Editorial Series: Hepatitis B Vaccine

Hepatitis B Vaccine: New Progress, New Problems

The recently-licensed hepatitis B vaccine is now available for distribution. The vaccine is the end result of careful research, innovative development and exquisite product evaluation. The vaccine itself is hepatitis B surface antigen that is derived from human plasma. The antigenic preparation is subjected to a series of physico-chemical techniques that separate infectious from non-infectious particles and destroy any possible live virus. Safety testing in animals is performed for each lot prior to human use. Studies of vaccine efficacy have involved meticulously designed clinical trials that have demonstrated the immunogenicity and effectiveness of the vaccine against hepatitis B among recipients at high risk of acute infection. In these trials, the incidence of side effects has been low and no serious toxicities have been identified.

The potential target population for hepatitis B vaccine is huge. It has been estimated that there are five million health care professionals in the United States who might be candidates for vaccine. In addition, there are 2.5 million male homosexuals, 400,000 clinical laboratory and blood bank technicians, 300,000 mentally retarded and others who are considered to be at high risk of acquiring hepatitis B. Obviously, individuals will have to be selected from these populations who are at highest risk for acquiring acute infection. Different strategies for screening and vaccination will have to be developed to determine who among the various target populations should be immunized. For some high risk groups with histories of frequent past exposures, it may be cost effective to screen for evidence of immunity prior to vaccination. For others with histories of less frequent past exposures, immunization without prior screening may be less costly. We must also decide who will bear the cost of screening and immunization. It is anticipated that a complete series of three immunizations will cost approximately $100. This cost could be borne by the individual, by an insurance carrier or, in the case of hospital employees, by the hospital itself. Some individuals at high risk for infection may feel that the potential benefit of vaccine justifies the cost. However, it is unrealistic to think that all high risk individuals will be able to afford the cost or feel that it is justified. Presently, there are few insurance carriers that will cover the expense of an immunization as costly as this. Finally, few hospitals will be able to bear the costs of immunization for all their employees. Even if vaccine is restricted to the highest risk subpopulations of employees, these costs may add up to tens of thousands or hundreds of thousands of dollars. On the other hand, hospitals will be under pressure to immunize all high-risk employees. The availability of hepatitis B vaccine will have medicolegal implications for hospitals and other institutions that have been identified as high-risk settings for hepatitis B. Failures to immunize high-risk individuals may be considered grounds for malpractice.

In addition to cost and medicolegal considerations, we must also take into account problems of potential side effects or toxicities of vaccination. Each time we interact with patients, we must weigh the benefits and risks of our actions. The benefits of hepatitis B vaccine in terms of reductions in rates of acute infection are well-documented. From the available studies, there is little doubt that hepatitis B vaccine is effective. Thus far, no serious consequences of vaccination have been identified. However, it must be remembered that the clinical trials are relatively few and followup has been relatively short. Low incidence or long-term side effects of an immunological or oncological nature might still become manifest. The memory of swine flu immunization and its unforeseen neurologic complications still lingers. Similarly, potential consequences of hepatitis B vaccine must be considered prior to any massive immunization campaign — or for that matter, prior to any individual immunization. In

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developing our immunization strategies, these risks and costs must be weighed against the potential benefits of immunization.

Hepatitis B vaccine truly is a "light at the end of the tunnel." The availability of this vaccine will have a profound effect on the health care of hospital employees, preventive practices of physicians and the natural history of hepatitis B and its complications. In the long run, it may have profound effects on reducing the morbidity and mortality of primary liver cell carcinoma in countries where this disease is endemic. We must keep our eyes and minds open; be aware of the cost implications of vaccination; and analyze and reanalyze new data regarding vaccine efficacy and complications as they become available. For each potential recipient of vaccine we must weigh the benefits and the risks of vaccination and consider alternative approaches such as deferred or post-exposure immunization. The development of hepatitis B vaccine and field application is exciting. But, like other important breakthroughs in science or medicine, this new advance also will bring with it new problems.

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Hepatitis B Vaccine— A Boon for Whom?

A killed vaccine to prevent hepatitis B virus (HBV) infection (Heptavax-B, Merck, Sharp and Dohme) has been licensed and hailed as a major triumph.[1,2] The vaccine will soon be widely available. In its trials thus far the vaccine appears to be antigenic, safe, and effective in preventing HBV infection. It undoubtedly will play an important role in reducing the rate of HBV infections in very high risk groups within the community (homosexuals, family contacts of patients with acute HBV infection, etc.).

While this vaccine certainly represents a major technological achievement, limited experience with the use of the vaccine in people, its expense, and a paucity of hard data on the annual risk of HBV infection within groups of workers in acute care hospitals will dictate considerably narrower application in its initial use in hospitals.[1] A brief discussion of the factors which most affect decisions on vaccination of hospital workers follows.

The most pressing question is which individuals within a hospital should be vaccinated. One answer to this hinges on the question of which individuals within a hospital are at higher risk of acquiring hepatitis B infection than individuals of the same age, race, socioeconomic status and sexual preference who are not hospital employees. Data to answer this question are not available since no incidence studies which include appropriate community controls have been done in hospital workers.

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Another solution is to pick those individuals within the hospital who are at highest risk of HBV infection relative to other hospital workers. Most information on HBV infection in hospitals is not of high quality. However, there are three papers which report annual incidence rates for HBV infection among hospital employees in non-outbreak situations. Hirschowitz et al[3] reported an apparent attack rate of 3% per year in 129 clinical laboratory personnel followed serially over a two-year period. Craig et al[4] found the same rate of seroconversion to HBV markers among phlebotomists (9/270 person-months) as among secretaries (3/94 person-months) for an annual rate of under 1% per year. However, they noted a decrease in the rate of seroconversion as the study progressed, indicating a possible influence of the study on the rate. The Centers for Disease Control has just issued incidence data from hemodialysis staff[5] with an HBV seroconversion rate of 2.6% per year. All other published studies of HBV markers in hospital staff have either reported prevalence rates only, or have been part of hepatitis outbreak investigations.

Before recommending vaccination of specific groups of hospital workers, it is helpful to briefly review other non-monetary considerations against vaccination of healthy individuals at low risk of exposure to infection. These considerations may well include most hospital staff.

The first issue to be addressed is that of any rare but severe side effects of vaccination. There is minimal data to address this question since only 4,000 people have received HBV vaccine so far, and these have been carefully screened and selected for lack of HBV markers.[1] Two kinds of effects might be expected. The first is the occurrence of unusual reactions seen with natural HBV infection such as transverse myelitis or polyarteritis nodosa. The second type of reaction could be more severe disease occurring when a vaccinated person is exposed to natural infection during the waning phases of immunity.[6] Such reactions have occurred with inactivated RSV, mycoplasma and measles vaccines.[7-9] Since the role of hypersensitivity in liver injury seen with HBV infection is still unclear,[6] and relatively few vaccinees have been followed long enough to evaluate what will happen when they are exposed to natural HBV infection in the waning phases of immunity, this remains an active concern. It is certainly true that neither of these potential problems, nor other potential pitfalls of vaccine made from human blood (extraneous viruses, etc.) have been observed. However, the small groups of vaccinees followed are not large enough to exclude these uncommon events with any certainty, as was demonstrated during the swine flue vaccination program.

This vaccine is an excellent immunogen, producing high titers of anti-Hb, following three doses in 95% of normal individuals.[10] Because of this high response rate, it is not currently anticipated that vaccinees should have antibody titers performed following vaccination. However, one wonders whether an individual who does not respond to HBV vaccination should continue to work in a "high-risk area" for HBV infection. Will national designation of certain job locations within a hospital as "high-risk" pose any additional legal or moral burdens on the institution and its infection control personnel? In addition, is 95% confidence enough to forestall either a