# The Immunogenicity and Safety of Intradermal Hepatitis B Vaccine

William L. Toffler, MD, Jeffrey S. Olenick, MD, Nina E. Wolf, RN, Zoe H. Retzlaff, RN, J. Robert Swanson, PhD, and Terry A. Kenny, MS

*Portland, Oregon*

*Background.* One of the chief barriers to a greater use of hepatitis B vaccine is the high cost of the vaccine itself. A number of small research trials have shown that an adequate immune response can be induced at a much lower cost by administering one tenth of the vaccine using an intradermal technique. The purpose of this study was to ascertain whether these results could be replicated in a larger clinical trial.

*Methods.* Vaccine recipients included health care providers, police officers, and firefighters. Recipients were given 0.1 mL of plasma-derived hepatitis B vaccine intradermally on days 1, 30, and 180. Antibody response was measured on day 210, with seroconversion defined as a sample-to-negative (S/N) ratio of greater than or equal to 10. Any local and systemic side effects were documented.

*Results.* Six hundred sixteen individuals completed the vaccination series, and seroconversion occurred in 534 (86.7%). The rate of seroconversion in those younger than 40 years was 91.2% and in those 40 years and older was 75.1%. The mean S/N ratio was 154.9 (range 0 to 620) and decreased with increasing age ($r = -.25$, $P = .0001$). Side effects were largely limited to local reactions.

*Conclusions.* The results support the use of the intradermal technique as a cost-effective alternative to the intramuscular route in individuals younger than 40 years. The intradermal technique may be used in older individuals if titers are obtained to assure seroconversion. Because of the restricted availability of the plasma-derived vaccine used in this study, similar trials with recombinant vaccine should be undertaken.

*Key words.* Viral hepatitis vaccines; injections, subcutaneous; cost control. *J Fam Pract 1991; 33:149-154.*

Numerous studies have documented the immunogenicity, safety, and efficacy of inactivated hepatitis B vaccine (Heptavax-B) when given as three intramuscular (IM) injections of 20 $\mu$g of hepatitis B surface antigen (HBsAg) protein.[1–4] Despite these data, there are other studies documenting the underuse of the vaccine even in high-risk groups including health care workers.[5,6] The fear of contracting acquired immunodeficiency syndrome (AIDS) as well as the high cost of the vaccine have been cited as potential explanations as to why many groups have not availed themselves of the vaccine.[7–10]

Concern regarding AIDS should no longer be an issue; the plasma-derived hepatitis B vaccine poses no demonstrable risk for acquiring AIDS.[8,9] Cost, however, remains a concern, since both the plasma-derived and the newer yeast-derived (recombinant) vaccines are comparable in price. To address the problem of cost, many workers have experimented with giving the plasma-derived vaccine by the intradermal route (ID) in smaller (and less costly) doses.[6,10–13] Presentation of antigen to the immune system intradermally results in a macrophage T-lymphocyte response, and the ID route has been used for immunization against tuberculosis, diphtheria, typhoid, cholera, influenza, rabies, and other infections.[14]

The preliminary studies of the use of ID hepatitis B vaccine demonstrate that a smaller amount of the vaccine can be given intradermally at a much lower cost with nearly equal immunogenic response as that obtained from the IM route. The studies published to date have often involved a small number of healthy and predominantly young individuals and have been conducted under research conditions. Some authors have expressed concerns regarding the applicability or reproducibility of the results when applied to larger populations in ordinary practice settings.[7,14] Large field trials have been conducted with rabies vaccinations in which successful ID

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*From the Department of Family Medicine, Oregon Health Sciences University, Portland, Oregon. Requests for reprints should be addressed to William L. Toffler, MD, Department of Family Medicine, Oregon Health Sciences University, 3181 SW Sam Jackson Park Rd, Portland, OR 97201.*



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delivery of the vaccine has been demonstrated.[15,16] No similar large-scale trials have been conducted using the ID technique with hepatitis B vaccine.

The purpose of this study was to demonstrate that an ID vaccination program for hepatitis B could produce the favorable results of smaller research-based studies in a high-volume employee health and family practice setting.

## Methods

The family practice center (FPC) of the Department of Family Medicine serves as the employee health service (EHS) of the Oregon Health Sciences University. The FPC is made up of 34 family physicians (9 faculty and 25 residents) and 10 nursing personnel. Annually, over 25,000 visits are made to the FPC, including over 2000 EHS visits. All blood drawing, immunizations, and data collection and recording were carried out by the regular nursing personnel under the direction of the FPC director.

### *Subjects*

Initially, the vaccine recipients included employees at OHSU who considered themselves at risk for exposure to hepatitis B or who had sustained an accidental exposure to blood. Individuals with exposure to blood and body fluids underwent other preventive measures such as administration of gamma globulin when necessary. The series was expanded after 8 months to include other populations at risk including police officers, firefighters, emergency medical personnel, and community health care providers. Involvement of these latter groups occurred at the request of the individual agencies, which were often seeking to reduce the cost of protecting the employees involved.

### *Vaccine Administration*

Recipients were given 0.1 mL of hepatitis B virus (HBV) vaccine (Heptavax-B, Merck Sharp & Dohme, West Point, Pa) by the ID route (2 $\mu$g of HBsAg). To ease administration and tracking of side effects, the ID injections were administered on the volar aspect of the forearm unless an alternative site was specifically requested by the individual. A visible cutaneous wheal was regarded as evidence that the vaccine had been effectively administered. This was achieved in more than 95% of the injections. If a visible wheal was not achieved, a second injection was administered. The vaccine was scheduled to be administered on days 1, 30 and 180. Second doses were given up to 4 months following their scheduled time. If a recipient went beyond this time, the series was restarted.

### *Assessment of Immunogenicity*

A serum sample was obtained approximately 1 month following completion of the immunization series. Serologic testing for antibodies to hepatitis B surface antigen (anti-HBs) was performed on each specimen using a commercial radioimmunoassay test kit (Abbott Laboratories, North Chicago, Ill). Seroconversion to the vaccination was defined consistent with recommendations by the Immunization Practices Advisory Committee (ACIP) as a sample-to-negative (S/N) ratio of greater than or equal to 10.[17] Those with an S/N ratio of less than 10 were considered to be nonresponders and were offered a fourth dose. Serologic testing for anti-HBs was repeated 1 month following this fourth dose.

In addition to the qualitative method outlined above, a subset consisting of 63 samples (drawn on a single day) was assayed again to quantitatively determine the level of anti-HBS and to better allow for correlation with other published data. The method described by Hollinger et al[18] was used. World Health Organization (WHO) hepatitis B immunoglobulin reference preparation was assayed as an unknown, and the measured concentration agreed with the expected values.

At the time the series was expanded, the rate of natural seroconversion was assessed in two subsets, including one consisting of a series of 61 consecutive individuals and another consisting of 191 police and firefighting personnel, by testing for the presence of hepatitis B surface antigen before beginning the immunization series.

### *Assessment of Side Effects*

Each recipient's previous injection site was examined by nursing personnel at the time of subsequent follow-up visits (for booster doses or for blood drawing for antibody titers). Each individual was questioned as to local or systemic reactions, and these were noted. Any untoward reactions were referred for further assessment.

## Results

### *Immunogenicity*

Six hundred sixteen individuals completed the vaccination series and returned for antibody testing. Seroconversion (S/N ratio $\geq$ 10) occurred in 534, giving an overall response rate of 86.7%. The remaining 82 indi-

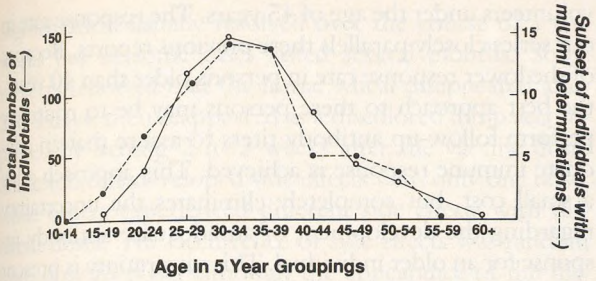


Figure 1. Age distribution of the total study population (unbroken line) as well as distribution of a subset of 62 subjects (broken line) who had quantitative antibody determinations.

viduals (13.3%) were nonresponders. The mean S/N ratio was 154.9, with a range of 0 to 620. The mean age of vaccine recipients was 35.5 years (range 18 to 62 years). The age distribution is shown in Figure 1. The mean time from first immunization to determination of the S/N ratio was 8.7 months. The mean S/N ratio decreased with increasing age ($r = -.25$, $P < .0001$) as shown in Figure 2. Similarly, the percentage of responders also decreased with increasing age ($\chi^2 = 50.3$, $df = 7$, $P < .0001$) as shown in Figure 3.

In the subset of subjects (63 persons) who had antibodies determined both as an S/N ratio and in mIU/mL, the mean antibody response was 947 mIU/mL with a range of 0 to 37,930 mIU/mL. This subset was similar to the entire group in the age distribution (Figure 1).

There were 43 nonresponders defined as either HBsAb negative or HBsAb positive but with an S/N ratio <10 who availed themselves of a fourth dose and had an antibody determination repeated 30 or more days after the fourth dose. Of these 43, 14 (32.5%) converted to an S/N ratio ≥10. Twenty-nine of the 43 were aged 40 years or older, and of this group, 9 (31.0%) converted to an S/N ratio ≥10. Of the 14 vaccine recipients who

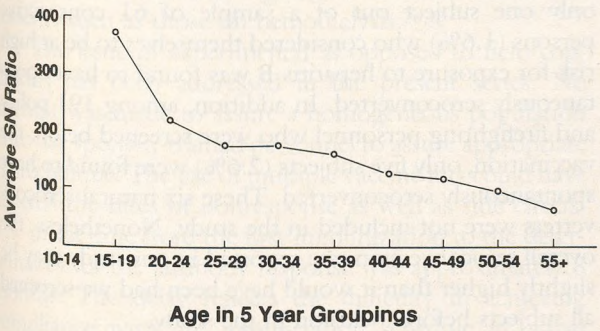


Figure 2. There is an inverse correlation between subject age and average sample-to-negative (S/N) ratio ($r = -.25$, $P < .0001$).

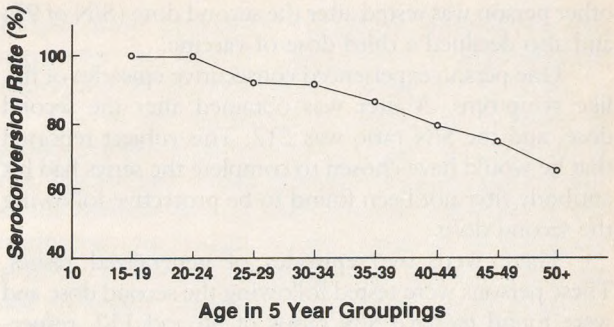


Figure 3. There is an inverse correlation between percent seroconversion rate and age expressed in 5-year groupings ($\chi^2 = 50.3$, $df = 7$, $P < .0001$).

were younger than 40 years of age, 5 (35.7%) converted to an S/N ratio ≥10.

## *Side Effects*

The most prevalent reactions (Table 1) were hyperpigmentation (34.2%), the development of induration approximately the same size (3 to 5 mm) as the original wheal (17.9%), and localized itching (6.7%). Less than 1% of the local side effects involved tenderness or erythema. Twenty-two other reactions were reported. There were 15 occurrences of flulike illness with symptoms of general malaise, achiness, low-grade fever, and nausea.

A total of five subjects stopped the series before completion of the immunization protocol because of side effects. Two of these five subjects experienced intense local reactions, and both discontinued the series after the second dose. One of these persons had a diffuse papular rash with itching, and a dermatologist was consulted. A skin biopsy was consistent with bites, and the reaction was not believed to be related to the vaccination. Antibody testing following the second vaccination yielded an S/N of 145, and the subject declined a third dose. The

Table 1. Side Effects from Intradermal Hepatitis B Vaccination (616 Participants, 1886 Total Doses)

| Side Effect | Observed Occurrence No. (%)* |
|---|---|
| Discoloration | 645 (34.2) |
| Induration | 337 (17.9) |
| Pruritis | 127 (6.7) |
| Tenderness | 5 (0.3) |
| Erythema | 3 (0.2) |
| Other† | 22 (1.2) |
| None reported | 1026 (54.4) |
| No available data | 183 (9.7) |

**Total of column will exceed 100% owing to multiple side effects in the same individual.*
*†15 flulike symptoms, 6 generalized rashes, 1 generalized hives.*

other person was tested after the second dose (S/N of 95) and also declined a third dose of vaccine.

One person experienced consecutive episodes of flu-like symptoms. A titer was obtained after the second dose, and the S/N ratio was 212. This subject reported that he would have chosen to complete the series had his antibody titer not been found to be protective following the second dose.

There were two episodes of generalized rashes. These persons were tested following the second dose and were found to have S/N ratios of 56 and 112, respectively, and they declined third doses. Only one person had an incident of generalized urticaria, possibly related to her history of recurrent "stress-induced" hives. She chose to continue the series under close supervision, and she was given two subsequent doses without further recurrence of hives.

## Discussion

This study demonstrates that low-dose ID hepatitis B vaccination can produce levels of antibody considered adequate to protect against hepatitis B. The population studied consisted of a heterogeneous group of actively employed persons of varying ages. No baseline health assessment of the subjects was made. The health background of the subjects was adequate to allow for employability, yet by no means were all of the subjects free of illness. The prevalence of medical cases in the overall study population that might have contributed to an absence of, or lower degree of, antibody response is not known. In some cases the health history of nonresponders was taken retrospectively, and in some instances individual problems such as diabetes, cancer and chemotherapy, and steroid treatment for an allergic reaction were noted to be present. At the same time, other nonresponders reported no ill health. Nevertheless, the results compare favorably to the results of large-scale hepatitis B vaccination trials using the standard IM technique, which showed that 7% to 15% of those vaccinated failed to respond with adequate antibody production.[19]

The results show an inverse relationship of immune response to age, which is similar to results demonstrated by others using the IM technique.[20,21] This declining immunogenicity with age has also been demonstrated by Goldwater et al[10] in a study of ID hepatitis B vaccination. This particular study involved a small number of subjects (eight) over the age of 30 years. Only 50% in this age group responded satisfactorily, as compared with 88.8% (71/80) in those younger than 30 years. Redfield and his group[6] demonstrated a 96% seroconversion rate in 25 volunteers under the age of 45 years. The response rate in our series closely parallels these previous reports. Because of the lower response rate in persons older than 40 years, the best approach to these persons may be to routinely perform follow-up antibody titers to assure that an adequate immune response is achieved. This approach adds a small cost, but completely eliminates the uncertainty regarding the development of an adequate antibody response for an older individual. This uncertainty is present regardless of the technique employed to deliver vaccine.

Measurement of antibody response in mIU/mL allows for more precision in comparing our results with other published data. The mean level of antibody response (947 mIU/mL) in a sample population of our study is similar to that reported in the study by Halsey et al[22] using an ID technique.[22] In the latter study, the ID technique resulted in a lower mean titer (1230 mIU/mL) than the IM technique (2692 mIU/mL), but the differences were not statistically different.

The reason for nonresponse in some persons may relate to a number of other factors. Nowicki and colleagues[23] demonstrated that healthy subjects who fail to respond to IM hepatitis B vaccination may have elevated levels of circulating lymphocytes that may be determined by differences in major histocompatibility complexes. The route of administration, obesity, weight-height index, and vaccine batch have also been related to immunogenicity and response rate.[23,24] Almost one third (32.5%) of those recipients who had positive but unprotective titers after three doses developed S/N ratios ≥10 after a fourth dose. This finding is consistent with the results of Hadler et al.[25] The practice of giving a fourth dose to vaccine recipients who are nonresponders or hyporesponders after three doses is consistent with the current recommendations of the ACIP.[26]

One weakness of the present series is that only some of the subjects were screened before entrance into the study to ascertain whether they had naturally seroconverted from prior exposure to hepatitis B antigen. Yet only one subject out of a sample of 61 consecutive persons (1.6%) who considered themselves to be at high risk for exposure to hepatitis B was found to have spontaneously seroconverted. In addition, among 191 police and firefighting personnel who were screened before the vaccination, only five subjects (2.6%) were found to have spontaneously seroconverted. These six natural seroconverters were not included in the study. Nonetheless, the overall seroconversion rate reported in our study may be slightly higher than it would have been had we screened all subjects before inclusion in the study.

In general, side effects were mild and were usually limited to local reactions (hyperpigmentation, induration, and itching) at the site of vaccination. The hyper-

pigmentation usually resolved over the course of a few weeks but in some cases lasted several months. Some subjects reported that the initial wheal disappeared after 2 to 3 days, then reappeared as a discolored lump accompanied by itching 2 to 3 weeks after the vaccine dose. Some subjects developed side effects with only one dose, while others experienced different side effects with different doses. The occurrence of side effects was random from dose to dose, although the appearance of the discolored area or lump was reported more often following the first dose. Since the subjects were not seen again for 5 months between the second and third doses, side effects may have been underreported because of the extended time between these doses. Most persons tolerated the local reactions, and many did not report hyperpigmented or firm areas until they were noticed by the nurse during follow-up. Underreporting also may have occurred if subjects only reported "unexpected" effects and neglected to report the development of the "expected" discolored or firm papule. Only two individuals had generalized rashes following the second dose, which could have been related to the vaccine. They had developed a strong immune response (S/N ratios of 56 and 112) and declined a third dose despite a lack of data regarding the duration of immunity after only two doses.

Even when three doses are given, the duration of the antibody response induced by ID injection is not clearly known. Persistence of antibody to HBsAg after vaccination has been convincingly shown to depend on the magnitude of initial antibody response, and antibody levels decline steadily with time.[27] Up to 50% of adult vaccinees who respond adequately to vaccine may have low or undetectable antibodies by 7 years after vaccination, yet both adults and children with declining antibody levels are still protected against disease.[26] In addition, at least one group of investigators[28] has suggested that high antibody titers do not seem to be more effective than low titers. Nonetheless, the peak antibody response may indeed be clinically significant in certain subsets of patients such as those on hemodialysis.[26,29]

The issue of experimental as opposed to field conditions has been addressed in the present series. No attempt was made to assure a homogeneous population or to use specially trained personnel to assure appropriate ID technique. The use of multiple vaccine lots could have affected the rates of nonresponse as well as side effects. The mean time from the first immunization to the determination of the antibody response was approximately 8 months. The delay reflects the difficulty in achieving compliance with an immunization schedule in actual practice. The series had to be restarted in 4 subjects (0.7% of the total) who failed to obtain their second immunization within 4 months of the scheduled time. Despite these difficulties, the results demonstrate that inactivated hepatitis B vaccine can be immunogenic when given by the ID route in a busy FPC or EHS.

Use of the ID technique allows for inclusion of groups previously excluded, not because they were not at risk, but because of cost-benefit considerations. Because of the reduced cost of using the ID technique at our institution, vaccination against hepatitis B was made available to hundreds of health care workers who were not previously eligible for the immunization program. The need for universal vaccination strategies is becoming stronger as at least 30% of patients with hepatitis B cannot be associated with an identifiable risk factor, thus excluding them from any immunization strategy that targets only high-risk groups.[30]

Although many factors stand as barriers to widespread immunization against hepatitis B, including fears regarding potential side effects or safety of the vaccine, the sheer cost of the vaccine is the factor restricting its availability to all but those who have adequate financial resources. The present cost of the vaccine alone is approximately $120, excluding the cost of administration of the three individual doses. Although genetically engineered vaccine holds the promise of decreased cost, no such reduction has yet occurred. The intradermal route requires only one tenth of the total dose of vaccine, yielding a commensurate reduction in the vaccine cost. Francis and Margolis[31] have underscored the possibility of worldwide elimination of hepatitis B transmission and note that we have the "way" (universal vaccination strategies), yet we need the "will." The will seems in no small sense to be linked to the cost of the way.

Although the potential impact of the present study has been blunted by the decision of the manufacturer to restrict plasma-derived vaccine to immunocompromised and dialysis patients, at least one trial has demonstrated immunogenicity using ID recombinant hepatitis B vaccine in a small group of 32 hospital employees.[32] Further studies using larger populations are clearly needed, and might well make the development and implementation of universal vaccination strategies an economic reality.

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