Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

COMVAX®

[HAEMOPHILUS b CONJUGATE (MENINGOCOCCAL PROTEIN CONJUGATE) and HEPATITIS B (RECOMBINANT) VACCINE]

DESCRIPTION

COMVAX® [Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B (Recombinant) Vaccine] is a sterile bivalent vaccine made of the antigenic components used in producing PedvaxHIB® [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)] and RECOMBIVAX HB® [Hepatitis B Vaccine (Recombinant)]. These components are the *Haemophilus influenzae* type b capsular polysaccharide [polyribosylribitol phosphate (PRP)] that is covalently bound to an outer membrane protein complex (OMPC) of *Neisseria meningitidis* and hepatitis B surface antigen (HBsAg) from recombinant yeast cultures.

Haemophilus influenzae type b and *Neisseria meningitidis* serogroup B are grown in complex fermentation media. The primary ingredients of the phenol-inactivated fermentation medium for *Haemophilus influenzae* include an extract of yeast, nicotinamide adenine dinucleotide, hemin chloride, soy peptone, dextrose, and mineral salts and for *Neisseria meningitidis* include an extract of yeast, amino acids and mineral salts. The PRP is purified from the culture broth by purification procedures which include ethanol fractionation, enzyme digestion, phenol extraction and diafiltration. The OMPC from *Neisseria meningitidis* is purified by detergent extraction, ultracentrifugation, diafiltration and sterile filtration.

The PRP-OMPC conjugate is prepared by the chemical coupling of the highly purified PRP (polyribosylribitol phosphate) of *Haemophilus influenzae* type b (Haemophilus b, Ross strain) to an OMPC of the B11 strain of *Neisseria meningitidis* serogroup B. The coupling of the PRP to the OMPC is necessary for enhanced immunogenicity of the PRP. This coupling is confirmed by analysis of the components of the conjugate following chemical treatment which yields a unique amino acid. After conjugation, the aqueous bulk is then adsorbed onto an amorphous aluminum hydroxyphosphate sulfate adjuvant (previously referred to as aluminum hydroxide).

HBsAg is produced in recombinant yeast cells. A portion of the 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 according to methods developed in the Merck Research Laboratories. The antigen is harvested and purified from fermentation cultures of a recombinant strain of the yeast *Saccharomyces cerevisiae* containing the gene for the *adw* subtype of HBsAg. The fermentation process involves growth of *Saccharomyces cerevisiae* on a complex fermentation medium which consists of an extract of yeast, soy peptone, dextrose, amino acids and mineral salts.

The HBsAg protein is released from the yeast cells by mechanical cell disruption and detergent extraction, and purified by a series of physical and chemical methods, which includes ion and hydrophobic chromatography, and diafiltration. The purified protein is treated in phosphate buffer with formaldehyde and then coprecipitated with alum (potassium aluminum sulfate) to form bulk vaccine adjuvanted with amorphous aluminum hydroxyphosphate sulfate. The vaccine contains no detectable yeast DNA, and 1% or less of the protein is of yeast origin.

The individual PRP-OMPC and HBsAg adjuvanted bulks are combined to produce COMVAX. Each 0.5 mL dose of COMVAX is formulated to contain 7.5 mcg PRP conjugated to approximately 125 mcg OMPC, 5 mcg HBsAg, approximately 225 mcg aluminum as amorphous aluminum hydroxyphosphate sulfate, and 35 mcg sodium borate (decahydrate) as a pH stabilizer, in 0.9% sodium chloride. The vaccine contains not more than 0.0004% (w/v) residual formaldehyde.

The potency of the PRP-OMPC component is measured by quantitating the polysaccharide concentration by an HPLC method. The potency of the HBsAg component is measured relative to a standard by an *in vitro* immunoassay.

The product contains no preservative.

COMVAX is a sterile suspension for intramuscular injection.

CLINICAL PHARMACOLOGY

Haemophilus influenzae type b Disease

Prior to the introduction of *Haemophilus b* conjugate vaccines, *Haemophilus influenzae* type b (Hib) was the most frequent cause of bacterial meningitis and a leading cause of serious, systemic bacterial disease in young children worldwide.[1-4]

Hib disease occurred primarily in children under 5 years of age, and in the United States prior to the initiation of a vaccine program was estimated to account for nearly 20,000 cases of invasive infections annually, approximately 12,000 of which were meningitis. The mortality rate from Hib meningitis is about 5%. In addition, up to 35% of survivors develop neurologic sequelae including seizures, deafness, and mental retardation.[5,6] Other invasive diseases caused by this bacterium include cellulitis, epiglottitis, sepsis, pneumonia, septic arthritis, osteomyelitis, and pericarditis.

Prior to the introduction of the vaccine, it was estimated that 17% of all cases of Hib disease occurred in infants less than 6 months of age. The peak incidence of Hib meningitis occurred between 6 to 11 months of age. Forty-seven percent of all cases occurred by one year of age with the remaining 53% of cases occurring over the next four years.[2,20]

Among children under 5 years of age, the risk of invasive Hib disease is increased in certain populations including the following:

- Daycare attendees[7,8,9]
- Lower socio-economic groups[10]
- Blacks[11] (especially those who lack the Km(1) immunoglobulin allotype)[12]
- Caucasians who lack the G2m(23) immunoglobulin allotype[13]
- Native Americans[14-16]
- Household contacts of cases[17]
- Individuals with asplenia, sickle cell disease, or antibody deficiency syndromes.[18,19]

Prevention of Hib Disease with Vaccine

An important virulence factor of the Hib bacterium is its polysaccharide capsule (PRP). Antibody to PRP (anti-PRP) has been shown to correlate with protection against Hib disease.[3,21] While the anti-PRP level associated with protection using conjugated vaccines has not yet been determined, the level of anti-PRP associated with protection in studies using bacterial polysaccharide immune globulin or nonconjugated PRP vaccines ranged from $\geq$0.15 to $\geq$1.0 mcg/mL.[22-28]

Nonconjugated PRP vaccines are capable of stimulating B-lymphocytes to produce antibody without the help of T-lymphocytes (T-independent). The responses to many other antigens are augmented by helper T-lymphocytes (T-dependent). PedvaxHIB is a PRP-conjugate vaccine in which the PRP is covalently bound to the OMPC carrier[29] producing an antigen which is postulated to convert the T-independent antigen (PRP alone) into a T-dependent antigen resulting in both an enhanced antibody response and immunologic memory.

Clinical Trials with PedvaxHIB

The protective efficacy of the PRP-OMPC component of COMVAX was demonstrated in a randomized, double-blind, placebo-controlled study involving 3486 Native American (Navajo) infants (The Protective Efficacy Study) who completed the primary two-dose regimen for lyophilized PedvaxHIB. This population has a much higher incidence of Hib disease than the United States population as a whole and also has a lower antibody response to Haemophilus b conjugate vaccines, including PedvaxHIB.[14-16,30,31]

Each infant in this study received two doses of either placebo or lyophilized PedvaxHIB (15 mcg Haemophilus b PRP) with the first dose administered at a mean of 8 weeks of age and the second administered approximately two months later; DTP (Diphtheria and Tetanus Toxoids and whole cell Pertussis Vaccine, Adsorbed) and OPV (Poliovirus Vaccine Live Oral Trivalent) were administered concomitantly. In a subset of 416 subjects, lyophilized PedvaxHIB (15 mcg Haemophilus b PRP) induced anti-PRP levels >0.15 mcg/mL in 88% and >1.0 mcg/mL in 52% with a geometric mean titer (GMT) of 0.95 mcg/mL one to three months after the first dose; the corresponding anti-PRP levels one to three months following the second dose were 91% and 60%, respectively, with a GMT of 1.43 mcg/mL. These antibody responses were associated with a high level of protection.

Most subjects were initially followed until 15 to 18 months of age. During this time, 22 cases of invasive Hib disease occurred in the placebo group (8 cases after the first dose and 14 cases after the second dose) and only 1 case in the vaccine group (none after the first dose and 1 after the second dose). Following the primary two-dose regimen, the protective efficacy of lyophilized PedvaxHIB was calculated to be 93% with a 95% confidence interval (C.I.) of 57-98%. In the two months between the first and second doses, the difference in number of cases of disease between placebo and vaccine recipients (8 vs

0 cases, respectively) was statistically significant (p=0.008). At termination of the study, placebo recipients were offered vaccine. All original participants were then followed two years and nine months from termination of the study. During this extended follow-up, invasive Hib disease occurred in an additional 7 of the original placebo recipients prior to receiving vaccine and in 1 of the original vaccine recipients (who had received only 1 dose of vaccine). No cases of invasive Hib disease were observed in placebo recipients after they received at least one dose of vaccine. Efficacy for this follow-up period, estimated from person-days at risk, was 96.6% (95 C.I., 72.2-99.9%) in children under 18 months of age and 100% (95 C.I., 23.5-100%) in children over 18 months of age.[31] Thus, in this study, a protective efficacy of 93% was achieved with an anti-PRP level of >1.0 mcg/mL in 60% of vaccinees and a GMT of 1.43 mcg/mL one to three months after the second dose.

Hepatitis B Disease

Hepatitis B virus is an important cause of viral hepatitis. According to the Centers for Disease Control (CDC), there are an estimated 200,000-300,000 new cases of Hepatitis B infection annually in the United States.[32] There is no specific treatment for this disease. The incubation period for hepatitis B is relatively long; six weeks to six months may elapse between exposure and the onset of clinical symptoms. The prognosis following infection with hepatitis B virus is variable and dependent on at least three factors: (1) Age — infants and younger children usually experience milder initial disease than older persons but are much more likely to remain persistently infected and become at risk of developing serious chronic liver disease; (2) Dose of virus — the higher the dose, the more likely acute icteric hepatitis B will result; and, (3) Severity of associated underlying disease — underlying malignancy or pre-existing hepatic disease predisposes to increased mortality and morbidity.[34]

Hepatitis B infection fails to resolve and progresses to a chronic carrier state in 5 to 10% of older children and adults and in up to 90% of infants; chronic infection also occurs more frequently after initial anicteric hepatitis B than after initial icteric disease.[34] Consequently, carriers of HBsAg frequently give no history of having had recognized acute hepatitis. It has been estimated that more than 285 million people in the world today are persistently infected with hepatitis B virus.[35] The CDC estimates that there are approximately 1 million-1.25 million chronic carriers of hepatitis B virus in the USA.[32] Chronic carriers represent the largest human reservoir of hepatitis B virus.

A serious complication of acute hepatitis B virus infection is massive hepatic necrosis while sequelae of chronic hepatitis B include cirrhosis of the liver, chronic active hepatitis, and hepatocellular carcinoma. Chronic carriers of HBsAg appear to be at increased risk of developing hepatocellular carcinoma. Although a number of etiologic factors are associated with development of hepatocellular carcinoma, the single most important etiologic factor appears to be chronic infection with hepatitis B virus.[36] According to the CDC, hepatitis B vaccine is recognized as the first anti-cancer vaccine because it can prevent primary liver cancer.[67]

The vehicles for transmission of the virus are most often blood and blood products but the viral antigen has also been found in tears, saliva, breast milk, urine, semen, and vaginal secretions. Hepatitis B virus is capable of surviving for days on environmental surfaces exposed to body fluids containing hepatitis B virus. Infection may occur when hepatitis B virus, transmitted by infected body fluids, is implanted via mucous surfaces or percutaneously introduced through accidental or deliberate breaks in the skin. Transmission of hepatitis B virus infection is often associated with close interpersonal contact with an infected individual and with crowded living conditions.[37]

Prevention of Hepatitis B Disease with Vaccine

Hepatitis B infection and disease can be prevented through immunization with vaccines that contain viral surface antigen (HBsAg) and induce formation of protective antibody (anti-HBs).[38-39]

Multiple clinical studies have defined a protective level of anti-HBs as 1) 10 or more sample ratio units (SRU or S/N) as determined by radioimmunoassay or 2) a positive result as determined by enzyme immunoassay.[40-46] Note: 10 SRU is comparable to 10 mIU/mL of antibody.[36] The ACIP and an international group of hepatitis B experts consider an anti-HBs titer ≥10 mIU/mL an adequate response to a complete course of hepatitis B vaccine and protective against clinically significant infection (antigenemia with or without clinical disease).[36,46]

Clinical Trials with RECOMBIVAX HB

In clinical studies, 100% of 92 infants under 1 year of age born of non-carrier mothers developed a protective level of antibody (anti-HBs ≥10 mIU/mL) after receiving three 5-mcg doses of RECOMBIVAX HB at intervals of 0, 1, and 6 months.[31]

In one clinical study of RECOMBIVAX HB (2.5 mcg), which examined a different regimen of RECOMBIVAX HB, protective levels of antibody were achieved in 98% of 52 healthy infants vaccinated at

2, 4, and 12 months of age. Protective anti-HBs levels were achieved in 100% of 50 infants vaccinated at 2, 4, and 15 months of age.[47]

The protective efficacy of three 5-mcg doses of RECOMBIVAX HB, given at birth (with Hepatitis B Immune Globulin), 1, and 6 months of age, has been demonstrated in neonates born of mothers positive for both HBsAg and HBeAg (a core-associated antigenic complex which correlates with high infectivity). In this trial, after nine months of follow-up, chronic infection had not occurred in 96% of 130 infants.[48] The estimated efficacy in prevention of chronic hepatitis B infection was 95% as compared to the infection rate in untreated historical controls.[49]

Immunogenicity of COMVAX

The immunogenicity of COMVAX (7.5 mcg Haemophilus b PRP, 5 mcg HBsAg) was assessed in 1602 infants and children 6 weeks to 15 months of age in 5 clinical studies. In 2 controlled clinical trials (n=684), the immune response of COMVAX was compared with that obtained using the monovalent vaccines, PedvaxHIB (7.5 mcg Haemophilus b PRP) and RECOMBIVAX HB (5 mcg HBsAg) given at separate sites, either concurrently or one month apart. The immunogenicity of COMVAX was further assessed in 2 uncontrolled studies (n=852). In the first, a complete three-dose series of COMVAX was administered concurrently with other routine pediatric vaccines. In the second, COMVAX was administered as the third dose of Haemophilus b PRP and HBsAg concurrently with routine pediatric vaccines. COMVAX was also administered as the control arm in the evaluation of an investigational vaccine (n=66).

These studies demonstrate COMVAX to be highly immunogenic. The antibody responses are summarized below.

Antibody Responses to COMVAX in Infants Not Previously Vaccinated with Hib or Hepatitis B Vaccine

In the pivotal, controlled, multicenter, randomized, open-label study, 882 infants approximately 2 months of age, who had not previously received any Hib or hepatitis B vaccine, were assigned to receive a three-dose regimen of either COMVAX or PedvaxHIB plus RECOMBIVAX HB at approximately 2, 4, and 12-15 months of age. The proportions of evaluable vaccinees developing clinically important levels of anti-PRP (percent with >1.0 mcg/mL after the second dose, n=762) and anti-HBs (percent with ≥10 mIU/mL after the third dose, n=750) were similar in children given COMVAX or concurrent PedvaxHIB and RECOMBIVAX HB (Table 1).

The anti-PRP response after the second dose among infants given COMVAX in this study was 72.4% (C.I. 68.7, 76.0) >1.0 mcg/mL with a GMT=2.5 mcg/mL (C.I. 2.2, 2.8) and was comparable to that of infants given the PedvaxHIB and RECOMBIVAX HB controls which was 76.3% (C.I. 70.2, 82.5) with a GMT=2.8 mcg/mL (C.I. 2.2, 3.5). These responses exceed the response of Native American (Navajo) infants in a previous study of lyophilized PedvaxHIB (60% >1.0 mcg/mL; GMT=1.43 mcg/mL) that was associated with a 93% reduction in the incidence of invasive Hib disease. The efficacy of COMVAX in the prevention of invasive Hib disease is expected to be similar to that obtained with monovalent lyophilized PedvaxHIB in the Protective Efficacy Trial (see CLINICAL PHARMACOLOGY, *Clinical Trials with PedvaxHIB*).

The anti-HBs response after the third dose among infants given COMVAX in this study was 98.4% ≥10 mIU/mL (C.I. 97.0, 99.3) with a GMT of 4467.5 (C.I. 3786.3, 5271.3) compared to 100.0% (C.I. 97.9, 100.0) with a GMT of 6943.9 (C.I. 5555.9, 8678.7) among infants given COMVAX or concurrent PedvaxHIB and RECOMBIVAX HB.

Although the difference in anti-HBs GMT is statistically significant (p=0.011), both values are much greater than the level of 10 mIU/mL previously established as marking a protective response to hepatitis B.[42,44-46,51,52] These GMTs are higher than those observed in young infants who received the currently licensed regimen of RECOMBIVAX HB consisting of 5-mcg doses administered on the standard 0, 1, and 6-month schedule (GMT ~ 1359.9 mIU/mL).[53-55] In addition, two studies have shown that infants given 2.5-mcg doses of RECOMBIVAX HB according to the schedule used for COMVAX (2, 4, and 12-15 months of age) developed GMTs of 1245-3424 mIU/mL.[47,64] While a difference in GMT may result in differential retention of ≥10 mIU/mL of anti-HBs after a number of years, this is of no apparent clinical significance because of immunologic memory.[56,57]

Because the HBsAg component of COMVAX induces a comparable anti-HBs response to that obtained with RECOMBIVAX HB, the efficacy of COMVAX is expected to be similar (Table 1).

Table 1
Antibody Responses to COMVAX, PedvaxHIB, and RECOMBIVAX HB in Infants Not Previously Vaccinated with Hib or Hepatitis B Vaccine

Vaccine	Age (months)	Time	n	Anti-PRP % Subjects with >0.15 mcg/mL	Anti-PRP % Subjects with >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)	n	Anti-HBs % Subjects ≥10 mIU/mL	Anti-HBs GMT (mIU/mL)
COMVAX		Prevaccination	633	34.4	4.7	0.1	603	10.6	0.6
(7.5 mcg PRP,	2	Dose 1*	620	88.9	51.5	1.0	595	34.3	4.2
5 mcg HBsAg)	4	Dose 2*	576	94.8	72.4***	2.5***	571	92.1	113.9
[N=661]	12/15	Dose 3**	570	99.3	92.6	9.5	571	98.4	4467.5***
PedvaxHIB		Prevaccination	208	33.7	5.8	0.1	196	7.1	0.5
(7.5 mcg PRP)	2	Dose 1*	202	90.1	53.5	1.1	198	41.9	5.3
+	4	Dose 2*	186	95.2	76.3***	2.8***	185	98.4***	255.7
RECOMBIVAX HB	12/15	Dose 3**	181	98.9	92.3	10.2	179	100.0***	6943.9***
(5 mcg HBsAg)									
[N=221]									

* Postvaccination responses were determined approximately two months after doses 1 and 2.
** Postvaccination responses were determined approximately one month after administration of dose 3.
More than three-quarters of the infants in the study received DTP and OPV concomitantly with the first two doses of COMVAX or PedvaxHIB plus RECOMBIVAX HB, and approximately one-third received M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live) with the third dose of these vaccines at 12 or 15 months of age.
*** C.I.'s of comparisons:
Dose 2 Anti-PRP: 95% C.I. on difference in % >1.0 mcg/mL (-11.2, 3.1); 95% C.I. on ratio of GMT (0.69, 1.17)
Dose 3 Anti-HBs: 95% C.I. on difference in % ≥10 mIU/mL (-2.9, -0.6); 95% C.I. on ratio of GMT (0.49, 0.91)

Antibody Responses to COMVAX in Infants Previously Vaccinated with Hepatitis B Vaccine at Birth

Two clinical studies assessed antibody responses to a three-dose series of COMVAX in 128 evaluable infants who were previously given a birth dose of hepatitis B vaccine. Table 2 summarizes the anti-PRP and anti-HBs responses of these infants. The antibody responses were clinically comparable to those observed in the pivotal trial of COMVAX (Table 1).

Table 2
Antibody Responses to COMVAX in Infants Previously Vaccinated with Hepatitis B Vaccine at Birth

Study	Age (months) at Vaccination	Time	n	Anti-PRP % Subjects with >0.15 mcg/mL	Anti-PRP % Subjects with >1.0 mcg/mL	Anti-PRP GMT (mcg/mL)	n	Anti-HBs % Subjects ≥10 mIU/mL	Anti-HBs GMT (mIU/mL)
		Prevaccination	119	24.4	5.9	0.1	71	25.4	2.9
Study 1	2	Dose 1			Not Measured				
[N=126]	4	Dose 2*	111	94.6	81.1	3.3	111	98.2	417.2
	14/15	Dose 3*	88	100	93.2	11.0	87	98.9	3500.7
		Prevaccination	17	58.8	0	0.2	15	6.7	0.7
Study 2	2	Dose 1**	17	88.2	47.1	0.9	16	81.3	35.2
[N=19]	4	Dose 2**	17	100	76.5	2.8	16	100	281.8
	15	Dose 3**	15	100	100	8.5	16	100	3913.4

* Postvaccination responses were determined approximately 2 months after dose 2 and 1 month after dose 3.
** Postvaccination responses were determined approximately 2 months after doses 1, 2, and 3.
Infants in these studies received DTP and OPV or eIPV (enhanced inactivated poliovirus vaccine) concomitantly with the first two doses of COMVAX, while the third dose of COMVAX was given concomitantly with DTaP (diphtheria and tetanus and acellular pertussis), OPV, and M-M-R® II at 14-15 months of age (Study 1) or with just M-M-R® II at 15 months of age (Study 2).

Interchangeability of COMVAX and Licensed Haemophilus b Conjugate Vaccines or Recombinant Hepatitis B Vaccines

Among 58 children previously given a primary course of PedvaxHIB, 90% (95% C.I. 78.8%, 96.1%) developed an anti-PRP response >1 mcg/mL with a GMT of 9.6 mcg/mL (95% C.I. 6.6, 14.1) in response to a dose of COMVAX at 12-15 months of age. Among 683 children previously given a primary course of another HIB or HIB-containing vaccine, 99% (95% C.I. 97.9%, 99.6%) developed an anti-PRP response >1 mcg/mL with a GMT of 14.9 mcg/mL (95% C.I. 13.7, 16.3) in response to a dose of COMVAX at 12-15 months of age.

In another study, COMVAX was administered either concomitantly or six weeks after vaccination with M-M-R® II and VARIVAX® (Varicella Virus Vaccine Live, Oka/Merck). Among 149 children who previously received 2 doses of monovalent Hepatitis B vaccine, 100% (95% C.I. 97.6%, 100.0%) developed an anti-HBs response ≥10 mIU/mL with a GMT of 2194.6 mIU/mL (95% C.I. 1667.8, 2887.8) in response to a dose of COMVAX at 12-15 months of age.

Antibody Responses to COMVAX and Concurrently Administered Vaccines

Immunogenicity results from open-labeled studies indicate that COMVAX can be administered concomitantly with DTP, DTaP, OPV, IPV (inactivated poliomyelitis vaccine), M-M-R II, and VARIVAX using separate sites and syringes for injectable vaccines.

DTP and DTaP

After a primary series of DTP (2, 4, 6 months of age) given concomitantly with COMVAX (2 and 4 months of age), 98.2% of 57 infants developed a 4-fold rise in antibody to diphtheria, 100% of 57 infants developed a 4-fold rise in antibody to tetanus, and 89.5% to 96.5% of 57 infants developed a 4-fold rise in antibody to pertussis antigens, depending on the assay used and adjusted for maternal antibody. In this trial, after 2 doses of COMVAX, 79.0% of 62 infants developed anti-PRP >1.0 mcg/mL and after 3 doses (2, 4, and 15 months of age), 100% of 59 infants developed ≥10 mIU/mL of anti-HBs.

After a primary series of DTaP and COMVAX given concomitantly at 2, 4, and 6 months of age, 100% of 18 infants had ≥0.01 antitoxin units/mL to diphtheria and tetanus and 94.4% to 100% of 18 infants developed a ≥4-fold rise in antibody to pertussis antigens, depending on the assay used and adjusted for maternal antibody. In this trial, after 2 doses of COMVAX, 85.7% of 63 infants developed anti-PRP >1.0 mcg/mL and after 3 doses administered on the compressed schedule of 2, 4, and 6 months of age, 92.9% of 56 infants developed ≥10 mIU/mL of anti-HBs.

OPV and IPV

After a primary series of OPV (2, 4, 6 months of age) given concomitantly with COMVAX (2 and 4 months of age), 98.3% of 60 infants had neutralizing antibody ≥1:4 to poliovirus type 1, 100% of 57 infants had neutralizing antibody ≥1:4 to poliovirus type 2 and 98.1% of 53 infants had neutralizing antibody ≥1:4 to poliovirus type 3. In this trial, after 2 doses of COMVAX, 79.0% of 62 infants developed anti-PRP >1.0 mcg/mL and after 3 doses, 100% of 59 infants developed ≥10 mIU/mL of anti-HBs.

After a primary series of IPV and COMVAX given concomitantly at 2, 4, and 6 months of age, 100% of 38 infants had neutralizing antibody ≥1:4 to poliovirus types 1, 2, and 3. In this trial, after 2 doses of COMVAX, 85.7% of 63 infants developed anti-PRP >1.0 mcg/mL and after 3 doses administered on the compressed schedule of 2, 4, and 6 months of age, 92.9% of 56 infants developed ≥10 mIU/mL of anti-HBs.

M-M-R II and VARIVAX

After concomitant vaccination of M-M-R II and VARIVAX with COMVAX (12 to 15 months of age), 99.4% of 313 children developed antibody to measles, 99.2% of 354 children developed antibody to mumps, 100% of 358 children developed antibody to rubella and 100% of 276 children developed antibody to varicella. In this trial, infants received the primary series of Hib vaccine and the first two doses of Hepatitis B vaccine in the first year of life. After the dose of COMVAX, 97.8% of 368 infants developed >1.0 mcg/mL of anti-PRP and 99.2% developed ≥10 mIU/mL of anti-HBs.

INDICATIONS AND USAGE

COMVAX is indicated for vaccination against invasive disease caused by *Haemophilus influenzae* type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age born of HBsAg negative mothers.

Infants born to HBsAg positive mothers should receive Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]).

Infants born to mothers of unknown HBsAg status should receive Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]).

Vaccination with COMVAX should ideally begin at approximately 2 months of age or as soon thereafter as possible. In order to complete the three-dose regimen of COMVAX, vaccination should be initiated no later than 10 months of age. Infants in whom vaccination with a PRP-OMPC-containing product (i.e., PedvaxHIB, COMVAX) is not initiated until 11 months of age do not require three doses of PRP-OMPC; however, three doses of an HBsAg-containing product are required for complete vaccination against hepatitis B, regardless of age. For infants and children not vaccinated according to the recommended schedule see DOSAGE AND ADMINISTRATION.

COMVAX will not protect against invasive disease caused by *Haemophilus influenzae* other than type b or against invasive disease (such as meningitis or sepsis) caused by other microorganisms. COMVAX will not prevent hepatitis caused by other viruses known to infect the liver. Because of the long incubation period for hepatitis B, it is possible for unrecognized infection to be present at the time the vaccine is given. The vaccine may not prevent hepatitis B in such patients.

As with other vaccines, COMVAX may not induce protective antibody levels immediately following vaccination and may not result in a protective antibody response in all individuals given the vaccine.

Use With Other Vaccines

Immunogenicity results from open-labeled studies indicate that COMVAX can be administered concomitantly with DTP, DTaP, OPV, IPV, M-M-R II, and VARIVAX using separate sites and syringes for injectable vaccines (see CLINICAL PHARMACOLOGY).

CONTRAINDICATIONS

Hypersensitivity to yeast or any component of the vaccine.

The decision to administer or delay vaccination because of current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. The ACIP has recommended that immunization should be delayed during the course of an acute febrile illness.[63] All vaccines can be administered to persons with minor illnesses such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness. Persons with moderate or severe febrile illness should be vaccinated as soon as they have recovered from the acute phase of the illness.

WARNINGS

Patients who develop symptoms suggestive of hypersensitivity after an injection should not receive further injections of the vaccine (see CONTRAINDICATIONS).

PRECAUTIONS

General

General care is to be taken by the health-care provider for the safe and effective use of this product.

As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur.

Use caution when vaccinating latex-sensitive individuals since the vial stopper contains dry natural latex rubber that may cause allergic reactions.

As reported with Haemophilus b Polysaccharide Vaccine and another Haemophilus b Conjugate Vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines.

The packaging stopper of this product contains natural rubber latex which may cause allergic reactions.

Instructions to Health-care Provider

The health-care provider should determine the current health status and previous vaccination history of the vaccinee.

The health-care provider should question the patient, parent or guardian about reactions to a previous dose of COMVAX, PedvaxHIB or other Haemophilus b conjugate vaccines or RECOMBIVAX HB or other hepatitis B vaccines.

Injection of a blood vessel should be avoided.

COMVAX should be given with caution in infants with bleeding disorders such as hemophilia or thrombocytopenia, with steps taken to avoid the risk of hematoma following the injection.

If COMVAX is used in persons with malignancies or those receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

COMVAX is not contraindicated in the presence of HIV infection.[68]

Information for Vaccine Recipients and Parents/Guardians

The health-care provider should provide the vaccine information required to be given with each vaccination to the patient, parent or guardian.

The health-care provider should inform the patient, parent or guardian of the benefits and risks associated with vaccination. For risks associated with vaccination, see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.

Laboratory Test Interactions

Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in the urine of some vaccinees for at least 30 days following vaccination with lyophilized PedvaxHIB[58]; in clinical studies with lyophilized PedvaxHIB, such children demonstrated a normal immune response to the vaccine. It is not known whether antigenuria will occur after vaccination with COMVAX.

Drug Interaction

Deferral of immunization may be considered in individuals receiving immunosuppressive therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

COMVAX has not been evaluated for its carcinogenic or mutagenic potential, or its potential to impair fertility.

Pregnancy

Pregnancy Category C: Animal reproduction studies have not been conducted with COMVAX. It is also not known whether COMVAX can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. COMVAX is not recommended for use in women of childbearing age.

Pediatric Use

Safety and effectiveness of COMVAX in infants below the age of 6 weeks and above the age of 15 months have not been established. However, studies have demonstrated that PedvaxHIB is safe and immunogenic when administered to infants and children up to the age of 71 months and RECOMBIVAX HB is safe and immunogenic in persons of all ages.

COMVAX should not be used in infants younger than 6 weeks of age because this will lead to a reduced anti-PRP response and may lead to immune tolerance (impaired ability to respond to subsequent exposure to the PRP antigen).[59-61]

Infants born to HBsAg-positive mothers should not receive COMVAX but instead should receive Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]). (See DOSAGE AND ADMINISTRATION.)

Geriatric Use

This vaccine is NOT recommended for use in adult populations.

ADVERSE REACTIONS

In clinical trials involving the administration of 7918 doses of COMVAX to 3561 healthy infants 6 weeks to 15 months of age, COMVAX was generally well tolerated. In these studies, infants received COMVAX with licensed pediatric vaccines (n=1745) or investigational vaccines (n=1816). Serious adverse experience data were available for all 3561 infants and non-serious adverse experience data were available for a subset of 1678 infants.

Pivotal Immunogenicity and Safety Study

In the pivotal, randomized, multicenter study, 882 infants were assigned in a 3:1 ratio to receive either COMVAX or PedvaxHIB plus RECOMBIVAX HB at separate injection sites at 2, 4, and 12-15 months of age. Children may have also received routine pediatric immunizations. The children were monitored daily for five days after each injection for injection-site and systemic adverse experiences. During this time, adverse experiences in infants who received COMVAX were generally similar in type and frequency to those observed in infants who received PedvaxHIB plus RECOMBIVAX HB.

The most frequently cited events were mild, transient signs and symptoms of inflammation at the injection site (i.e., pain/soreness, erythema, and swelling/induration), somnolence, and irritability, all of which were prompted for on report cards filled out by parents of vaccinated children. Table 3 summarizes the frequencies of injection-site and systemic adverse experiences within five days of vaccination that were reported among $\geq$1.0% of children in this pivotal trial.

Table 3
Local Reactions and Systemic Complaints Within 5 Days After Injection Reported to Occur in ≥1.0%† of Children Given a 3-Dose Course of COMVAX Compared to These Events in Children Given Concomitant Injections of PedvaxHIB and RECOMBIVAX HB

Event	Injection 1‡		Injection 2‡		Injection 3	
	COMVAX (N=660) %	PedvaxHIB and RECOMBIVAX HB*** (N=221) %	COMVAX (N=645) %	PedvaxHIB and RECOMBIVAX HB*** (N=213) %	COMVAX (N=593) %	PedvaxHIB and RECOMBIVAX HB*** (N=193) %
Injection Site Reactions						
Pain/Soreness*	34.5	37.6	24.3	25.8	23.9	21.2
Erythema (>1 in.)*	22.4 (2.7)	25.8 (2.7)	25.7 (1.4)	23.5 (3.3)	27.2 (3.0)	24.4 (1.6)
Swelling/Induration (>1 in.)*	27.6 (3.0)	33.5 (4.1)	30.4 (2.9)	31.0 (3.8)	27.2 (3.2)	29.5 (4.1)
Systemic Complaints						
Irritability*	57.0	46.6	50.7	44.1	32.2	29.0
Somnolence*	49.5	47.1	37.4	31.9	21.1	22.3
Crying—						
unusual, high pitched*	10.6	8.6	6.7	2.3	2.9	3.6
not otherwise specified	2.3	2.3	1.4	2.3	0.7	1.6
prolonged (>4 hrs.)*	2.4	2.3	0.8	1.4	0.2	0
Anorexia	3.9	2.3	2.0	0.9	0.8	0.5
Vomiting	2.1	1.8	2.5	0.9	1.0	1.6
Otitis media	0.5	0	2.0	1.4	2.7	1.6
Fever (°F, rectal equiv.)**						
101.0-102.9	14.2	11.9	13.8	12.2	10.5	6.4
≥103.0	0.8	0	1.6	1.4	2.7	4.3
Diarrhea	1.7	1.8	0.8	0.9	2.2	0.5
Upper respiratory infection	0.5	0.5	1.1	0.9	1.3	0.5
Rash	0.8	0	0.9	0	0.8	0.5
Rhinorrhea	0.2	0	1.1	0.9	1.3	2.1
Respiratory congestion	0.6	0.5	1.2	0.9	0.3	0.5
Cough	0.2	0	0.9	0.5	0.2	1.0
Candidiasis, oral	0.3	0.5	0.8	0	0.2	0
Rash, diaper	0.5	0.5	0.5	0.9	0.2	0

† Overall frequency of each event listed above is ≥1% even though the frequency after a given dose may be <1%.
‡ Most children received DTP and OPV concomitantly with the first two doses of COMVAX or PedvaxHIB and RECOMBIVAX HB.
* Events prompted for on Vaccination Report Card given to parents/guardians of vaccinees.
** N for injections 1, 2, and 3 equals 655, 639, and 588, respectively, for COMVAX; N for injections 1, 2, and 3 equals 218, 213, and 187, respectively, for PedvaxHIB and RECOMBIVAX HB.
*** Injection site reactions for PedvaxHIB and RECOMBIVAX HB based on occurrence with either of the monovalent components.

Infants Previously Vaccinated with Hepatitis B Vaccine

In a group of infants (N=126) given a three-dose course of COMVAX after previously receiving a dose of Hepatitis B Vaccine (Recombinant) at or shortly after birth, the type, frequency, and severity of adverse experiences did not appear to be greater than those observed in infants in the pivotal study who did not receive hepatitis B vaccine at birth.

Infants 6 Weeks to 15 Months of Age

In clinical trials, 3285 doses of COMVAX were administered to 1678 infants who were monitored for injection-site and systemic adverse experiences from Days 0 to 5 after each injection of vaccine. Of these, 855 infants had safety data following vaccination at approximately 2 months of age, 836 infants at approximately 4 months of age and 1573 infants at 12 to 15 months of age. The most frequently reported adverse experiences (≥1% of subjects for at least one injection), without regard to causality are listed in decreasing order of frequency within each body system:

Injection Site Reactions: Pain/tenderness/soreness, swelling/induration, erythema; *Body as a Whole:* Fever; *Digestive System:* Anorexia, diarrhea, vomiting; *Nervous System/Psychiatric:* Irritability, somnolence, crying; *Respiratory System:* Upper respiratory infection, rhinorrhea, cough, rhinitis; *Skin:* Rash; *Special Senses:* Otitis media.

Post-Marketing Experience

As with any vaccine, there is the possibility that broad use of COMVAX could reveal adverse experiences not observed in clinical trials. The following additional adverse reactions have been reported with the use of the marketed vaccine.

Hypersensitivity

Anaphylaxis, angioedema, urticaria, erythema multiforme

Hematologic

Thrombocytopenia

Nervous System

Seizure, febrile seizures

Potential Adverse Effects

In addition, a variety of adverse effects have been reported with marketed use of either PedvaxHIB or RECOMBIVAX HB in infants and children through 71 months of age. These adverse effects are listed below.

PedvaxHIB

Hematologic/Lymphatic

Lymphadenopathy

Skin

Sterile injection-site abscess; pain at the injection site

RECOMBIVAX HB

Hypersensitivity

Symptoms of hypersensitivity including reports of rash, pruritus, edema, arthralgia, dyspnea, hypotension, and ecchymoses

Cardiovascular System

Tachycardia; syncope

Digestive System

Elevation of liver enzymes

Hematologic

Increased erythrocyte sedimentation rate

Musculoskeletal System

Arthritis

Nervous System

Bell's Palsy; Guillain-Barré Syndrome

Psychiatric/Behavioral

Agitation; somnolence; irritability

Skin

Stevens-Johnson Syndrome; alopecia

Special Senses

Conjunctivitis; visual disturbances

Adverse Event Reporting

Patients, parents and guardians should be instructed to report any serious adverse reactions to their health-care provider who in turn should report such events to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS), 1-800-822-7967. The health-care provider should inform the parent or guardian of the National Vaccine Injury Compensation Program (NVICP), 1-800-338-2382.

DOSAGE AND ADMINISTRATION

FOR INTRAMUSCULAR ADMINISTRATION

Do not inject intravenously, intradermally, or subcutaneously.

Recommended Schedule

Infants born to HBsAg negative mothers should be vaccinated with three 0.5 mL doses of COMVAX, ideally at 2, 4, and 12-15 months of age. If the recommended schedule cannot be followed, the interval between the first two doses should be at least six weeks and the interval between the second and third dose should be as close as possible to eight to eleven months.

Infants born to HBsAg-positive mothers should receive Hepatitis B Immune Globulin and Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]).

Infants born to mothers of unknown HBsAg status should receive Hepatitis B Vaccine (Recombinant) at birth and should complete the hepatitis B vaccination series given according to a particular schedule (see manufacturer's circular for Hepatitis B Vaccine [Recombinant]).

The subsequent administration of COMVAX for completion of the hepatitis B vaccination series in infants who were born to HBsAg positive mothers and received HBIG or infants born to mothers of unknown status has not been studied.

COMVAX should not be administered to any infant before the age of 6 weeks.

Modified Schedules

Children previously vaccinated with one or more doses of either hepatitis B vaccine or Haemophilus b conjugate vaccine

Children who receive one dose of hepatitis B vaccine at or shortly after birth may be administered COMVAX on the schedule of 2, 4, and 12-15 months of age. There are no data to support the use of a three-dose series of COMVAX in infants who have previously received more than one dose of hepatitis B vaccine. However, COMVAX may be administered to children otherwise scheduled to receive concurrent RECOMBIVAX HB and PedvaxHIB.

Children not vaccinated according to recommended schedule for COMVAX

Vaccination schedules for children not vaccinated according to the recommended schedule should be considered on an individual basis. The number of doses of a PRP-OMPC-containing product (i.e., COMVAX, PedvaxHIB) depends on the age that vaccination is begun. An infant 2 to 10 months of age should receive three doses of a product containing PRP-OMPC. An infant 11 to 14 months of age should receive two doses of a product containing PRP-OMPC. A child 15 to 71 months of age should receive one dose of a product containing PRP-OMPC. Infants and children, regardless of age, should receive three doses of an HBsAg-containing product.

COMVAX is for intramuscular injection. The *anterolateral thigh* is the recommended site for intramuscular injection in infants. Data suggests that injections given in the buttocks frequently are given into fatty tissue instead of into muscle. Such injections have resulted in a lower seroconversion rate (for hepatitis B vaccine) than was expected.

Injection must be accomplished with a needle long enough to ensure intramuscular deposition of the vaccine. The ACIP has recommended that for intramuscular injections, the needle should be of sufficient length to reach the muscle mass itself. In a clinical trial with COMVAX (see CLINICAL PHARMACOLOGY, *Antibody Responses to COMVAX in Infants Not Previously Vaccinated with Hib or Hepatitis B Vaccine*, Table 1) vaccination was accomplished with a needle length of 5/8 inches in accordance with ACIP recommendations in effect at that time.[62] ACIP currently recommends that needles of longer length (7/8 to 1 inch) be used.[63]

The vaccine should be used as supplied; no reconstitution is necessary.

Shake well before withdrawal and use. Thorough agitation is necessary to maintain suspension of the vaccine.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. After thorough agitation, COMVAX is a slightly opaque, white suspension.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of infectious agents from one person to another.

Interchangeability of COMVAX and Licensed Haemophilus b Conjugate Vaccines or Recombinant Hepatitis B Vaccines

Since 1990, the Advisory Committee on Immunization Practices (ACIP) and the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) have recommended routine immunization of infants starting at 2 months of age with a polysaccharide-protein conjugate vaccine to prevent invasive Hib disease.[32,33]

Three Hib vaccines are licensed for infant vaccination: 1) oligosaccharide conjugate Hib vaccine (HbOC) (HibTITER®*), 2) polyribosylribitol phosphate-tetanus toxoid conjugate (PRP-T) (ActHIB®* and OmniHIB®*), and 3) Haemophilus b conjugate vaccine (meningococcal protein conjugate) (PRP-OMPC) (PedvaxHIB). According to the ACIP, these products are now considered interchangeable for primary as well as booster vaccination.[66]

Because vaccination recommendations limited to high-risk individuals have failed to substantially lower the overall incidence of hepatitis B infection, both the Advisory Committee on Immunization Practices (ACIP) and the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) have endorsed universal infant immunization as part of a comprehensive strategy for the control of hepatitis B infection.[32,50]

HOW SUPPLIED

No. 4898 — COMVAX is supplied as 7.5 mcg PRP polysaccharide conjugated to approximately 125 mcg OMPC and 5 mcg HBsAg in a box of 10 single dose vials.

NDC 0006-4898-00.

Storage

Store vaccine at 2-8°C (36-46°F). Storage above or below the recommended temperature may reduce potency.

DO NOT FREEZE since freezing destroys potency.

REFERENCES

1. Cochi, S.L., et al. JAMA *253:* 521-529, 1985.
2. Schlech, W.F., III, et al. JAMA *253:* 1749-1754, 1985.
3. Peltola, H., et al. N Engl J Med *310:* 1561-1566, 1984.
4. Cardoz, M., et al. Bull WHO *59:* 575-584, 1981.
5. Sell, S.H., et al. Pediatr *49:* 206-217, 1972.
6. Taylor, H.G., et al. Pediatr *74:* 198-205, 1984.
7. Hay, J.W., et al. Pediatr *80*(3): 319-329, 1987.
8. Redmond, S.R., et al. JAMA *252:* 2581-2584, 1984.
9. Istre, G.R., et al. J Pediatr *106:* 190-195, 1985.
10. Fraser, D.W., et al. J Infect Dis *127:* 271-277, 1973.
11. Tarr, P.I., et al. J Pediatr *92:* 884-888, 1978.
12. Granoff, D.M., et al. J Clin Invest *74:* 1708-1714, 1984.
13. Ambrosino, D.M., et al. J Clin Invest *75:* 1935-1942, 1985.
14. Coulehan, J.L., et al. Pub Health Rep *99:* 404-409, 1984.
15. Losonsky, G.A., et al. Pediatr Infect Dis J *3:* 539-547, 1985.
16. Ward, J.I., et al. Lancet *1:* 1281-1285, 1981.
17. Ward, J.I., et al. N Engl J Med *301:* 122-126, 1979.
18. Ward, J.I., et al. J Pediatr *88:* 261-263, 1976.
19. Bartlett, A.V., et al. J Pediatr *102:* 55-58, 1983.
20. Centers for Disease Control. MMWR *34*(15): 201-205, 1985.
21. Santosham, M., et al. N Engl J Med *317:* 923-929, 1987.
22. Siber, G.R., et al. Infect Immun *45:* 248-254, 1984.
23. Smith, D.H., et al. Pediatr *52:* 637-644, 1973.
24. Robbins, J.B., et al. Pediatr Res *7:* 103-110, 1973.

* HibTITER is a registered trademark of Lederle Laboratories, ActHIB is a registered trademark of Aventis Pasteur Inc. and OmniHIB is a registered trademark of GlaxoSmithKline.

25. Kaythy, H., et al. J Infect Dis *147:* 1100, 1983.

26. Peltola, H., et al. Pediatr *60:* 730-737, 1977.

27. Ward, J.I., et al. Pediatr *81:* 886-893, 1988.

28. Daum, R.S., et al. Pediatr *81:* 893-897, 1988.

29. Marburg, S., et al. J Am Chem Soc *108:* 5282-5287, 1986.

30. Letson, G.W., et al. Pediatr Infect Dis J *7*(111): 747-752, 1988.

31. Data on file at Merck Research Laboratories.

32. Centers for Disease Control. MMWR *40*(RR-1):1-25, 1991.

33. Committee on Infectious Disease. Update Pediatrics *88*(1): 169-172, 1991.

34. Robinson, W.S. "Principles and Practice of Infectious Diseases," G.L. Mandell; R.G. Douglas; J.E. Bennett (eds), vol. 2, New York, John Wiley & Sons, 1985, pp. 1002-1029.

35. Maynard, J. E., et al. "Viral Hepatitis and Liver Disease", A.J. Zuckerman (ed.), Alan R. Liss, Inc., 1988, pp. 967-969.

36. Centers for Disease Control. MMWR *39*(RR-2): 5-26, 1990.

37. Wands, J.R., et al. "Principles of Internal Medicine," G.W. Thorn, R.D. Adams, E. Braunwald, K.J. Isselbacher, R.G. Petersdorf (eds), vol. 2, McGraw-Hill, 1977, pp. 1590-1598.

38. Sitrin, R.D., Wampler, D.E., Ellis, R.W. Survey of licensed hepatitis B vaccines and their production processes. In: Ellis RW, ed. Hepatitis B vaccines in clinical practice. New York: Marcel Dekker, Inc., 1993, pp. 83-101.

39. West, D.J. Scope and design of hepatitis B vaccine clinical trials. In Ellis RW, ed. Hepatitis B vaccines in clinical practice. New York: Marcel Dekker, Inc., 1993, pp. 159-177.

40. Hadler, S.C., et al. NEJM *315*(4): 209-214, 1986.

41. Szmuness, W., et al. NEJM *303:* 833-841, 1980.

42. Francis, D.P., et al. Ann Int Med *97:* 362-366, 1982.

43. Szmuness, W., et al. NEJM *307:* 1481-1486, 1982.

44. Szmuness, W., et al. Hepatology *1:* 377-385, 1981.

45. Coutinho, R.A., et al. BMJ *286:* 1305-1308, 1983.

46. International Group: Immunisation against hepatitis B, Lancet *1*(8590): 875-876, 1988.

47. Keyserling, H.L., et al. J Pediatr *125*(1): 67-69, 1994.

48. Stevens, C.E.; Taylor, P.E.; Tong, M.J., et al. "Viral Hepatitis and Liver Diseases." A.J. Zuckerman (ed.), Alan R. Liss, Inc., 1988, pp. 982-983.

49. Stevens, C.E., et al. Pediatr *90*(1, Part 2): 170-173, 1992.

50. Universal Hepatitis B Immunization, Committee on Infectious Diseases. Pediatr *89*(4): 795-800, 1992.

51. Centers for Disease Control. MMWR *34:* 313-24, 329-35, 1985.

52. Centers for Disease Control. MMWR *36:* 353-60, 366, 1987.

53. West, D.J., et al. Pediatr Clin North Am *37:* 585-601, 1990.

54. Seto, D., et al. Pediatr Res *31*(4 Pt 2): 179A, 1992.

55. Froehlich, H. Pediatr Res *31*(4 Pt 2): 92A, 1992.

56. Jilg, W., et al. Infection *17*: 70-6, 1989.

57. West, D.J., et al. Vaccine *14*: 1019-27, 1996.

58. Goep, J.G., et al. Pediatr Infect Dis J *1*(1): 2-5, 1992.

59. Keyserling, H.L., et al. Program and Abstracts of the 30th ICAAC, 1990. (Abst. 63).

60. Ward, J.I., et al. Program and Abstracts of the 32nd ICAAC, 1992. (Abst. 984).

61. Lieberman, J.M., et al. Infect Dis, 199 (Abst.1028).

62. Centers for Disease Control. MMWR *38*(13): 205-228, 1989.

63. Centers for Disease Control. MMWR *43*(RR-1): 1994.

64. Reisenger, K.S., et al. Pediatr Res (4 pt. 2): 179A, 1993.

65. Centers for Disease Control. MMWR *46*(54): 74, 1998.

66. Centers for Disease Control. MMWR *47*(1): 9, 1998.

67. Centers for Disease Control. Federal Register, *64*(35):9044-9045, February 23, 1999.

68. Centers for Disease Control. MMWR *42*(RR-4): 1-18, April 9, 1993.

Manuf. and Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued December 2010

Printed in USA