cutoff).

Refer to Table 1 for anti-HBs responses and GMTs for other time intervals.

3. Clinical Complaints:

Clinical follow-up data are available for 126, 94 and 74 participants, who received lot C-K564 vaccine, after injection number 1, 2, and 3, respectively. Follow-up data are available for 96, 83 and 57 subjects, who received lot C-L215 vaccine, after injection number 1, 2, and 3, respectively. The overall frequencies of complaints follow.

Study 795

RESULTS (CONT.):

Type of Complaint	Vaccine Lot	Frequency in % by Injection No. 1	2	3
Injection Site	C-K564	30(38/126)	29(27/94)	22(16/74)
	C-L215	16(15/96)	5(4/83)	19(11/57)
Systemic	C-K564	18(22/126)	17(16/94)	12(9/74)
	C-L215	15(14/96)	8(7/83)	9(5/57)

Refer to Tables 2 and 3 for listings of specific complaints after each injection. Maximum temperature data are presented in Tables 4 amd 5.

There were serious or alarming reactions attributable to vaccine.

HBV Markers (Anti-HBc)

One subject who was positive for anti-HBc prior to vaccination, continued to be transiently positive for anti-HBc post-vaccination. The subject was negative for HBsAg and did not seroconvert for anti-HBs as of five months after enrollment in the study.

ALT Elevations

Two subjects with normal pre-vaccination ALT levels, developed elevated ALT levels (1.5-2.0 times the upper limit of normal) one month after the first injection and one month after the third injection, respectively. Another participant with an unknown pre-vaccination ALT level, developed an elevated ALT level (2.0 times the upper limit of normal) one month after the second injection. All three subjects received vaccine lot C-L215. They were negative for anti-HBc and HBsAg and were not clinically ill.

One subject with an elevated pre-vaccination ALT level (1.5 x the upper limit of normal) continued to have a similar elevation one month after the first injection of vaccine (Lot C-L215). He was negative for anti-HBc and HBsAg and was not ill.

Table 1

Antibody Responses Among Health Care Personnel Following Vaccination with
10 mcg Injections of Yeast Recombinant Hepatitis B Vaccine
Lots #979/C-K564 and #819900/18066/C-L215 at 0, 1, and 6 Months in Study #795

	10 mcg (lot #979/C-K564)					10 mcg (lot #819900/18066/C-L215)				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders	
Time (Mos.)	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	28 (36/129)	22 (29/129)	1.1	33.2	47.4	23 (22/96)	20 (19/96)	0.8	26.1	31.1
2	83 (99/119)	66 (79/119)	20.3	41.7	66.9	71 (66/93)	58 (54/69)	8.3	32.5	44.8
3	91 (79/87)	85 (74/87)	40.2	60.6	69.2	90 (62/69)	78 (54/69)	31.8	46.0	62.1
6	95 (112/118)	92 (109/118)	71.2	87.6	93.3	94 (83/88)	88 (77/88)	47.6	62.6	73.9
7/8	100 (76/76)	100 (76/76)	2143.1	2143.1	2143.1	99 (79/80)	99 (79/80)	2436.1	2655.2	2655.2

00222

Table 2
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (140 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	36 (28.6%)	11 (8.7%)	6 (4.8%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	38 (30.2%)
PAIN	25 (19.8%)	8 (6.3%)	4 (3.2%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	27 (21.4%)
SORENESS	7 (5.6%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (5.6%)
TENDERNESS	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)
SWELLING	1 (0.8%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
ECCHYMOSIS	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
OTHER	3 (2.4%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.4%)
SYSTEMIC	11 (8.7%)	9 (7.1%)	7 (5.6%)	5 (4.0%)	2 (1.6%)	4 (3.2%)	22 (17.5%)
WHOLE BODY/GENERAL	8 (6.3%)	9 (7.1%)	7 (5.6%)	5 (4.0%)	2 (1.6%)	4 (3.2%)	19 (15.1%)
CHILLS	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
SWEATING	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (148 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
FATIGUE/WEAKNESS	4 (3.2%)	4 (3.2%)	3 (2.4%)	2 (1.6%)	0 (0.0%)	1 (0.8%)	10 (7.9%)
HEADACHE	3 (2.4%)	4 (3.2%)	3 (2.4%)	1 (0.8%)	1 (0.8%)	3 (2.4%)	10 (7.9%)
CHEST PAIN	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
ILLNESS, NOS	2 (1.6%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.6%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
RHINITIS	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)	1 (0.8%)
MUSCULOSKELETAL	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
MYALGIA	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)
DIGESTIVE SYSTEM	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	3 (2.4%)
NAUSEA	2 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	3 (2.4%)
PERSONS WITH COMPLAINTS	40 (31.7%)	18 (14.3%)	12 (9.5%)	6 (4.8%)	2 (1.6%)	4 (3.2%)	49 (38.9%)
PERSONS WITH NO COMPLAINTS	86 (68.3%)	108 (85.7%)	114 (90.5%)	120 (95.2%)	124 (98.4%)	121 (96.8%)	77 (61.1%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (148 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH NO DATA	21 (14.3%)	21 (14.3%)	21 (14.3%)	21 (14.3%)	21 (14.3%)	21 (14.4%)	21 (14.3%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (146 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	20 (21.3%)	17 (18.1%)	7 (7.4%)	3 (3.2%)	1 (1.1%)	0 (0.0%)		27 (28.7%)
PAIN	13 (13.8%)	8 (8.5%)	3 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		16 (17.0%)
SORENESS	2 (2.1%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (3.2%)
TENDERNESS	1 (1.1%)	1 (1.1%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
ERYTHEMA (REDNESS)	1 (1.1%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
STIFFNESS/TIGHTNESS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
PRURITIS (ITCHING)	1 (1.1%)	2 (2.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
NUMBNESS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
LYMPHADENOPATHY, REGIONAL	0 (0.0%)	2 (2.1%)	2 (2.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
ECCHYMOSIS	1 (1.1%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	0 (0.0%)		2 (2.1%)
PARESTHESIA	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
SYSTEMIC	9 (9.6%)	8 (8.5%)	4 (4.3%)	2 (2.1%)	2 (2.1%)	0 (0.0%)		16 (17.0%)

Table 2 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (146 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
WHOLE BODY/GENERAL	8 (8.5%)	5 (5.3%)	3 (3.2%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	13 (13.0%)
FATIGUE/WEAKNESS	4 (4.3%)	5 (5.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (6.4%)
HEADACHE	4 (4.3%)	1 (1.1%)	2 (2.1%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	8 (8.5%)
ILLNESS, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	1 (1.1%)
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	1 (1.1%)
RESPIRATORY	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
UPPER RESPIRATORY INFECT., NOS	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
HEMIC AND LYMPHATIC	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
LYMPHADENOPATHY, CERVICAL	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
DIGESTIVE SYSTEM	1 (1.1%)	2 (2.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.2%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)
NAUSEA	1 (1.1%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.2%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (146 PATIENTS) - DOSE 2							
	DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
VOMITING	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.1%)
NERVOUS SYSTEM	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
VERTIGO/DIZZINESS	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.1%)
PERSONS WITH COMPLAINTS	28 (29.8%)	21 (22.3%)	9 (9.6%)	5 (5.3%)	3 (3.2%)	0 (0.0%)		33 (35.1%)
PERSONS WITH NO COMPLAINTS	66 (70.2%)	73 (77.7%)	85 (90.4%)	89 (94.7%)	91 (96.8%)	94 (100.0%)		61 (64.9%)
PERSONS WITH NO DATA	35 (27.1%)	35 (27.1%)	35 (27.1%)	35 (27.1%)	35 (27.1%)	35 (27.1%)		35 (27.1%)

00228

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (126 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	15 (20.3%)	9 (12.2%)	3 (4.1%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	16 (21.6%)
PAIN	12 (16.2%)	5 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (16.2%)
SORENESS	2 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.7%)
SWELLING	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
PRURITIS (ITCHING)	0 (0.0%)	4 (5.4%)	2 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (5.4%)
SYSTEMIC	6 (8.1%)	4 (5.4%)	5 (6.8%)	2 (2.7%)	3 (4.1%)	2 (2.7%)	9 (12.2%)
WHOLE BODY/GENERAL	3 (4.1%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	4 (5.4%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
SENSATION OF WARMTH, GENERAL	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
FATIGUE/WEAKNESS	2 (2.7%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	3 (4.1%)
HEADACHE	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	2 (2.7%)
INFECTIOUS SYNDROMES	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)

Table 2(cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (126 PATIENTS) - DOSE 3 DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
INFLUENZA, NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)		1 (1.4%)
MUSCULOSKELETAL	2 (2.7%)	2 (2.7%)	2 (2.7%)	0 (0.0%)	1 (1.4%)	1 (1.4%)		3 (4.1%)
ARTHRALGIA (OTHER)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
SHOULDER PAIN	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
OTHER	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)		1 (1.4%)
DIGESTIVE SYSTEM	1 (1.4%)	1 (1.4%)	2 (2.7%)	1 (1.4%)	2 (2.7%)	1 (1.4%)		3 (4.1%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)		1 (1.4%)
DIARRHEA	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	0 (0.0%)		2 (2.7%)
NAUSEA	1 (1.4%)	1 (1.4%)	0 (0.0%)	1 (1.4%)	1 (1.4%)	0 (0.0%)		2 (2.7%)
UROGENITAL SYSTEM	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
URINARY TRACT INFECTION	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)		1 (1.4%)
INSOMNIA/DISTURBED SLEEP	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	0 (0.0%)		1 (1.4%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (126 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
PERSONS WITH COMPLAINTS	19 (25.7%)	13 (17.6%)	8 (10.8%)	3 (4.1%)	3 (4.1%)	2 (2.7%)	22 (29.7%)
PERSONS WITH NO COMPLAINTS	55 (74.3%)	61 (82.4%)	66 (89.2%)	71 (95.9%)	70 (95.9%)	71 (97.3%)	52 (70.3%)
PERSONS WITH NO DATA	19 (20.4%)	19 (20.4%)	19 (20.4%)	19 (20.4%)	20 (21.5%)	20 (21.5%)	19 (20.4%)

Table 3

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (97 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	12 (12.5%)	4 (4.2%)	4 (4.2%)	2 (2.1%)	2 (2.1%)	2 (2.1%)	15 (15.6%)
PAIN	8 (8.3%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (8.3%)
SORENESS	2 (2.1%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.1%)
ERYTHEMA (REDNESS)	0 (0.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
SWELLING	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
PAPULE(S)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
LYMPHADENOPATHY, REGIONAL	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	2 (2.1%)
SYSTEMIC	5 (5.2%)	10 (10.4%)	5 (5.2%)	2 (2.1%)	1 (1.0%)	0 (0.0%)	14 (14.6%)
WHOLE BODY/GENERAL	5 (5.2%)	5 (5.2%)	3 (3.1%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	10 (10.4%)
CHILLS	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
SWEATING	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (97 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
FATIGUE/WEAKNESS	2 (2.1%)	2 (2.1%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)		6 (6.3%)
HEADACHE	3 (3.1%)	2 (2.1%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)		4 (4.2%)
LIGHTHEADED	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
ILLNESS, NOS	1 (1.0%)	2 (2.1%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (4.2%)
RESPIRATORY	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)		1 (1.0%)
PHARYNGITIS (SORE THROAT)	0 (0.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)		1 (1.0%)
COUGH	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
MUSCULOSKELETAL	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
ARTHRALGIA, MONOARTICULAR	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
DIGESTIVE SYSTEM	0 (0.0%)	3 (3.1%)	1 (1.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)		4 (4.2%)
DYSPEPSIA/HEARTBURN	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)
DIARRHEA	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)		1 (1.0%)

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (97 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
NAUSEA	0 (0.0%)	2 (2.1%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.1%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
DEPRESSION	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)
PERSONS WITH COMPLAINTS	15 (15.6%)	13 (13.5%)	9 (9.4%)	4 (4.2%)	3 (3.1%)	2 (2.1%)	26 (27.1%)
PERSONS WITH NO COMPLAINTS	81 (84.4%)	83 (86.5%)	87 (90.6%)	92 (95.8%)	93 (96.9%)	94 (97.9%)	70 (72.9%)
PERSONS WITH NO DATA	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (97 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	3 (3.6%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	4 (4.8%)
PAIN	2 (2.4%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	3 (3.6%)
PRURITIS (ITCHING)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	1 (1.2%)
OTHER	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
SYSTEMIC	3 (3.6%)	2 (2.4%)	2 (2.4%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	7 (8.4%)
WHOLE BODY/GENERAL	2 (2.4%)	2 (2.4%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	5 (6.0%)
SENSATION OF WARMTH, GENERAL	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
FATIGUE/WEAKNESS	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)
HEADACHE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	1 (1.2%)
LIGHTHEADED	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
ILLNESS, NOS	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
RESPIRATORY	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	2 (2.4%)	1 (1.2%)	3 (3.6%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (97 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PHARYNGITIS (SORE THROAT)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)	1 (1.2%)		3 (3.6%)
UPPER RESPIRATORY INFECT., NOS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
COUGH	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
CARDIOVASCULAR	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
BRADYCARDIA/BRADYARRHYTHMIA	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
MUSCULOSKELETAL	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
ARTHRALGIA (OTHER)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
DIGESTIVE SYSTEM	1 (1.2%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (3.6%)
DIARRHEA	1 (1.2%)	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (2.4%)
NAUSEA	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.2%)
PERSONS WITH COMPLAINTS	5 (6.0%)	3 (3.6%)	3 (3.6%)	2 (2.4%)	3 (3.6%)	1 (1.2%)		10 (12.0%)
PERSONS WITH NO COMPLAINTS	78 (94.0%)	80 (96.4%)	80 (96.4%)	81 (97.6%)	80 (96.4%)	82 (98.8%)		73 (88.0%)
PERSONS WITH NO DATA	2 (2.4%)	2 (2.4%)	2 (2.4%)	2 (2.4%)	2 (2.4%)	2 (2.4%)		2 (2.4%)

00236

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (94 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	6 (10.5%)	8 (14.0%)	8 (14.0%)	6 (10.5%)	4 (7.0%)	3 (5.3%)	11 (19.3%)
PAIN	2 (3.5%)	4 (7.0%)	5 (8.8%)	4 (7.0%)	3 (5.3%)	3 (5.3%)	6 (10.5%)
TENDERNESS	3 (5.3%)	2 (3.5%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	4 (7.0%)
ERYTHEMA (REDNESS)	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
WARMTH	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
SWELLING	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.5%)
PRURITIS (ITCHING)	0 (0.0%)	1 (1.8%)	2 (3.5%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	2 (3.5%)
SYSTEMIC	3 (5.3%)	2 (3.5%)	1 (1.8%)	2 (3.5%)	2 (3.5%)	2 (3.5%)	5 (8.8%)
WHOLE BODY/GENERAL	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
HEADACHE	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
INFECTIOUS SYNDROMES	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	2 (3.5%)
INFLUENZA, NOS	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	2 (3.5%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (94 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
RESPIRATORY	2 (3.5%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	1 (1.8%)	1 (1.8%)		3 (5.3%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	1 (1.8%)		1 (1.8%)
LARYNGITIS	2 (3.5%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (3.5%)
DIGESTIVE SYSTEM	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
OTHER	1 (1.8%)	1 (1.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
NERVOUS SYSTEM	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
VERTIGO/DIZZINESS	0 (0.0%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (1.8%)
PERSONS WITH COMPLAINTS	9 (15.8%)	10 (17.5%)	9 (15.8%)	8 (14.0%)	6 (10.5%)	5 (8.8%)		14 (24.6%)
PERSONS WITH NO COMPLAINTS	48 (84.2%)	47 (82.5%)	48 (84.2%)	49 (86.0%)	51 (89.5%)	52 (91.2%)		43 (75.4%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 4
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (148 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	89 (87.3%)	98 (91.6%)	98 (93.3%)	100 (96.2%)	101 (100.0%)	96 (99.0%)			88 (80.7%)
99 - 99.9	13 (12.7%)	8 (7.5%)	7 (6.7%)	3 (2.9%)	0 (0.0%)	1 (1.0%)			19 (17.4%)
100 - 100.9	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (0.9%)
101 - 101.9	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0 (0.0%)			1 (0.9%)
TEMPERATURE TAKEN	102 (68.9%)	107 (72.3%)	105 (70.9%)	104 (70.3%)	101 (68.2%)	97 (65.5%)			109 (73.6%)
TEMPERATURE NOT TAKEN	46 (31.1%)	41 (27.7%)	43 (29.1%)	44 (29.7%)	47 (31.8%)	51 (34.5%)			39 (26.4%)

Table 4 (cont)
PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (146 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	64 (87.7%)	70 (93.3%)	71 (94.7%)	69 (94.5%)	68 (95.8%)	63 (94.0%)			60 (78.9%)
99 - 99.9	9 (12.3%)	5 (6.7%)	4 (5.3%)	4 (5.5%)	3 (4.2%)	4 (6.0%)			16 (21.1%)
TEMPERATURE TAKEN	73 (50.0%)	75 (51.4%)	75 (51.4%)	73 (50.0%)	71 (48.6%)	67 (45.9%)			76 (52.1%)
TEMPERATURE NOT TAKEN	73 (50.0%)	71 (48.6%)	71 (48.6%)	73 (50.0%)	75 (51.4%)	79 (54.1%)			70 (47.9%)

00240

Table 4 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CK564
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (126 PATIENTS) - DOSE 3							NUMBER WITH MAX TEMP
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
NORMAL	0 (0.0%)	1 (2.3%)	1 (2.3%)	1 (2.3%)	1 (2.4%)	1 (2.4%)		0 (0.0%)
< 99	36 (87.8%)	37 (84.1%)	40 (90.9%)	43 (97.7%)	38 (90.5%)	39 (92.9%)		38 (79.2%)
99 - 99.9	4 (9.8%)	3 (6.8%)	2 (4.5%)	0 (0.0%)	2 (4.8%)	2 (4.8%)		6 (12.5%)
100 - 100.9	1 (2.4%)	2 (4.5%)	0 (0.0%)	0 (0.0%)	1 (2.4%)	0 (0.0%)		3 (6.3%)
101 - 101.9	0 (0.0%)	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
102 - 102.9	0 (0.0%)	1 (2.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.1%)
TEMPERATURE TAKEN	41 (32.5%)	44 (34.9%)	44 (34.9%)	44 (34.9%)	42 (33.3%)	42 (33.3%)		48 (38.1%)
TEMPERATURE NOT TAKEN	85 (67.5%)	82 (65.1%)	82 (65.1%)	82 (65.1%)	84 (66.7%)	84 (66.7%)		78 (61.9%)

Table 5

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (97 PATIENTS) - DOSE 1								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	85 (92.4%)	90 (93.8%)	88 (91.7%)	90 (95.7%)	89 (95.7%)	85 (95.5%)			83 (86.5%)
99 - 99.9	6 (6.5%)	4 (4.2%)	7 (7.3%)	3 (3.2%)	4 (4.3%)	3 (3.4%)			10 (10.4%)
100 - 100.9	1 (1.1%)	2 (2.1%)	1 (1.0%)	1 (1.1%)	0 (0.0%)	1 (1.1%)			3 (3.1%)
TEMPERATURE TAKEN	92 (94.8%)	96 (99.0%)	96 (99.0%)	94 (96.9%)	93 (95.9%)	89 (91.8%)			96 (99.0%)
TEMPERATURE NOT TAKEN	5 (5.2%)	1 (1.0%)	1 (1.0%)	3 (3.1%)	4 (4.1%)	8 (8.2%)			1 (1.0%)

00242

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (97 PATIENTS) - DOSE 2								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	71 (93.4%)	74 (92.5%)	75 (93.8%)	75 (94.9%)	73 (91.2%)	72 (91.1%)			67 (83.7%)
99 - 99.9	4 (5.3%)	5 (6.3%)	4 (5.0%)	4 (5.1%)	6 (7.5%)	6 (7.6%)			10 (12.5%)
100 - 100.9	0 (0.0%)	1 (1.2%)	1 (1.2%)	0 (0.0%)	1 (1.2%)	1 (1.3%)			2 (2.5%)
101 - 101.9	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			1 (1.2%)
TEMPERATURE TAKEN	76 (78.4%)	80 (82.5%)	80 (82.5%)	79 (81.4%)	80 (82.5%)	79 (81.4%)			80 (82.5%)
TEMPERATURE NOT TAKEN	21 (21.6%)	17 (17.5%)	17 (17.5%)	18 (18.6%)	17 (17.5%)	18 (18.6%)			17 (17.5%)

00243

Table 5 (cont)

PATIENT COUNT MAXIMUM TEMPERATURES
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0795
TREATMENT :
LOT NUMBER : CL215
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

MAX TEMPERATURE (DEG F, ORAL)	TOTAL VACCINEES (94 PATIENTS) - DOSE 3								NUMBER WITH MAX TEMP
	DAYS POST VACCINATION								
	0	1	2	3	4	5			
< 99	38 (80.4%)	40 (85.1%)	41 (87.2%)	44 (95.7%)	39 (88.6%)	39 (86.7%)			38 (80.9%)
99 - 99.9	3 (7.0%)	6 (12.8%)	6 (12.8%)	1 (2.2%)	3 (6.8%)	4 (8.9%)			6 (12.8%)
100 - 100.9	2 (4.7%)	1 (2.1%)	0 (0.0%)	1 (2.2%)	2 (4.5%)	2 (4.4%)			3 (6.4%)
TEMPERATURE TAKEN	43 (45.7%)	47 (50.0%)	47 (50.0%)	46 (48.9%)	44 (46.8%)	45 (47.9%)			47 (50.0%)
TEMPERATURE NOT TAKEN	51 (54.3%)	47 (50.0%)	47 (50.0%)	48 (51.1%)	50 (53.2%)	49 (52.1%)			47 (50.0%)

SAT-LA.10

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

F. Deinhardt*, W. Jilg, G. Zoulek, B. Lorbeer, and B. Wilske
Max von Pettenkofer-Institute, 8000 Munchen 2, Western Germany

Thirty healthy, young volunteers free of any HBV markers were vaccinated with a recombinant hepatitis B vaccine prepared by Merck, Sharp & Dohme, West Point, PA. Ten µg HBsAg were administered intramuscularly at time 0, and one month later. Seroconversion rates and geometric mean concentrations after 1, 2 and 3 months were compared with an age- and sex-matched control group vaccinated with 20 µg of plasma derived vaccine (Merck Sharp & Dohme) (Table 1).

Table 1: Comparison of immune response after recombinant vaccine and plasma derived vaccine.

month	seroconversion %		anti-HBs (geom. mean) mIU	
	recombinant vaccine	plasma vaccine	recombinant vaccine	plasma vaccine
1	27	44	8.6	15.2
2	70	95	37.8	52.5
3	97	95	27.4	164.4

In the recombinant vaccine group, 38% of the total anti-HBs at month 3 was directed against the determinant a of HBsAg, compared to 30% in the control group. No increase in antibody titers against candida albicans was found in recipients of the recombinant vaccine 4 weeks after the second injection as compared to prevaccination levels. No serious side effects were observed in any of the vaccinated individuals.

Deinhardt F, Jilg W, Zoulek G, Lorbeer B, Wilske B. Clinical evaluation of a recombinant hepatitis B vaccine. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Straton, 1984:699.

CLINICAL EVALUATION OF A RECOMBINANT HEPATITIS B VACCINE

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Summary Recombinant hepatitis B vaccine prepared from antigen expressed in yeast was given to 30 healthy young volunteers. Seroconversion rates and anti-HBs levels were compared with those in a control group matched for age and sex who had received plasma-derived hepatitis B vaccine. 4 weeks after the third immunisation results were similar in the two groups. In the recombinant vaccine group the immune response developed more slowly during the early phase and seroconversion rates and mean anti-HBs levels were slightly lower in males; this probably reflects use of a lower dose of recombinant vaccine (10 μg compared with 20 μg of the plasma vaccine). Side-effects were slight and antibody titres against *Candida albicans* were not increased in recipients of the recombinant vaccine.

Introduction

CURRENT hepatitis B vaccines are effective and safe.[1] However, because they are prepared from plasma of human hepatitis B virus carriers, supply is restricted by the amount of plasma available and by the cost of purifying the hepatitis B surface antigen (HBsAg) to render it free from hepatitis B virus and other possible infectious agents. Thus, to meet the worldwide need for hepatitis B vaccine, new means of preparation are required. Lately, vectors carrying the DNA sequence for HBsAg were prepared[2] and the antigen was expressed in the yeast *Saccharomyces cerevisiae*.[3] Yeast cells assemble the HBsAg polypeptides into particles similar to the 22 nm particles found in human plasma; yeast HBsAg, however, unlike human HBsAg is not glycosylated. A vaccine developed from yeast HBsAg stimulated antibody production in mice, grivet monkeys, and chimpanzees; and when vaccinated chimpanzees were challenged with human hepatitis B virus of different subtypes, they were completely protected.[4] We now report the immunisation of 30 healthy young volunteers with the first hepatitis B vaccine produced by recombinant DNA technology.

Subjects, Materials, and Methods

Subjects

30 healthy medical students and laboratory workers were studied (17 female, 13 male; mean age 25±3 yr, range 21–34). Subjects in the control group had been immunised with plasma-derived vaccine in an earlier study;[5] they were matched by age and sex to the study group (table I). Before vaccination, all subjects were negative for HBsAg, anti-HBs, and antibodies against hepatitis B core antigen (anti-HBc), and their aminotransferase levels were normal (alanine and aspartate aminotransferases ≤17 and ≤10 IU/l, respectively).

TABLE I—SEX AND AGE DISTRIBUTION OF THE TWO VACCINATION GROUPS*

	Total		Female		Male	
	No	Age (yr)	No	Age (yr)	No	Age (yr)
Recombinant vaccine	30	24·9±3·1 (21–34)	17	24·6±3·5 (21–34)	13	25·3±2·6 (23–32)
Plasma-derived vaccine	41	25·0±2·7 (21–32)	23	24·7±3·0 (21–32)	18	25·4±2·3 (23–32)

*Means and standard deviations (range).

Vaccines

The recombinant hepatitis B vaccine was prepared by Merck Sharp & Dohme research laboratories (lot 934/CJ 625). It consists of purified HBsAg, subtype *adw*, produced in recombinant *S cerevisiae* and absorbed on aluminium hydroxide. 1 ml of vaccine contained 10 μg of HBsAg. Plasma vaccine was also subtype *adw* (lot 773/801-2/ C-F 732-2 Merck Sharp & Dohme). Subjects in the study group received 10 μg of recombinant vaccine intramuscularly at 0, 1, and 6 months; subjects in the control group received 20 μg of plasma-derived vaccine at the same intervals. (Since the recombinant vaccine was treated with formalin only, and not with pepsin and urea, it was initially thought to be more immunogenic than the plasma vaccine.) Blood samples were taken on the day of the first vaccination and then monthly. Subjects were asked to keep daily records of body temperature and side-effects for 5 days after each injection.

Serology

HBsAg, anti-HBs, and anti-HBc were tested by radioimmunoassay with commercially available kits ('AUSRIA II', 'AUSAB', 'CORAB', Abbott Laboratories). Anti-HBs concentrations in IU/l were calculated by the method of Hollinger et al,[6] the first WHO reference preparation 1977 being used in a dilution of 1:400.[7] Because *S cerevisiae* and *C albicans* have common antigenic determinants,[8] antibodies against *C albicans* were determined by passive haemagglutination in 26 subjects on day 0 and 4 weeks after the second and third injections of recombinant vaccine. Sera were examined for antibodies against the determinant *a* of HBsAg as previously described.[9]

Results

Seroconversion rates and mean anti-HBs levels during the course of immunisation are shown in table II. The immune response in the recombinant vaccine group was less pronounced during the first months than in the plasma vaccine group, as shown by lower seroconversion rates and lower mean anti-HBs levels. These differences became non-significant after the booster dose at month 6 when 29 out of 30 subjects (97%) were anti-HBs positive (control, 41 out of 41) with a geometric mean anti-HBs level of 2135 IU/l (control, 4299 IU/l). All anti-HBs-positive individuals in the recombinant vaccine group had anti-HBs values above 10 IU/l; 2 (6·7%) were low responders (anti-HBs below 100 IU/l), 3 (10%) were intermediate responders (anti-HBs 101–1000 IU/l), and 22 (73·3%) were normal to high responders (anti-HBs greater than 1000 IU/l). Similar values

Jilg W, Schmidt M, Zoulek G, Lorbeer B, Wilske B, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet 1984; 2:1174-5.

TABLE II—IMMUNE RESPONSES AFTER VACCINATION

Month	Seroconversion (%)		Anti-HBs (IU/l)*		p†
	Recombinant vaccine (n = 30)	Plasma-derived vaccine (n = 41)	Recombinant vaccine	Plasma-derived vaccine	
1	8 (27)	18 (44)	9	15	<0·05
2	21 (70)	39 (95)	28	53	<0·05
3	28 (93)	39 (95)	29	164	<0·05
4	28 (93)	39 (95)	63	228	<0·05
5	28 (93)	39 (95)	79	273	<0·05
6	28 (93)	39 (95)	68	263	<0·05
7	29 (97)	41 (100)	2135	4299	>0·05

*Anti-HBs is given as the geometric mean in responders only.
†Wilcoxon's rank-sum test.

TABLE III—IMMUNE RESPONSES IN MALES AND FEMALES (AFTER THREE INOCULATIONS)

	Recombinant vaccine	Plasma-derived vaccine	p*
Males:			
Seroconversion (%)†	12/13 (92)	18/18 (100)	
Anti-HBs (IU/l)‡	911	3894	<0·05
Females:			
Seroconversion (%)†	17/17 (100)	23/23 (100)	
Anti-HBs (IU/l)‡	3282	4640	>0·05

*Wilcoxon's rank-sum test.
†Numbers of anti-HBs-positive subjects divided by the total number.
‡Geometric mean.

were obtained in the control group. Although the immune responses to the two vaccines were similar after the full course of immunisation, responses of male and female subjects differed. In both groups all the women seroconverted and the geometric mean anti-HBs levels did not differ significantly (3282 IU/l vs 4640 IU/l). However, in males receiving recombinant vaccine the seroconversion rate was 92% vs 100%, and the geometric mean anti-HBs was 911 vs 3894 IU/l (table III).

Preliminary tests indicate that recombinant vaccine, like the plasma-derived vaccine, induces antibodies against both the *a* and the *d* components of HBs antigen. After month 3, about 38% of the total anti-HBs was directed against determinant *a*.

No important side-effects were observed after immunisation with the recombinant vaccine. Minor local symptoms such as transient pain, itching, burning, and slight swelling at the injection site were reported after 24 of the 90 injections. On no occasion did body temperature rise above 37·9°C.

Of 26 subjects tested, all had antibodies against *C albicans* on day 0 (titres from 1:80 to 1:320) and titres did not increase after immunisation.

Discussion

Three doses of 10 μg recombinant hepatitis B vaccine gave seroconversion rates and geometric mean anti-HBs levels similar to those induced by three doses of 20 μg plasma-derived vaccine. The results were also comparable with those obtained in large trials of conventional vaccines.[10,11]

The immune response to the recombinant vaccine, however, was less strong during the early phase (1–6 months) in all subjects, and in males mean anti-HBs values were lower in the recombinant group even after the complete course of immunisation. These results are comparable with findings in subjects immunised with a smaller dose (5 μg) of conventional vaccine (Jilg W, Zachoval R, Schmidt M, Deinhardt F, unpublished), and may reflect the use of smaller amounts of antigen. Antigen content of both recombinant vaccine and plasma-derived vaccine is determined as HBsAg protein. The vaccines are produced and treated differently, however;[4,12] therefore similar protein content does not necessarily mean similar immunogenicity. The yeast and plasma derived HBsAg differed in reactivity in radioimmunoassay tests; the reactivity of the HBsAg produced in yeast was only 20–50% of the reactivity of plasma-derived HBsAg.[4] Thus, weight-for-weight the immunogenicity of the recombinant vaccine seems to be less than that of the plasma-derived vaccine. Another explanation for the lower immune response may be that 10 μg of recombinant vaccine was given per single dose compared with 20 μg of plasma-derived vaccine. A higher dose (20 or 40 μg) of the recombinant vaccine would probably give the same results as the plasma-derived vaccine.

Despite the slightly lower immunity achieved with the recombinant vaccine, protection will probably be as good as with the conventional vaccine, in that all 29 subjects with detectable anti-HBs had values above the protection level of 10 IU/l.[13] In 73%, anti-HBs levels after the third vaccination were more than 1000 IU/l; this has been shown to guarantee persistence of anti-HBs above the protective limit for at least 3 years.[14] In addition, all subjects who seroconverted had antibodies against the common determinant *a* of HBsAg, indicating cross-protection against infections with other subtypes of HBsAg. Side-effects after the recombinant vaccine were negligible and did not differ from those observed after plasma-derived vaccine. The absence of a rise in antibodies against *C albicans* indicates that no cross-reacting yeast antigens were present in the vaccine.

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REFERENCES

1. Deinhardt F. Control of hepatitis A and B with vaccines. *Ann Clin Res* 1982; 14: 236–44.
2. Valenzuela P, Gray P, Quiroga M, Zaldivar J, Goodman HM, Rutter WJ. Nucleotide sequence of the gene coding for the major protein of hepatitis B surface antigen. *Nature* 1979; 280: 815–19.
3. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. *Nature* 1982; 298: 347–50.
4. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. *Nature* 1984; 307: 178–80.
5. Zachoval R, Jilg W, Lorbeer B, Schmidt M, Deinhardt F. Passive-active immunization against hepatitis B. *J Infect Dis* 1984; 150: 112–17.
6. Mellinger PB, Adam E, Hosburg D, Melnick JL. Response to hepatitis B vaccine in a young adult population. In: Szmuness W, Alter HJ, Maynard JE, eds. Viral hepatitis: 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 491–96.
7. World Health Organization. *WHO Tech Rep Ser* no 630; 1979: 39
8. Tsuchiya T, Fukazawa Y, Kuroshima S. Serological classification of the genus *Candida*. In: Tokyo Research Committee of Candidiasis. Studies of candidiasis in Japan. Tokyo: Educational Ministry of Japan, 1981: 34–36.
9. Jilg W, Deinhardt C, Deinhardt F, Rasmussen-Karoyannis AJ, Papaevangelou GJ, Mushahwar IK, Overby LR. Hepatitis B surface antigen (HBsAg) subtype – specific antibodies in persons vaccinated against hepatitis B. *J Med Virol* 1984; 13: 171–78.
10. Szmuness W, Stevens CE, Zang EA, Harley EJ, Kellner A. A controlled clinical trial on the efficacy of the hepatitis B vaccine (Heptavax B): A final report. *Hepatology* 1981; 1: 377–85.
11. Cremer J, Jungeyr P, Courouce AM, et al. Randomised placebo-controlled trial of hepatitis B surface antigen vaccine in French homosexual/bisexual males. *J Medical Virol* 1981; 1: 495–98.
12. Hollinger FB, Buynak EB, McAleer WJ, McLean AA. Human hepatitis B vaccine. In: Krugman S, Shevlach S, eds. Proceedings of the European Symposium on Hepatitis B Antigen: Merck Sharp & Dohme International, 1981: 120–30.
13. Goudeau A, Courouce P, Borne F, et al. Prevention of hepatitis B by active and passive-active immunization. In: Szmuness W, Alter HJ, Maynard JE, eds. Viral hepatitis 1981 International Symposium. Philadelphia: Franklin Institute Press, 1982: 509–25.
14. Jilg W, Schmidt M, Zachoval R, Deinhardt F. Persistenz von Antikörpern gegen Hepatitis B-Oberflächenantigen nach Impfung gegen Hepatitis B. *Dtsch Med Wochenschr* (in press).

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Antibody and Clinical Responses Among Healthy Adults to a Hepatitis B Vaccine Made by Recombinant DNA

Currently, all commercial hepatitis B vaccines are comprised of HBsAg purified from the plasma of human carriers of the virus. However, the use of recombinant DNA technology to effect synthesis of surface antigen by a culture of microorganisms is an attractive alternative to infected human plasma as a source of HBsAg for vaccine. Good expression of the gene for HBsAg has been effected in yeast *(1)*.

Recently, antigen purified from fermentation cultures of a recombinant strain of the yeast, *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg was formulated into a vaccine through absorption on alum adjuvant. Two methods were utilized for the purification of the HBsAg. Immune affinity chromatography uses specific antigen-antibody binding to effect purification, while the second method, hydrophobic interaction chromatography followed by gel exclusion chromatography, depends upon the selection of water-immiscible molecules followed by separation on the basis of molecular size.

The physical and chemical characteristics of vaccine made from HBsAg produced in yeast are very similar to those of vaccine prepared with HBsAg purified from human plasma. Furthermore, the yeast recombinant hepatitis B vaccine has been shown to be both immunogenic and protective in animals *(2)*.

We report here the clinical and antibody responses obtained in the first three human clinical studies of the yeast recombinant vaccine involving a total of 101

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Scolnick EM, McLean AA, West DJ, Dienstag JL, Watkins E, Deinhardt F. Antibody and clinical responses among healthy adults to a hepatitis B vaccine made by recombinant DNA. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. Viral Hepatitis and Liver Disease. Orlando:Grune and Stratton, 1984: 315-17.

vaccinees. Participants were healthy, nonpregnant, adult volunteers. At entry, subjects were negative for all hepatitis B serologic markers, had a normal ALT level, and had not received any other hepatitis B vaccine.

Participants in the studies received a 1.0-ml intramuscular injection of the yeast recombinant hepatitis vaccine containing 10 μg of HBsAg at 0, 1 and 6 months. The vaccine used was from one of two lots. (Lot 934 prepared by the immune affinity chromatography method and Lot 972 prepared by the hydrophobic interaction chromatography method.) Vaccinees were asked to record their temperature daily for 5 days after each injection of vaccine and to report any local or systemic reactions that occurred during that period.

Postvaccination blood samples were taken for the determination of hepatitis B serologic markers and ALT. In addition, a radioimmunoassay for the detection of antibody to antigens in an extract of yeast lacking the gene for HBsAg was applied to pre- and postvaccination samples.

The vaccine was well tolerated. There have been no serious adverse effects attributable to vaccine and no evidence of hepatitis B infection among the vaccinees (i.e., no elevation of ALT and no antigenemia). Local reactions consisting principally of mild soreness at the injection site, generally lasting 1–2 days, have been reported following 20%–80% of injections with vaccine purified by the immune affinity chromatography method (Lot 934) and 16%–25% of injections with vaccine purified by the hydrophobic interaction chromatography method. Systemic complaints including fatigue, headache, elevated temperature (101° F–102° F, oral), gastrointestinal disturbance, symptoms of upper respiratory infection and nosebleed have been reported following 4%–33% of injections (Table 23.1). There have been no significant increases in antibody to antigens in yeast extract associated with vaccination.

Table 23.1
Clinical Responses among Healthy Adults to 10 μg Doses of Recombinant Hepatitis B Vaccine Administered at 0, 1 and 6 Months

			Proportion (%) of Vaccinees with Clinical Complaints within 5 Days of Vaccination		
Study #	Vaccine Lot #	Site	Dose 1 (%)	Dose 2 (%)	Dose 3 (%)
779	934	Local	12/15 (80)	11/15 (73)	11/15 (73)
		Systemic	5/15 (33)	3/15 (20)	1/15 (7)
	972	Local	6/24 (25)	3/19 (16)	
		Systemic	1/24 (4)	3/19 (16)	
792	934	Local	19/28 (68)	11/28 (39)	
		Systemic	5/28 (18)	4/28 (14)	
795	934	Local	5/25 (20)	6/19 (32)	
		Systemic	5/25 (20)	1/19 (5)	

Table 23.2
Seroconversion Frequencies for Anti-HBs among Healthy Adults Receiving 10 μg Doses of Recombinant Hepatitis B Vaccine at 0, 1 and 6 Months

		Proportion (%) of Vaccinees with Antibody				
Study #	Vaccine Lot #	1 Mo.	2 Mo.	3 Mo.	6 Mo.	7 Mo.
779	934	6/15 (40)	14/15 (93)	15/15 (100)	15/15 (100)	14/14 (100)
	972	7/24 (29)	13/19 (68)	12/14 (86)		
792	934	11/28 (39)	21/23 (91)	13/13 (100)		
795	934	8/30 (27)	21/30 (70)	19/22 (86)		

Antibody responses to 10 μg doses of the yeast recombinant vaccine have been comparable to those observed in previous studies with 20 μg doses of vaccine prepared from plasma-derived HBsAg. At 1 month, 27%–40% of the vaccinees were positive for anti-HBs. By 2 months, 68%–93% of the vaccinees had anti-HBs, and at 3 months 86%–100% were antibody positive (Table 23.2). The third dose of vaccine at 6 months has been given to 15 persons in one of the studies, resulting in a more than 25-fold increase in geometric mean titer.

REFERENCES

1. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 1982; 298:347–350.
2. McAleer WJ, Buynak EB, Maigetter RZ, et al. Human hepatitis B vaccine from recombinant yeast. Nature 1984; 307:178–180.

PROGRAM:	Alum-Adsorbed Yeast Recombinant Hepatitis B Vaccine, Study 798
PURPOSE:	To evaluate antibody and clinical responses to 5 mcg, 10 mcg, and 20 mcg doses of the vaccine among healthy adult paramedics who are negative for hepatitis B virus serologic markers.
VACCINE:	Yeast Recombinant Hepatitis B Vaccine Lot #974/C-K446 (20 mcg HBsAg/ml)
PRINCIPAL INVESTIGATOR:	F. Blaine Hollinger, M.D. Professor of Medicine, Virology and Epidemiology Baylor College of Medicine Department of Virology and Medicine Texas Medical Center Houston, TX 77030
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STUDY LOCATION:	Baylor College of Medicine Department of Virology and Medicine Texas Medical Center Houston, TX 77030
DATE INITIATED:	April 11, 1984
DATE COMPLETED:	In progress.

Study 798

STUDY POPULATION: The study population is comprised of 109 male paramedical personnel in the Houston area who were initially negative for HBsAg, anti-HBc and anti-HBs, had a normal ALT level and had not previously received any hepatitis B vaccine.

STUDY PROCEDURE: Participants are entered into the study as members of triplets, one at each dose level, matched on body weight (within 9 lbs.).

Eligible participants receive an intramuscular injection of vaccine at 0, 1, and 6 months. The volume (dose) of the injections received by an individual is 1.0 ml (20 mcg HBsAg), 0.5 ml (10 mcg HBsAg), or 0.25 ml (5 mcg HBsAg).

Vaccine recipients are asked to record their temperature daily for five days after each injection of vaccine and also to record any local or systemic complaints that they may have during this period.

A blood specimen (approximately 30 ml) is obtained from each participant approximately four weeks before vaccination and on the day of vaccination. Post-vaccination blood samples are obtained at 1, 2, 3, 6, 8, 12, and 24 months. All samples are assayed for HBsAg, anti-HBc, anti-HBs, and ALT. Samples with an anti-HBs titer $\geq$25 mIU/ml are tested to determine the proportions of anti-a and anti-d activity. Samples may be assayed for yeast antibody as required.

RESULTS: HEALTH CARE PERSONNEL:

5 mcg Lot #974/C-K446 at 0, 1, and 6 months
10 mcg Lot #974/C-K446 at 0, 1, and 6 months
20 mcg Lot #974/C-K446 at 0, 1, and 6 months

1. Number Vaccinated:

Dose Level	Injection No. 1	2	3
5 mcg	36	36	36
10 mcg	37	37	37
20 mcg	36	35	35

Study 798

RESULTS (CONT.):

2. Serologic Results:

Serology data are available, at 7/8 months, for 36, 35, and 35 participants who received 5, 10, and 20 mcg injections of vaccine, respectively.

The seroconversion rates and GMTs at 7/8 months are presented below.

Dose Levels	% with Anti-HBs S/N ≥ 2.1	% with Anti-HBs mIU/ml ≥ 10	GMT (mIU/ml) All Vaccinees	GMT (mIU/ml) Responders S/N ≥ 2.1	GMT (mIU/ml) Responders mIU/ml ≥ 10
5 mcg	97(35/36)	83(30/36)	72.9	82.2	136.9
10 mcg	97(34/35)	97(35/36)	513.1	620.6	620.6
20 mcg	100(35/35)	91(32/35)	733.0	733.0	1193.3

Refer to Table 1 for anti-HBs responses and GMTs at 12 months and for other time intervals.

Two subjects were found to be anti-HBs positive on the day of the first injection of vaccine (10 mcg dose). One of these vaccinees had a 3-fold rise in anti-HBs at one month and a >4-fold rise at two months. The other participant developed a >4-fold rise in anti-HBs titer five months after the second injection of vaccine.

3. Clinical Complaints:

Clinical follow-up data after each injection are available for 33, 33, and 32 participants who received 5, 10, and 20 mcg injections of vaccine, respectively. The overall frequencies of complaints follow.

Study 798

RESULTS (CONT.):

Type of Complaint	Dose Level	Frequency in % by Injection No. 1	2	3
Injection Site	5 mcg	14(5/35)	3(1/33)	9(3/34)
	10 mcg	11(4/37)	18(6/33)	19(7/36)
	20 mcg	25(9/36)	28(9/32)	21(7/34)
Systemic	5 mcg	34(12/35)	15(5/33)	18(6/34)
	10 mcg	30(11/37)	15(5/33)	28(10/36)
	20 mcg	33(12/36)	28(9/32)	21(7/34)

Refer to Tables 2 through 4 for listings of specific clinical complaints by dose level and injection number. Maximum temperature data are presented in Tables 5 through 7.

There were no serious or alarming reactions attributable to vaccine.

Reactions reported to the DoBRR

A 32-year old male subject had an elevated ALT level at the time of his third injection of vaccine. Two weeks after the third injection of vaccine, the subject was symptomatic for anorexia and vomiting. He was icteric, had dark urine and elevated bilirubin and ALT levels. He was negative for anti-HAV, HBsAg, and anti-HBc. He was diagnosed as having non A non B hepatitis. This illness was not considered related to the vaccine.

PUBLICATIONS:

Hollinger FB, Sanchez Y, Troisi C, Dreesman GR, Melnick JL. Immunogenicity and reactogenicity of new hepatitis B vaccines. Hepatology 1984; 4:1027 (Abstract).

Hollinger FB, Troisi CL, Pepe PE. Anti-HBs responses to vaccination with a human hepatitis B vaccine made by recombinant DNA technology in yeast. J Infect Dis 1986; 1:156-9.

Table 1

Antibody Responses Among Healthy Adults Following Vaccination with
5, 10, or 20 mcg Injections of Yeast Recombinant Hepatitis B Vaccine
Lot #974/C-K446 at 0, 1, and 6 Months in Study #798

	5 mcg					10 mcg					20 mcg				
	% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)			% with Anti-HBs		GMT (mIU/ml)		
				Responders					Responders					Responders	
Time (Mos.)	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10	S/N≥2.1	mIU/ml ≥ 10	All Vaccinees	S/N≥2.1	mIU/ml ≥ 10
1	11 (4/36)	6 (2/36)	0.7	6.4	27.0	29 (10/35)	8.6 (3/35)	2.2	6.1	34.0	29 (10/35)	11 (4/35)	1.5	8.7	72.9
2	22 (8/36)	14 (5/36)	1.6	18.3	60.7	74 (26/35)	40 (14/35)	8.1	14.2	63.3	83 (29/35)	34 (12/35)	10.7	14.8	94.6
3	44 (16/36)	17 (6/36)	1.9	5.8	26.0	86 (30/35)	37 (13/35)	10.1	11.9	61.6	89 (31/35)	57 (20/35)	14.3	16.4	38.1
6	61 (22/36)	28 (10/36)	2.9	7.5	21.2	94 (33/35)	63 (22/35)	16.0	18.1	38.3	91 (31/34)	79 (27/34)	30.0	40.3	57.6
7/8	97 (35/36)	78 (28/36)	51.0	57.9	113.6	97 (34/35)	97 (34/35)	381.0	475.8	475.8	100 (35/35)	89 (31/35)	539.0	539.0	1021.5
12	83 (30/36)	47 (17/36)	12.7	17.6	55.1	97 (34/35)	86 (30/35)	74.5	90.4	130.1	97 (34/35)	86 (30/35)	184.6	217.4	370.9

00255

30991/2
1/3/86

Table 2
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	4 (11.4%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
PAIN	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
SORENESS	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
NUMBNESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
SYSTEMIC	8 (22.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (34.3%)
WHOLE BODY/GENERAL	8 (22.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (22.9%)
FLUSH	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
FATIGUE/WEAKNESS	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
HEADACHE	5 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)
INTEGUMENTARY SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
MACULAR RASH	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
DIGESTIVE SYSTEM	1 (2.9%)	1 (2.9%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (14.3%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

	TOTAL VACCINEES (36 PATIENTS) - DOSE 1						
	DAYS POST VACCINATION						NUMBER
CLINICAL COMPLAINTS	0	1	2	3	4	5	WITH COMPLAINTS
ABDOMINAL PAINS/CRAMPS	0 (0.0%)	0 (0.0%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)
DIARRHEA	0 (0.0%)	1 (2.9%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.6%)
NAUSEA	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
NERVOUS SYSTEM	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
VERTIGO/DIZZINESS	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
ORGANS OF SPECIAL SENSE	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
EYE PAIN	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	11 (31.4%)	2 (5.7%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (45.7%)
PERSONS WITH NO COMPLAINTS	24 (68.6%)	33 (94.3%)	32 (91.4%)	35 (100.0%)	0 (0.0%)	0 (0.0%)	19 (54.3%)
PERSONS WITH NO DATA	1 (2.8%)	1 (2.8%)	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.8%)

00257

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 2						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
SORENESS	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
SYSTEMIC	5 (15.2%)	4 (12.1%)	2 (6.1%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	5 (15.2%)
WHOLE BODY/GENERAL	2 (6.1%)	2 (6.1%)	2 (6.1%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	4 (12.1%)
MALAISE	0 (0.0%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
HEADACHE	2 (6.1%)	2 (6.1%)	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	3 (9.1%)
RESPIRATORY	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
PHARYNGITIS (SORE THROAT)	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
UPPER RESPIRATORY INFECT., NOS	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
MUSCULOSKELETAL	2 (6.1%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.1%)
MYALGIA	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)
NECK PAIN	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
ORGANS OF SPECIAL SENSE	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
EARACHE	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
PERSONS WITH COMPLAINTS	6 (18.2%)	4 (12.1%)	2 (6.1%)	1 (3.0%)	0 (0.0%)	0 (0.0%)		6 (18.2%)
PERSONS WITH NO COMPLAINTS	27 (81.8%)	29 (87.9%)	31 (93.9%)	32 (97.0%)	1 (100.0%)	0 (0.0%)		27 (81.8%)
PERSONS WITH NO DATA	3 (8.3%)	3 (8.3%)	3 (8.3%)	3 (8.3%)	0 (0.0%)	0 (0.0%)		3 (8.3%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	2 (5.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (8.8%)
PAIN ON INJECTION	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
PAIN	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
SORENESS	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
PARESTHESIA	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
SYSTEMIC	3 (8.8%)	3 (8.8%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		6 (17.6%)
WHOLE BODY/GENERAL	3 (8.8%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (11.8%)
FEVER (TEMP. NOT REPORTED)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
FATIGUE/WEAKNESS	2 (5.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (5.9%)
HEADACHE	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
RESPIRATORY	0 (0.0%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)
RHINITIS	0 (0.0%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.9%)

Table 2 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 5 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (36 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
DIGESTIVE SYSTEM	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
OTHER	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
UROGENITAL SYSTEM	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
OTHER	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)
PERSONS WITH COMPLAINTS	4 (11.8%)	4 (11.8%)	3 (8.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (23.5%)
PERSONS WITH NO COMPLAINTS	30 (88.2%)	30 (88.2%)	31 (91.2%)	34 (100.0%)	0 (0.0%)	0 (0.0%)	26 (76.5%)
PERSONS WITH NO DATA	1 (2.9%)	1 (2.9%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	1 (2.9%)

Table 3
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	3 (8.1%)	0 (0.0%)	2 (5.4%)	1 (2.7%)	0 (0.0%)	0 (0.0%)		4 (10.8%)
SORENESS	2 (5.4%)	0 (0.0%)	2 (5.4%)	1 (2.7%)	0 (0.0%)	0 (0.0%)		4 (10.8%)
PRURITIS (ITCHING)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
PARESTHESIA	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
SYSTEMIC	7 (18.9%)	5 (13.5%)	3 (8.1%)	1 (2.7%)	0 (0.0%)	0 (0.0%)		11 (29.7%)
WHOLE BODY/GENERAL	5 (13.5%)	4 (10.8%)	3 (8.1%)	1 (2.7%)	0 (0.0%)	0 (0.0%)		8 (21.6%)
FATIGUE/WEAKNESS	3 (8.1%)	4 (10.8%)	2 (5.4%)	1 (2.7%)	0 (0.0%)	0 (0.0%)		6 (16.2%)
MALAISE	1 (2.7%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
HEADACHE	2 (5.4%)	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (8.1%)
INTEGUMENTARY SYSTEM	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
RASH, NOS	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
RESPIRATORY	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 1							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
UPPER RESPIRATORY INFECT., NOS	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
MUSCULOSKELETAL	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
MYALGIA	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
INSOMNIA/DISTURBED SLEEP	0 (0.0%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.7%)
PERSONS WITH COMPLAINTS	10 (27.0%)	5 (13.5%)	5 (13.5%)	2 (5.4%)	0 (0.0%)	0 (0.0%)		14 (37.8%)
PERSONS WITH NO COMPLAINTS	27 (73.0%)	32 (86.5%)	32 (86.5%)	35 (94.6%)	0 (0.0%)	0 (0.0%)		23 (62.2%)
PERSONS WITH NO DATA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 2 — DAYS POST VACCINATION							NUMBER WITH COMPLAINTS
	0	1	2	3	4	5		
REACTION, LOCAL (INJECT. SITE)	4 (12.1%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)		6 (18.2%)
SORENESS	3 (9.1%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		4 (12.1%)
TENDERNESS	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)		2 (6.1%)
PRURITIS (ITCHING)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
SYSTEMIC	2 (6.1%)	3 (9.1%)	2 (6.1%)	3 (9.1%)	0 (0.0%)	0 (0.0%)		5 (15.2%)
WHOLE BODY/GENERAL	1 (3.0%)	3 (9.1%)	2 (6.1%)	3 (9.1%)	0 (0.0%)	0 (0.0%)		4 (12.1%)
FATIGUE/WEAKNESS	0 (0.0%)	3 (9.1%)	2 (6.1%)	3 (9.1%)	0 (0.0%)	0 (0.0%)		4 (12.1%)
HEADACHE	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
DIGESTIVE SYSTEM	1 (3.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (6.1%)
DIARRHEA	0 (0.0%)	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
NAUSEA	1 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (3.0%)
PERSONS WITH COMPLAINTS	6 (18.2%)	3 (9.1%)	3 (9.1%)	3 (9.1%)	1 (100.0%)	0 (0.0%)		11 (33.3%)

00264

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 2							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
PERSONS WITH NO COMPLAINTS	27 (81.8%)	30 (90.9%)	30 (90.9%)	30 (90.9%)	0 (0.0%)	0 (0.0%)		22 (66.7%)
PERSONS WITH NO DATA	4 (10.8%)	4 (10.8%)	4 (10.8%)	4 (10.8%)	0 (0.0%)	0 (0.0%)		4 (10.8%)

00265

Table 3 (cont)
PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 3						
	DAYS POST VACCINATION						NUMBER WITH COMPLAINTS
	0	1	2	3	4	5	
REACTION, LOCAL (INJECT. SITE)	5 (13.9%)	3 (8.3%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (19.4%)
PAIN ON INJECTION	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
PAIN	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
SORENESS	2 (5.6%)	3 (8.3%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (11.1%)
TENDERNESS	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.6%)
PARESTHESIA	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
SYSTEMIC	6 (16.7%)	5 (13.9%)	3 (8.6%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	10 (27.8%)
WHOLE BODY/GENERAL	5 (13.9%)	1 (2.8%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (16.7%)
FATIGUE/WEAKNESS	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
HEADACHE	3 (8.3%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (8.3%)
LIGHTHEADED	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)
ACHINESS	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.8%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 3 — DAYS POST VACCINATION 0	1	2	3	4	5		NUMBER WITH COMPLAINTS
INTEGUMENTARY SYSTEM	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
MACULAR RASH	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
PRURITIS/ITCHING	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
RESPIRATORY	1 (2.8%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		2 (5.6%)
RHINITIS	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
PHARYNGITIS (SORE THROAT)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
MUSCULOSKELETAL	0 (0.0%)	1 (2.8%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		2 (5.6%)
ARTHRALGIA (OTHER)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
BACK PAIN	0 (0.0%)	0 (0.0%)	1 (2.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
NECK PAIN	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
SHOULDER PAIN	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
DIGESTIVE SYSTEM	1 (2.8%)	2 (5.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (8.3%)
NAUSEA	1 (2.8%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		2 (5.6%)

Table 3 (cont)

PATIENT COUNT CLINICAL COMPLAINTS
RECOMBINANT HEPATITIS B VACCINE

STUDY : 0798
TREATMENT :
LOT NUMBER : CK446
DOSE : 10 MCG
PATIENT CLASS: HEALTH CARE PERSONNEL

CLINICAL COMPLAINTS	TOTAL VACCINEES (37 PATIENTS) - DOSE 3							NUMBER WITH COMPLAINTS
	DAYS POST VACCINATION							
	0	1	2	3	4	5		
OTHER	0 (0.0%)	1 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
PSYCHIATRIC/BEHAVIORAL	0 (0.0%)	1 (2.8%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
INSOMNIA/DISTURBED SLEEP	0 (0.0%)	1 (2.8%)	1 (2.9%)	1 (2.9%)	0 (0.0%)	0 (0.0%)		1 (2.8%)
PERSONS WITH COMPLAINTS	9 (25.0%)	8 (22.2%)	4 (11.4%)	2 (5.7%)	0 (0.0%)	0 (0.0%)		12 (33.3%)
PERSONS WITH NO COMPLAINTS	27 (75.0%)	28 (77.8%)	31 (88.6%)	33 (94.3%)	0 (0.0%)	0 (0.0%)		24 (66.7%)
PERSONS WITH NO DATA	1 (2.7%)	1 (2.7%)	2 (5.4%)	2 (5.4%)	0 (0.0%)	0 (0.0%)		1 (2.7%)