

Hepatitis B - Its Prevention by Vaccine

Pages with reference to book, From 45 To 48

H-B-Vax*, the first vaccine developed in the United States for protection against hepatitis B infection was found effective against hepatitis B in two major clinical studies.

Positive results from the first large-scale clinical trial (SzmUness et al., 1980) showed 92 percent efficacy in protecting high-risk individuals against hepatitis B. Additional studies confirmed the high immunogenic effect of the 20 mcg dose of vaccine.

Incidence and Impact of the Disease

Hepatitis B (formerly known as serum hepatitis) is the most serious of the three currently known viral forms of the disease and is believed to be responsible for half of all clinical hepatitis seen in the U.S. and for the majority of deaths among all cases. The other two viral forms are hepatitis A (often called infectious hepatitis), which is more common but milder than hepatitis B; and hepatitis non-A, non-B, a recently discovered form of the disease now under widespread study. (Cases of hepatitis may also occur as a complication of other conditions, such as viral or parasitic disease, or exposure to toxic substances).

Even mild, asymptomatic cases of hepatitis B often result in chronic illness, subsequent liver damage and death.

Hepatitis B is endemic throughout the world. The prevalence of hepatitis B surface antigen in the general population is less than 0.5 percent in the US. and Western Europe, 1 to 2 percent in South America and Southern Europe, 3 to 5 percent in North Africa and in many parts of the USSR, and 6 to 10 percent and higher in SubSaharan Africa and Southeast Asia. The overall rate of infection varies between 7 and 10 percent in the US. and between 60 and 80 percent in Southeast Asia or Africa. Even in countries like those in Northern and Western Europe and other highly developed countries with a relatively low prevalence, certain populations are at high risk of acquiring the disease and have cumulative infection rates of up to 70 percent. In countries or areas

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with a high prevalence rate, the entire population is at risk and infection often occurs during childhood. Many patients who survive hepatitis B infection each year will go on to become chronic carriers of the virus; some will be carriers for the rest of their lives. The carriers pose a constant threat of contagion to their families, close friends, and other persons in contact with them. A significant proportion of these carriers die of liver disease, including non-alcoholic cirrhosis and hepatitis B related liver cancer, called primary hepatocellular carcinoma (PHC).

Primary hepatocellular carcinoma is one of the world's most common tumors. It occurs in areas where there is a high carrier rate of hepatitis B virus, as measured by hepatitis B surface antigen.

In a large scale study of 22,707 male civil servants in Taiwan, of whom 15.2 percent had the surface antigen, Beasley et al. (1981) found the incidence of Hepatocellular carcinoma in the positive group was 1158 per 100,000 as opposed to 5 per 100,000 in the negative group. Thus the relative risk of developing PHC was 223 times greater for the men who were in the positive group.

Viola and others (1981) reported on a study of 100 chronic carriers of hepatitis B surface antigen in London, 77 of whom were male homosexuals. Seven of these patients died of hepatocellular carcinoma. Seventy-three of the 100 participants had some evidence of abnormal liver function, including chronic persistent hepatitis, chronic active hepatitis, cirrhosis, or hepatocellular carcinoma.

Discovery of the virus: In the late 1960s and early 1970s, a virus designated as the "Dane particle" was found to be the cause of hepatitis B. The virus has a core and an outer shell and produces a large excess of surface antigen, known as hepatitis B surface antigen (HbsAg). The antigen appears as spheres or tubules along with the Dane particle. Once transmitted, the virus usually has a long

incubation period, lasting two to six months, before signs of illness appear (this is in contrast to hepatitis A, which has an incubation period of two to six weeks).

Transmission of hepatitis B

The hepatitis B surface antigen is often found in the blood of human beings who are infected with the virus. (A blood test that identifies the surface antigen has been used since 1971 to help screen out infected blood from blood banks and to eliminate potential donors who are carrying the hepatitis B virus in their blood.)

In the US. and other western countries, contact with infected blood and blood components is a prime means for hepatitis B virus transmission among health care professionals who routinely work with infected patients and infected fluids. Direct exposure to the virus may occur through accidental puncture of the skin with needles contaminated by infected human blood, or through contact of the mucous membranes with infected body fluids and secretions.

The virus can also enter the body through minute, often unrecognized breaks in the skin -dermatoses, bumps or scratches. Staff members and patients in renal dialysis units are at particular risk.

There is a documented high rate of hepatitis B virus infection among spouses of those acutely ill with hepatitis B and among male homosexuals, who may experience seksual intimacy with many different partners. In these instances, the virus is transmitted via infected saliva or semen.

In the general public, puncture of the skin with infected needles, as may occur with ear piercing, illicit drug use, tattooing or acupuncture, can also transmit hepatitis B infection.

Although the vehicles for transmission of the hepatitis B virus are predominantly blood and blood products, viral antigen has also been found in tears, saliva, breast milk, semen, and vaginal Secretions. Poor sanitation and close intimate contact favour the spread of the virus.

In many parts of Asia and Africa, where 5-10 percent of the children are infected during the first year of life, the disease is transmitted from the mother to the child at the time of birth or shortly afterward. Evidence indicates that those who acquire infection during early life are more likely to become chronic carriers of the virus.

Tests for a newly described hepatitis B "ei antigen (HBeAg) have been found helpful in identifying those hepatitis carriers who are most likely to disseminate infection. The presence of the "e" antigen seems to be a marker for the degree of infectivity.

Populations at high risk from Hepatitis B

1. Health care professionals - physicians and surgeons, dentists, pathologists, blood and kidney specialists, nurses, medical laboratory technicians, and blood bank personnel.
2. Household and other intimate contacts of patients with acute hepatitis B or with chronic carriers. For example, clients and staff of institutions for the mentally retarded and classroom contacts of deinstitutionalized mentally handicapped persons who are chronic carriers.
3. Patients and staff in renal dialysis and hematology/oncology units.
4. Patients requiring frequent and/or large-volume blood transfusions or clotting factor cdncentrates.
5. Persons at increased risk of the disease because of their sexual practices; for example, persons who repeatedly contact sexually transmitted diseases, homosexually active males, and female prostitutes.
6. Populations where there is a high incidence of hepatitis B; for example, many countries in Asia and Africa, and some southern European countries.

Passive Protection

The efficacy of immune serum globulin in preventing or modifying hepatitis A was first reported in 1944. Since the 1940s, the safety of immune serum globulin preparations and their efficacy in providing short-term protection for people known or suspected to be directly exposed to hepatitis A or B, have been well documented.

Studies have demonstrated that use of hepatitis B immune globulin following known exposure does reduce the attack rate. People who take the recommended dose - one injection as soon as possible after exposure and a second injection 28 to 30 days later - generally maintain protective levels of antibody

for two months or longer.

To prepare such globulin, it is necessary to obtain units of plasma from human donors with high titers of antibody against hepatitis B. High-titer plasma is easily produced by giving a single dose of the vaccine to people who have low titer of hepatitis B antibody. However, the protection conferred by hepatitis B immune globulin is only passive and short term.

Development of the vaccine

The genesis of today's hepatitis B vaccine began with the discovery in 1964 of the hepatitis B surface antigen, originally known as the Australia antigen because it was first isolated in an Australian aborigine, by Blumberg of the University of Pennsylvania School of Medicine. The subsequent demonstration of the relationship between the Australia antigen and hepatitis B virus opened the door to the means of detecting hepatitis B carriers through blood testing, for serodiagnosis of hepatitis B infection, and for vaccine development, even in the absence of a means of growing the virus in the laboratory.

In 1971, progress toward vaccine development was made by the observation of Krugman and colleagues at the New York University Medical Center that heated human serum containing hepatitis B virus and surface antigen could be rendered noninfectious while retaining the ability to stimulate hepatitis B virus antibody and protect against illness caused by hepatitis B virus.

The vaccine was developed by Hilleman and his associates at the Merck Institute for Therapeutic Research, who began their work in 1968. The method for preparing the vaccine consists of a series of complex physical and chemical steps for separating the antigen from the impurities present in the original human plasma.

Many different tests are carried out in the course of vaccine production to assure the precise content and composition of surface antigen and the absence of extraneous virus. Testing is conducted in artificial media, in cell culture and in animal species, including chimpanzees, that are susceptible to hepatitis B virus infection. At least three different steps (urea, pepsin and formalin) in the purification-inactivation procedure inactivate the virus. This provides a backup system to ensure that no residual virus is left in the product.

The final vaccine is given as a preparation of the surface antigen incorporated in an aluminum hydroxide adjuvant to assure stimulation of maximal antibody response in man.

Preliminary trials

Early studies at the Merck Institute for Therapeutic Research by Hilleman and his team documented the potency of the vaccine in a variety of animal species. Demonstration of the vaccine's protective efficacy in preventing hepatitis B in chimpanzees prepared the way for human studies.

First studies in man were initiated in 1975 among employees at Merck Sharp and Dohme in West Point, Pennsylvania, by Krugman and his wife, and these tests demonstrated efficacy and potency of the vaccine for man. Expanded human studies were carried out by the Merck team that led to the development of an optimal regimen for human immunization.

Szmuness et al, (1980) conducted the first large-scale, double-blind trial of the vaccine in humans. A group of 549 male homosexuals received the vaccine and 534 received alum adjuvant alone. Both preparations were coded and indistinguishable from each other. None of the study subjects had evidence of previous infection with hepatitis B.

In selecting a population for testing the vaccine, the investigators chose homosexual men because the prevalence of hepatitis B carriers in this group has been found to be considerably higher than in the general population.

Following the experimental regimen, the vaccines received a 40 µg dose initially, followed by a second 40 µg dose at one month and a third dose of 50 µg at six months. Each participant was scheduled for ten visits over a two-year period; once a month for the first three months and then once every three months, at which time blood specimens were taken and tested for all markers of hepatitis B infection.

Side effects: Information on side effects following - vaccination was obtained from 73 percent of the participants. Of those receiving the vaccine, 243 percent reported side effects, as did 21.4 percent of those receiving the alum adjuvant placebo.

Mild soreness at the site of injection was the most frequent complaint. Rash, nausea, vomiting, joint pain, fatigue and low grade fever were reported almost as frequently by those receiving placebo as by those receiving the vaccine. The overall incidence of side effects was less than with other killed vaccines.

Antibody response: Within one month of the first injection c-f vaccine, 31.4 percent developed specific antibody against the antigen in the vaccine. Within two months - one month after the second vaccination - this rate increased to 77 percent; within three months, to 87 percent; and within six months, but prior to the third dose, to 90 percent. The third dose of vaccine at six months increased the antibody response rate to 96 percent, and greatly elevated the existent antibody titer needed to stimulate memory cells and to provide more lasting immunity.

Although it was striking that 96 percent of those vaccinated in the trial responded to the vaccine, the most important finding in the human efficacy trial was that hepatitis B virus antibody induced by the vaccine protected against the disease. It may be expected, therefore, that the vaccine will protect against hepatitis B, whatever the mode of transmission.

The titers remained essentially unchanged for the rest of the 18-month follow-up

Incidence of infection: Overall, the attack rate for hepatitis B in the vaccinees was 14 times less than in the placebo recipients. The difference in attack rates became significant very early - during the first 75 days of the study. Thus, the vaccine was 92.3 percent effective in protecting against hepatitis B, as judged by evidence of liver damage, and 76.5 percent effective in reducing the incidence of any signs of hepatitis B infection that accompanied inapparent infection. All persons who responded with development of antibody were protected.

Factors related to availability of hepatitis B vaccine

Vaccine production and testing: Because the hepatitis B virus cannot presently be grown in the laboratory, the vaccine is prepared from highly purified surface antigen derived from the plasma of human donors who are chronic carriers of the virus.

The vaccine production and testing cycle is long and complex -- 65 weeks from the input of plasma at the beginning of the process through final release of packaged vials. This is the longest production and testing cycle of any vaccine currently in production.

The manufacturing process begins with the collection of plasma which is tested for sterility and assayed for virus antigen prior to pooling.

The manufacturing steps include (1) defibrination to remove protein from the plasma; (2) purification and concentration of the surface antigen by centrifugation and column chromatography; (3) digestion with the enzyme pepsin to remove extraneous protein and further purification in a step involving treatment with urea; (4) sterilization by filtration; (5) inactivation with formalin; (6) pooling; (7) absorption of the aluminum hydroxide adjuvant in which the surface antigen is incorporated to assure stimulation of maximal antibody response in man; and (8) filling. At least 105.5 infectious units of virus are destroyed in each of three steps that included pepsin digestion, urea treatment and formaldehyde inactivation. Each stage of the manufacturing cycle is accompanied by extensive testing to assure sterility, identity and purity of the materials being processed. The adjuvant adsorption and filling steps can be initiated only after a six-month safety test in chimpanzees has been performed on inactivated bulk materials.

Following completion of the filling procedure, further testing to assure sterility and purity of the finished product will be conducted by the manufacturer. In addition, samples from every lot will be sent to the Bureau of Biologics for certification testing. No lot can be released without this certification. The specially designed and constructed facility in which the vaccine is being manufactured actually consists of a series of sterile laboratories -or discrete processing zones -- in which the various stages of

the vaccine production process are carried out. All critical work is performed under sterile conditions. Each manufacturing zone contains its own individual filtered-air system to provide maximum containment for the process. Stainless steel processing vessels are equipped with clean-in-place and sterilize-in-place systems which drain from individual manufacturing zones into a large sterilization tank. Process materials are moved from zone to zone in bioenclosed vessels. All air exhausted from critical manufacturing areas is filtered prior to release in the environment, and all sewage from the facility is fully processed in a self-contained system.

Referenees

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