Development of Hepatitis B Vaccine

SUMMARY OF THE ORIGINAL ARTICLE

Vaccine Against Human Hepatitis B

Eugene B. Buynak, PhD; Robert R. Roehm; Alfred A. Tytell, PhD; Alexander U. Bertland II, PhD; George P. Lampson, MS; Maurice R. Hilleman, PhD, DSc

A highly purified and inactivated vaccine was made of hepatitis B virus surface antigen. The vaccine was tested exhaustively for safety by ordinary procedures and additionally in chimpanzees and marmosets. It was highly potent and induced antibody in guinea pigs, grivet monkeys, and chimpanzees after three doses of vaccine were given subcutaneously. Chimpanzees given three doses of vaccine were protected against challenge with 1000 chimpanzee-infectious doses of live human hepatitis B virus given intravenously in controlled studies. Tests of the vaccine for control of hepatitis B in man are to be carried out.

See www.jama.com for full text of the original *JAMA* article.

JAMA. 1976;235(26):2832-2834.

Commentary by R. Palmer Beasley, MD, MS

THE ARTICLE BY BUYNAK AND COLLEAGUES, PUBLISHED in *JAMA* in 1976,[1] slipped by almost unnoticed during an uncomfortable centenary marked by the reunification of North and South Vietnam, a deepening US recession, the swine flu vaccination debacle, the defeat of President Ford, the first outbreak of legionnaires disease, the largest earthquake of the 20th century in Tangshan, China, and the first Ebola virus outbreak (Zaire). The good news was that smallpox was almost gone and the 1976 Nobel Prize in Medicine and Physiology was to be awarded to Blumberg for discovery of hepatitis B virus (HBV) and to Gajdusek for his work on kuru.

Nothing in the article[1] anticipated that the new HBV vaccine might become the world's first cancer vaccine and part of the World Health Organization (WHO) childhood program. The authors reported a study that successfully protected 6 chimpanzees with three 20-μg doses of a highly purified hepatitis B surface antigen (HBsAg) vaccine compared with 5 unvaccinated control chimpanzees that became infected with the same challenge. Ironically, the chimpanzee (*Pan troglodytes*), the only animal known to be susceptible to human HBV and the basis for the successful vaccine tests, was placed on the list of endangered species in 1976.

The authors[1] stated that the source of the vaccine was concentrated, highly purified, formalin-treated, hepatitis B virus coat surface (HBsAg) from 4 overtly healthy human hepatitis B carrier plasma donors. The highly unusual source and methods were an unprecedented means of making a vaccine (conventionally grown on artificial media, tissue culture, or embryonated eggs) and were developed because HBV does not grow on any laboratory media. Prior vaccines were conventionally classified as killed or live-attenuated. Little in the article pointed to the blockbuster importance of the HBV vaccine, but for HBV researchers it was a time for celebration.

Much was new about the HBV vaccine. Unlike all prior vaccines, which were grown in vitro, the new HBV vaccine came directly from human plasma prepared by ultracentrifugation processes aimed at concentrating and purifying the antigenic virus coat and treatment with 1:1000 formalin aimed at eradicating other organisms (eg, viruses) that could have escaped the physical purification. In many subsequent meetings the senior author (Hilleman) assured the world that he was convinced that nothing living could get past the physical purification. Nonetheless, further "killing steps" with pepsin and 8 molar urea were added to the formalin before the HBV vaccine was submitted to the US Food and Drug Administration (FDA) for licensure. Concern for safety was substantial and increased when the HIV/AIDS epidemic was recognized in June 1981, just 5 months before the HBV vaccine was licensed by the FDA.[2] Even

Author Affiliation: Division of Epidemiology and Disease Control, University of Texas School of Public Health, Houston.
Corresponding Author: R. Palmer Beasley, MD, MS, Division of Epidemiology and Disease Control, University of Texas School of Public Health, 1200 Herman Pressler, Houston, TX 77030 (R.P.Beasley@uth.tmc.edu).

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/24/2017

though the plasma vaccine is one of the best vaccines ever developed—safe, highly immunogenic, and efficacious—medical professionals lacked enthusiasm because of the increasing HIV/AIDS pandemic and continuing posttransfusion occurrence of non-A, non-B hepatitis. Thus, the Hilleman team went to work again and developed a new yeast-derived recombinant vaccine.

The article by Buynak et al[1] did not mention the HBV clinical or epidemiological problem the new vaccine was to address or the next steps to be taken with the vaccine. In fact, it appears that the FDA had already reviewed the chimpanzee data and approved clinical trials to evaluate safety and immunogenicity in adult humans. An alum adjuvant was added and the route of introduction was changed to intramuscular by the time the protective efficacy studies in gay men were undertaken by Szmuness et al[3] and by Francis et al.[4] Both studies showed the vaccine to be highly protective and verified the previously documented immunogenicity and safety.

In October 1979, in anticipation of expanding the efficacy trials to newborns, I became the first person working in Asia to receive the HBV vaccine. Soon small-scale immunogenicity studies were begun in adults in Taiwan where the first institutional review board in Asia had been established under National Institutes of Health guidelines. Studies in Taiwan had established that about 95% of infants were infected at birth by their mothers and became long-term HBV carriers[5] and that this vertical transmission could be prevented by hepatitis B immune globulin (HBIG) administered at birth.[6]

There was an eagerness to determine whether the HBV vaccine would prevent vertical transmission in infants. But it was necessary to establish that the HBV vaccine was as immunogenic in China and Taiwan as it was in white and black populations in the United States. After the vaccine proved to be equally effective in Chinese adults, a series of studies were conducted in younger healthy Chinese volunteers. All children, infants, and eventually newborns responded with a brisk immune response and no complications, other than mild redness at the inoculation site in about 5% of vaccine recipients.[7] In 1981 efficacy trials were begun in newborns of carrier mothers, which promptly showed that the vaccine in combination with HBIG was highly protective.[8]

Of particular interest was the unexpectedly vigorous immune responsiveness of newborns to the HBV vaccine. The immature immune system of newborns is poorly responsive to most vaccines, which is why infant immunization schedules for previous vaccines conventionally began at 6 to 8 weeks of age. Worse, the studies in Taiwan demonstrated that young age was the principal determinant of the HBV chronic carrier state,[6,9-11] so it was generally assumed that HBV vaccine would not work well in newborns. But, it was known from the Taiwan studies that minutes counted for HBIG to be effective because perinatal transmission of HBV almost always occurs during the process of labor and delivery. Therefore vaccination of newborns was continued after vaccination was moved progressively downward in age and excellent immunogenicity was demonstrated at each young age. Almost all newborns respond vigorously to at-birth immunization, providing hope for preventing perinatal transmission.

The importance of preventing HBV carrier state began to be clear as studies suggested that HBV might cause hepatocellular carcinoma (HCC). Prior interest had been directed at morbidity and mortality from heart disease and stroke but rates from these causes were low. Reviewing the records, it became apparent that the single most frequent cause of death was HCC. Using a nested case-control design, it was found that almost all patients with HCC were HBsAg positive, in contrast to about 12% of the controls.[11] This led to the establishment of the large prospective study of Chinese government employees in which it was shown that HBsAg carriers are at very high risk of developing HCC.[12]

Acceptance that chronic HBV infection causes HCC evolved slowly. I tried to convince WHO to incorporate HBV vaccine into its routine childhood immunization program but there was substantial skepticism and resistance. I attended multiple WHO technical meetings emphasizing various aspects of the problem—the disease, the virus, liver cancer, and immunization. Hilleman was often part of the meetings on vaccine. WHO had no hepatitis program and very little money to support a world childhood immunization program. Aside from their doubts, the reality of the available research findings, and their shortage of money, WHO leaders were reluctant to endorse an immunization program that would require at-birth immunization and might compete with routine vaccination for diphtheria, polio, tuberculosis, and measles.

In 1992, I appeared before the World Health Assembly and successfully argued that HBV should become the seventh immunogen in the WHO global childhood immunization program—the first cancer vaccination. The model programs are Taiwan and Thailand, both having demonstrated enormous declines in HBsAg in children and declines in HCC and are on their way toward HBV eradication. Although a total of 171 countries now have at-birth HBV policies, implementation has been spotty and there is much to be done. WHO, which relies on donated staff from the Hepatitis Branch of the US Centers for Disease Control and Prevention, is a highly underfunded program. But even the US efforts have had mixed achievements—far less than expected. An Institute of Medicine committee is currently reviewing US policies and programs for hepatitis control. The past 3 decades have witnessed much progress toward eradicating hepatitis B; much more work is needed before eradication is accomplished.

Financial Disclosures: None reported.
Funding/Support: Dr Beasley's HBV vaccine studies were sponsored by Merck Sharp & Dohme, which provided the vaccine and operational costs but not investigator

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/24/2017

salaries or other personal benefits. Other studies by Dr Beasley referenced herein were sponsored by the National Institutes of Health (NIH) and/or the government of Taiwan. HBIG used in his studies was provided by several HBIG manufacturers, such as Cutter Laboratories or purchased using funds from one or more of the sources mentioned.

Additional Contributions: The studies in Taiwan were conducted with the permission of the Taiwan government and under institutional review board approval following NIH guidelines.

Disclaimer: The opinions herein are solely those of the author. All information and opinions published by the author represented the work of his team without restrictions by Merck Sharp & Dohme, which did not review the papers prior to publication.

REFERENCES

1. Buynak EB, Roehm RR, Tytell AA, Bertland AU II, Lampson GP, Hilleman MR. Vaccine against human hepatitis B. *JAMA*. 1976;235(26):2832-2834.

2. Schmeck HM Jr. Vaccine for hepatitis B, judged highly effective, is approved by F.D.A. *New York Times*. November 17, 1981.

3. Szmuness W, Stevens CE, Harley EJ, et al. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. *N Engl J Med*. 1980;303(15):833-841.

4. Francis DP, Hadler SC, Thompson SE, et al. The prevention of hepatitis B with vaccine: report of the Centers for Disease Control multi-center efficacy trial among homosexual men. *Ann Intern Med*. 1982;97(3):362-366.

5. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med*. 1975;292(15):771-774.

6. Beasley RP, Hwang LY, Lin CC, et al. Hepatitis B immune globulin (HBIG) efficacy in the interruption of perinatal transmission of hepatitis B virus carrier state. *Lancet*. 1981;2(8243):388-393.

7. Lee GC, Hwang LY, Beasley RP, Chen SH, Lee TY. Immunogenicity of hepatitis B virus vaccine in healthy Chinese neonates. *J Infect Dis*. 1983;148(3):526-529.

8. Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet*. 1983;2(8359):1099-1102.

9. Beasley RP, Hwang LY. Postnatal infectivity of hepatitis B surface antigen-carrier mothers. *J Infect Dis*. 1983;147(2):185-190.

10. Beasley RP, Hwang LY, Lin CC, et al. Incidence of hepatitis B virus infections in pre-school children in Taiwan. *J Infect Dis*. 1982;146(2):198-204.

11. Beasley RP, Hwang LY, Lin CC, Ko YC, Twu SJ. Incidence of hepatitis among students at a university in Taiwan. *Am J Epidemiol*. 1983;117(2):213-222.

12. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus: a prospective study of 22,707 men in Taiwan. *Lancet*. 1981;2(8256):1129-1133.

©2009 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 04/24/2017