Persistence of Anti-HBs among Health Care Personnel Immunized with Hepatitis B Vaccine

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Abstract: Health care personnel who received the hepatitis B vaccine (Heptavax-B^R, MSD) were followed for persistence of hepatitis B surface antibody (anti-HBs). Response occurred in 135/146 (92.5 percent) vaccinees. Loss of anti-HBs (<72 RIA units; 10 S/N) occurred in 35.9 percent during the 36-month surveillance. Stepwise discriminant analysis found age and magnitude of initial antibody level, but not weight-height index, to be predictive of antibody loss over the 36 months. Twenty-four of 27 employees (88.9 percent) who lost anti-HBs responded to a fourth vaccine dose. In contrast, three of eight initial non-responders (37.5 percent) developed antibody after a fourth vaccine dose. (*Am J Public Health* 1990; 80:590–593.)

Introduction

Hepatitis B virus (HBV) infection is a significant occupational risk to health care personnel.[1–3] Safety and immunogenicity of the hepatitis B vaccine have been demonstrated in immunocompetent health care personnel.[4] However, current evidence from studies of healthy vaccinees and male homosexuals suggests serum antibody will not be maintained indefinitely.[5–9] Whether loss of demonstrable antibody can be equated with loss of protection against disease is not known.

The objectives of the present study were to determine prevalence of baseline antibody to hepatitis B surface antigen (anti-HBs) in our population, to evaluate response rate, and to monitor persistence of anti-HBs serially over three years. Non-responders and those responders who lost antibody (transient responders) were also evaluated and compared to the persistent responder group.

Methods

Participants were health care personnel at the Veterans Administration Medical Center, Buffalo, New York. The study was approved by the Human Studies Subcommittee and each participant signed informed consent prior to enrollment.

The clinic nurse recorded height, weight, health problems and/or medications upon entry into the study. A baseline serum sample was obtained and three doses of Heptavax-B^R (MSD) (20 mcg) were administered intramuscularly according to current recommendations; second and third doses were given one and six months after the first.[10]

Serum samples were collected 7, 12, 24, and 36 months following the first vaccine dose for determination of anti-HBs. Non-responders and those employees with demonstrable loss of anti-HBs to levels less than or equal to 72 radioimmunoassay (RIA) units were given a fourth vaccine dose (20 mcg). Fourth doses were given to non-responders two to three months after the third dose. Transient responders received fourth doses at variable intervals with respect to the third dose but within two to three months of a serum sample demonstrating anti-HBs ≤ 72 RIA units. Serum anti-HBs was then determined one month later. All sera from non-responders were tested for the presence of hepatitis B surface antigen (HBsAg).

Participants were asked to report any known or suspected exposure to HBV. Exposures were investigated by study personnel to determine whether a true HBV exposure occurred.

Serum Studies

Serum anti-HBs was determined in duplicate by radioimmunoassay (AUSAB, Ausria II; Abbott Laboratories, North Chicago, IL). Anti-HBs levels were quantitated according to manufacturer's directions and reported as radioimmunoassay units (RIA units).[11] In our laboratory, 72 RIA units correlated with 10 S/N units (ratio of sample counts per minute to mean counts per minute in antibody negative controls).

Vaccine response was defined as an anti-HBs value of greater than 72 RIA units (10 S/N). Those with a maximal anti-HBs value of 72 or less either 7 or 12 months after the first vaccine dose were considered nonresponders. Persistent responders were those whose anti-HBs values exceeded 72 RIA units (10 S/N) throughout the period of study. Those responders whose anti-HBs values initially exceeded 72 RIA units but declined below this value during the course of the study were considered transient responders.

Weight-height index was calculated as weight (kg)/{height (m)}^{p}, where p equals 2 for males and 1.5 for females.[12]

Statistical Analysis

Data analysis was accomplished with the use of the Statistical Package for Social Sciences (SPSS-PC) (v.2.0; SPSS Inc., Chicago, IL; 1988). Students t-test for unpaired data and stepwise discriminant analysis were performed; 95% confidence intervals (CI) for mean differences were calculated.[13]

Results

Baseline Screen for Anti-HBs

Of 184 employees screened for the presence of serum anti-HBs, 14 (7.6 percent) were found to be positive (>8 RIA units; 2.1 S/N). Anti-HBs levels in six of the 14 sera (42.9 percent) were 72 RIA units or less while eight sera (57.1 percent) exceeded this value. Those with baseline anti-HBs > 8 RIA units were excluded from further analysis.

Response to Vaccination

Of the 170 employees with negative baseline serum, 17 employees either did not complete vaccination or were lost to

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follow-up and seven employees received injections in the buttocks. All of these were excluded from further analysis.

Among the 146 employees remaining, 135 (92.5 percent) responded while 11 (7.5 percent) were non-responders. The mean age of the study population was 36.0 ± 9.9 years. Non-responders (mean 40.5 years) were slightly older than responders (mean 35.7 years; 95% CI of difference = 2.8, 12.4). The mean calculated weight-height index for responders (29.6 ± 6.3) and non-responders (28.9 ± 5.3) was similar.

Persistence of anti-HBs

Antibody concentrations declined to 72 RIA units (10 S/N) or less in 6 of 133 employees (4.5 percent) at 12 months, 21 of 115 (18.3 percent) at 24 months, and in 33 of 103 (32.0 percent) at 36 months after the first vaccine dose (Figure 1). The duration of anti-HBs was related to the magnitude of the antibody response measured seven months after the first vaccine dose (Table 1).

To further characterize the persistent and transient responders, 92 individuals were evaluated from whom serial anti-HBs values were available 7, 12, 24 and 36 months after the first vaccine dose. These 92 individuals were similar with respect to age, initial anti-HBs level and weight-height index when compared to the 43 responders for whom follow-up was incomplete. Anti-HBs levels were maintained above 72 RIA units (10 S/N) in 59 individuals (64.1 percent) for the 36-month period, while 33 (35.9 percent) were transient responders.

Stepwise discriminant analysis revealed that magnitude of the initial anti-HBs concentration and age were significant discriminators of antibody persistence or loss within the 36-month period. Transient responders were older than persistent responders and the magnitude of initial anti-HBs was substantially higher among persistent responders. The weight-height index (WT-HT) was not found to be of predictive value (Table 2).

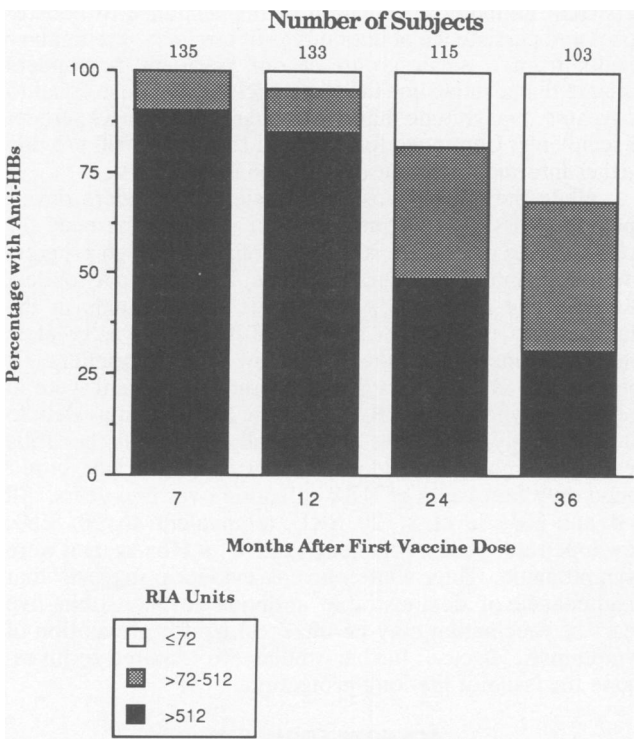

FIGURE 1—Persistence of Anti-HBs over Three Years in Health Care Personnel Who Responded to the Three-dose Vaccine Series

TABLE 1—Loss of Anti-HBs 36 Months after Vaccination (N = 103)

Initial Anti-HBs[a]		No. < 10 S/N /total (%)	Duration of Anti-HBs (months)[b]
RIA Units	S/N		
72–512	10–50	11/11 (100)	16.3 ± 6.2
>512–5000	50–1000	14/21 (66.7)	25.5 ± 7.1
>5000	>1000	8/71 (11.3)	32.6 ± 3.4

[a]measured 7 months after first vaccine dose.
[b]mean ± standard deviation of time (months) that anti-HBs ≥ 10 S/N.

Exposure to HBV

Twenty-five employees reported 110 exposures to potentially HBsAg positive blood or body fluid. Exposures involved direct contamination of mucous membranes or abraded skin with blood or other body fluids; none was an accidental needle stick. Antigen status of the patients was determined or known in 104 of the 110 (95 percent) incidents and 30 (29 percent) involved HBsAg positive patients. The 30 documented exposure events occurred among nine employees, two of whom were non-responders. None of the nine employees developed HBsAg.

Revaccination of Non-responders and Transient Responders

Response to a fourth vaccine dose was assessed in 27 transient responders and eight non-responders. In comparison to the response elicited following the initial three-dose series, anti-HBs following the fourth dose was of similar or greater magnitude in 24 of 27 (88.9 percent) transient responders. Anti-HBs exceeded initial magnitude by three-fold or greater in 13 individuals (48.2 percent), was of similar magnitude in 11 (40.7 percent), and declined in two individuals (7.4 percent). In one case (3.7 percent), the fourth dose failed to evoke any anti-HBs response. However, this individual initially demonstrated a low antibody response to the three-dose series (anti-HBs = 112 RIA units; 18 S/N). Persistence of anti-HBs following the fourth dose in this subpopulation is under continued evaluation.

In contrast, five of eight non-responders (62.5 percent) given a fourth dose failed to respond. Among the three individuals who responded, anti-HBs persisted above 72 RIA units (10 S/N) for 9, 27, and 36 months, respectively.

Discussion

The results of this study corroborate the findings of others but also provide important additional information about persistence of antibody levels and response to booster injections in recipients of plasma-derived hepatitis B vaccine (Heptavax-B). Since we found a low prevalence of hepatitis B markers among our employees (7.6 percent), these observations support the contention that antibody response and decline in our employee population was indicative of the vaccination process and not inadvertent exposures to contaminated blood and body fluids.

In the present study, initial response rate, magnitude of mean peak anti-HBs and loss of antibody within the first year were very similar to that reported by Dienstag, *et al*,[4] (Table 3), although the relation to age was not as strong as relation to initial response. Other studies[12,14,15] have found age to be an important factor distinguishing responders and nonresponders.

TABLE 2—Comparison of Persistent and Transient Responders followed Serially for 36 Months* (N = 92)

	Persistent	Transient	Difference (95% CI)	p-value[b]
anti-HBs[a]	29951 ± 19409	7470 ± 14450	22481 (14896, 30066)	.00001
age	33.9 ± 8.7	41.7 ± 9.7	7.8 (3.9, 11.7)	.0002
WT-HT	29.4 ± 4.8	31.1 ± 8.7	1.7 (−1.1, 4.4)	.2128

*data expressed as mean ± standard deviation.
[a]initial antibody level at 7 months post dose 1 expressed in RIA units.
[b]stepwise discriminant analysis.

TABLE 3—Response to Vaccination among Two Populations of Health Care Personnel

	Dienstag et al[a] (N = 645)	VAMC (N = 135)
Initial Anti-HBs[b]		
≥100,000	43.1%	NA
≥51,200	NA	23.8%
≥1,000	79.2%	79.4%
≥512	87.0%	90.4%
Mean Peak Anti-HBs[b]	26,718	26,606
Transient Responders[c]	2.3%	4.5%

[a]reference number 4.
[b]RIA units.
[c]Anti-HBs loss within 12–13 months of the first vaccine dose.

Although the influence of injection site on response rate is well established,[16] the role of obesity as a factor in response rate is less clear. In our study, no association was found between likelihood of response and weight-height index as a measure of obesity. In a previous study reporting an association,[12] all vaccine was administered in the buttocks with a 1-inch needle and thus the overall seroconversion rate was low as might be expected (55.7 percent). Horowitz, *et al,*[7] found an association between body mass index (weight/height^2) greater than 25 and prevalence of low antibody levels (<10 mIU/ml) at a median time of 39 months post-vaccination. The subpopulation with low anti-HBs (<10 mIU/ml) included non-responders as well as responders who lost antibody since vaccination. A recent case control study reported by the Centers for Disease Control (CDC) used an age-adjusted logistic model and found an association between obesity and nonresponse for females over the age of 19 years. A similar association was not found for males.[17]

Antibody persistence among vaccine responders in health care populations is of particular interest. During our 36-month surveillance, 32 percent of responders lost antibody (<10 S/N). Jilg, *et al,*[5] in a brief report of "healthy vaccinees" (inclusion groups not further characterized) found antibody in 27.5 percent of the study population fell to 10 IU/l (equivalent to 10 S/N) or below after four years. The authors do not comment on site of vaccine injection, age of their study population, or HBV exposure events.

Several additional studies have attempted to evaluate either initial response or antibody persistence following vaccination of health care personnel. However, vaccine was administered via gluteal injections in two reports[14,15] and response rate was low as expected. In an additional two reports,[9,10] initial antibody levels post vaccination (deltoid injections) were not obtained. Both authors assumed a response rate of 90–95 percent and thus the subset of employees reported to be negative for anti-HBs at the respective serum sampling times included non-responders and low level responders. Additionally, since baseline prevalence of anti-HBs is also unknown in these populations, those with persistent antibody as a result of natural infection cannot be distinguished from vaccine responders.

Extensive long-term follow-up of vaccinees has been reported by Hadler, *et al,* in a study of male homosexuals[6] and by Wainwright, *et al,* in an Eskimo population.[9] In the Hadler study, anti-HBs was maintained above 10 SRU (sample ratio units; equivalent to 10 S/N) in 93, 70, 65, 60, and 58 percent of the population at 12, 24, 36, 48, and 60 months of follow-up, respectively. Similar to Hadler's data, anti-HBs in our study was maintained above 72 RIA units (10 S/N or 10 SRU) in 95, 82, and 68 percent of vaccinees at 12, 24, and 36 months of follow-up. Preliminary review of our 48-month data indicates 52 percent of vaccinees are above 10 S/N (unpublished observation). This percentage is similar to that of Barnes, *et al,*[8] at 48 months (55 percent > 10 S/N). In contrast, Wainwright, *et al,*[9] report 73 percent above 10 S/N at five years post-vaccination for ages 20–49 and 63 percent for those over 50 years of age. Similar to our finding, initial antibody level was a stronger predictor of antibody persistence than age.

Characterization of responders who subsequently experience a loss of anti-HBs has not been previously reported. We found these transient responders to be somewhat older and have lower initial anti-HBs levels than those with persistent antibody. Evaluation of the response to booster doses and persistence of antibody is in progress. Preliminary results from a small group of our transient responders indicate that a single booster dose elicits a response equal to or greater in magnitude than the initial response in 89 percent of recipients. Continued follow-up of this group will provide further information about persistence of antibody.

While the majority of our transient responders developed anti-HBs after a fourth dose of vaccine, the need for booster doses of vaccine is controversial. Although progressive loss of anti-HBs occurs over time, immunity may outlast demonstrable antibody. Among male homosexuals in the Hadler study,[6] the risk of hepatitis B infection was greatest among vaccine non-responders or low level responders. Of the hepatitis B infections that occurred, 76 percent were in individuals whose anti-HBs was below 10 SRU (equivalent to 10 S/N). Only two cases of clinically important hepatitis developed among responders. Likewise, Wainwright, *et al,*[9] found only four cases of HBV infection over five years. All had anti-HBs level < 20 SRU (equivalent to 20 S/N), developed anti-HBc, remained negative for HbsAg, and were asymptomatic. Thus while current evidence suggests that maintenance of demonstrable antibody levels within five years of vaccination may be unnecessary for prevention of symptomatic disease, further studies are required to investigate the issue of life-long protection.

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Maternal and Child Health Law Changes Explained

Recent legislative changes in the maternal and child health block grant program were spelled out in a letter sent by Dr. Robert G. Harmon, HRSA Administrator, to state health officers. The letter is intended to assist states in applying for fiscal 1991 maternal and child health block grant funds and in submitting the fiscal 1989 annual report on state activities funded under this program.

The law was amended by the Omnibus Budget Reconciliation Act of 1989 (Public Law 101-239). The amendments "create a new framework for action on maternal and child health for the 1990s," Dr. Harmon noted.

The amendments, which increase the authorization for appropriations to $686 million for fiscal 1990 and subsequent years, are designed to:

- Promote the PHS Health Objectives for the Nation for the Year 2000;
- Assure expenditure of funds for preventive and primary care services for children and for services for children with special health care needs;
- Improve data collection and analysis; and
- Increase overall accountability in the administration of the program.

The amendments also make structural changes in the block grant to improve state planning, accountability, and targeting of federal funds to priority populations. The changes:

- Prescribe new requirements for the use of allotment funds;
- Establish a new application requirement;
- Establish new state and federal reporting on services, expenditures and health status of target populations; and
- Mandate additional state and federal activities to promote improved access to maternal and child health services.

The changes reflect "work remaining to be done by federal and state authorities in developing effective statewide systems of comprehensive, community-based family-centered continuous care," Dr. Harmon wrote. "They encourage using resources better through effective coordination of MCH block grant activities with those of other major maternal and child health assistance programs providing related services to similar populations."

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