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PERSISTENCE OF ANTIBODY IN HEALTH CARE WORKERS VACCINATED AGAINST HEPATITIS B: A STUDY ON VACCINE EFFECTIVENESS OVER TIME

by

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Preventive Medicine and Environmental Health in the Graduate College of The University of Iowa

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MASTER'S THESIS

This is to certify that the Master's thesis of

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CHAPTER I

INTRODUCTION

The hepatitis B virus (HBV) was first discovered in 1965 and first associated with the clinical disease of hepatitis in 1967. In 1990, the World Health Organization (WHO) estimated that over a billion people currently living had been infected with HBV and that more than 200 million people world-wide were currently infected. Additionally, WHO estimated that HBV infection is responsible for one to two million deaths annually. HBV is thought to be the single most important cause of persistent viremia in humans. The HBV is responsible for approximately 80% of cases of primary hepatocellular carcinoma and is second only to tobacco in its importance as a known human carcinogen (1).

Over 300,000 cases of hepatitis B occur annually in the United States. It is estimated that approximately 12,000 of these cases occur in health care workers, resulting in up to 200 deaths annually (2). In response to this, the Occupational Safety and Health Administration (OSHA) now requires healthcare facilities to offer the hepatitis B vaccination to its employees at no cost, Federal Register, December 6, 1991.

The first vaccine, plasma derived Heptavax B, was licensed by the USFDA in November 1981 and became available in July 1982 for pre-exposure prophylaxis (3). In 1986 a recombinant form of the vaccine was released. After the release of the recombinant vaccine the utilization of the plasma derived vaccine decreased greatly and it is no longer produced in the United States. Both forms of the vaccine stimulated an adequate serum antibody response shortly after completion of the vaccine series in 95-

99% of healthy adults and adolescents immunized (1). At this time there is no recommendation for routine booster doses for previously vaccinated health care workers.

Statement of the Problem

It has been estimated that there are over 300 million worldwide carriers of the hepatitis B virus. It is expected that 40% of these individuals will die of resultant liver disease (5). Among the 12,000 health care workers affected it is estimated that 15 will die of fulminant hepatitis, 1,000 will become chronic HBV carriers and eventually 200-300 will die of cirrhosis or primary hepatocellular carcinoma (4).

The exposure of health care workers to HBV infected individuals, primarily asymptomatic carriers, is what places them at increased risk of developing an occupational HBV infection. It has been estimated that 0.5 to 1.7% of all patients admitted to hospitals or seen in dental clinics are HBV carriers; the HBV carrier status is unknown in 80% of this population (4). In addition to health care workers, those at particularly high risk for HBV infection, and thus carrier status, include intravenous drug abusers who share needles, male homosexuals, the sexually promiscuous, transfused patients, and hemophiliacs (1). Certain geographic areas also have a higher prevalence of chronic HBV carriers: Southeast Asia, sub-Saharan Africa, Oceania, and the Mediterranean region (1).

The HBV is transmitted to health care workers primarily through blood contact. Overt accidents with needles and other sharps are most often recognized as being the means of transmission. Lacerations, scratches, mucous membrane exposures, and dermatitis have also been implicated in transmission. It is important to recognize that approximately 80% of HBV infections in the work place can not be accounted for by recognized exposures (4). Additionally, not all contact with viremic blood results in infection. The risk for infection varies with the type of contact; the recognition of

contact; remedial actions taken; and the infectivity of the carrier. Risk for infection ranges from 25% for those exposed to blood from a patient who is HBeAg positive to 5% for those exposed to blood from an HBeAg negative patient (4).

The incidence of HBV infection among health care workers has decreased in the last decade. This may be potentially related to the introduction of the HBV vaccine in 1982 and the implementation of universal precautions and body substance isolation throughout the 1980's (4). However, it is estimated that only 30-40% of health care workers overall have been vaccinated (6).

When the HBV vaccine was introduced, the duration of the vaccine's immunity was not known. The loss of protective anti-HBs levels has been studied primarily between the two and five year point with relatively small sample sizes among groups of health care workers (refer to literature review). A major question regarding the use of the vaccine is related to the duration of protective antibody and the need for booster injections.

The Purpose of The Study

The purpose of this study is to evaluate the serologic evidence of immunity to hepatitis B in those health care workers who had anti-HBs serum levels drawn at the University of Iowa Hospitals and Clinics (UIHC) from 1988 to 1992 This study will evaluate epidemiologic determinants for measurable antibody over time following prior immunization. It has been hypothesized that sex, age, body mass index, race, smoking status, site and type of immunization are independent risk factors associated with absent or non protective anti-HBs levels post-vaccination (see literature review). Hepatitis B serological results will be linked to risk factor data abstracted from employee health records to determine the relative importance of each potential risk factor for immunity over time post-vaccination.

Research Questions

1. What proportion of employees sustaining a sharps injury or exposure were previously vaccinated?

2. What proportion of health care workers have protective levels of anti-HBs post-vaccination at specific time intervals?

3. What are the independent risk factors for absence of protective anti HBs immunity over time post-vaccination?

Definitions

Hepatitis B virus (HBV): The intact viron is referred to as the Dane particle. It is a 42-nm-diameter sphere made up of an outer shell 7-nm thick composed of hepatitis B surface antigen (HBsAg) and an inner core 28-nm in diameter possessing the hepatitis B core antigen (HBcAg), hepatitis B e antigen (HBeAg), DNA polymerase, and a small (3200 bases), circular, mostly double-stranded DNA genome (1).

Hepatitis B surface antigen (HBsAg): HBsAg is found on the surface of the Dane particle and is also found in a free state in the blood. Smaller 22-nm spherical particles and tubular particles with a 22-nm cross-sectional diameter represent HBsAg. The HBsAg is made up of three large polypeptides. The HBsAg found in the blood in a free state represent HBsAg that was produced in great excess during HBV replication. It is detected in blood and body fluids by radioimmunoassay or enzyme-linked immunosorbent assays (ELISA). Current assays detect 5-10 ng protein/ml, or 10^{10} particles per milliliter. HBsAg is found through out body fluids; in saliva, semen and breast milk as well as blood serum. The presence of HBsAg generally correlates with infectivity. HBsAg typically appears in the serum late in the incubation period and persists through most or all of the clinical stages of acute hepatitis B. Its disappearance almost always signals the end of hepatitis B infection and is shortly followed by

detectable serum anti-HBs. Individuals who fail to clear HBsAg from the serum are chronically infected; either associated with chronic liver disease or as a chronic HBsAg carrier without liver disease (1).

Hepatitis B core antigen (HBcAg): This antigen is associated with the core of the Dane particle in serum or in hepatocytes and with disrupted Dane particles. In hepatocytes, exclusively nuclear localization of HBcAg is generally associated with viremia but rarely with active liver disease. Cytoplasmic HBcAg expression correlates with viremia and active liver disease. HBcAg is not found in serum, although anti-HBcAg is found in serum shortly after HBsAg is detectable and represents the earliest humoral immune response to HBV antigens (1).

Hepatitis B e antigen (HBeAg): HBeAg is contained in a cryptic form within the Dane particle, revealed after proteolytic enzyme or detergent treatment; and in a soluble form in some HBsAb-positive sera. It is found in the nucleus of infected hepatocytes. The biologic function of HBeAg is still unknown but it appears to have no role in viral replication. The clinical importance of HBeAg relates to its serving as a marker for significant chronic liver disease and for increased infectivity. Loss of HBeAg positivity and appearance of anti-HBe in serum generally indicates lower infectivity and decreased severity of HBV-associated liver disease, but serum without HBeAg is still infectious (1).

Hepatitis B core antibody (anti-HBc): Anti-HBc provides the earliest evidence of a humoral response to the HBV. It occurs late in the incubation period corresponding to the appearance of HBsAg in serum. Anti-HBc declines to low values with convalescence and can persist at low levels for many years. Its presence strongly suggests acute HBV infection. Anti-HBc may be the only marker of HBV infection between the decline of HBsAg and the appearance of anti-HBs. This time period is called the "core window" (1).

Hepatitis B surface antibody (anti-HBs): Anti-HBs is detectable later in convalescence, often after HBsAg has disappeared, and generally signifies the end of infection. It is also the antibody produced in response to vaccination. Anti-HBs lasts many years and its presence protects against reinfection (1).

Hepatitis B e antibody (anti-HBe): Anti-HBe usually appears shortly after HBeAg declines in the early convalescent period. In individuals who develop chronic HBV infection, HBeAg usually persists and anti-HBe does not develop (1).

Plasma derived vaccine: Vaccine that is prepared from plasma obtained from asymptomatic, high titer, HBsAg carriers. Vaccine production includes purification by ultra centrifugation and a three-step chemical process that inactivates all known classes of viruses found in human blood. In its final form plasma derived HB vaccine is a suspension of alum-adsorbed 22nm HBsAg particles in a concentration of 20µg/ml of HBsAg protein. Plasma derived vaccine is no longer produced in the United States (4).

Recombinant vaccine: This vaccine is a recombinant DNA preparation produced in yeast (*Saccharomyces cerevisiae*) that contains a plasmid for the HBsAg gene. Purified HBsAg is separated from the yeast cells by biochemical and biophysical techniques. The final preparation contains no more than 5% yeast-derived protein. Two manufacturers distribute recombinant HB vaccines: Recombivax HB (Merck Vaccine Division) and Engerix-B (SmithKline Beecham) (4).

Protective immunity: Immunity is implied and considered protective by an antibody response to the vaccine of 10 milli-International units (mIU/ml) or greater (4). Another antibody measurement method is sample counts/negative control counts (S/N) radioimmunoassay units. With this system antibody levels of 10 S/N radioimmunoassay units or greater is considered protective (7).

CHAPTER II

REVIEW OF LITERATURE

Literature pertaining to the effectiveness of the hepatitis B (HB) vaccine has focused on several groups. Specific study populations include those thought to be "healthy" adults with "normal" immune systems and groups of individuals with possible alteration or compromise in immune status (e.g., homosexual males, infants, and dialysis patients).

The purpose of this study is to evaluate HB vaccine in relationship to health care workers. For the most part, health care workers represent "healthy" adults with intact immune systems. For this reason the literature review will focus on "healthy" adults with intact immune systems.

Literature will be reviewed for information regarding the duration of vaccine immunogenicity and for data on specific risk factors associated with vaccine failure to produce adequate levels of anti-HBs. These factors include sex, age, body mass index (weight in kilograms/height in meters^2), race, smoking status, immunization site, and vaccine type.

Little data is available regarding the long term efficacy of the HB vaccine. All the studies done to evaluate long term efficacy pertain to plasma derived vaccine, either Heptavax-B or Hevac B. Heptavax-B was produced in the United States and was first licensed for use in November 1981 and available for use in July 1982 (3). Hevac B was a French vaccine tested outside of the United States and is not approved for use in the United States.

Most studies have used the level of 10mIU/ml (10 milli-International Units per milliliter) as the cut off point for immunity for anti-HBs levels. Some studies have used other units of measure but all related their levels to the standard of 10mIU/ml. Studies using the Hevac B vaccine used different dosing schedules from the Heptavax-B vaccine. The two Hevac B vaccine studies reviewed also differed from each other in dosing schedule.

Duration of Immunity

A Hevac B vaccine study conducted in Taiwan by Chan et al. (8) looked at the duration of immunity using low dose immunization at 0, 1, 2, and 12 months. Susceptible hospital personnel were randomly assigned to 3 groups and given either 5µg, 2µg, or 1µg doses of the vaccine, at the intervals above, intramuscularly (IM). Subjects were followed for 4 years. Of the individuals who responded to the initial vaccination with adequate immune antibody levels and completed follow-up, more than 90% in all groups had persistence of anti-HBs; 95% (84/88) after 4 years in the 5µg group; 92% (72/78) in the 2µg group and 95% (81/85) in the 1µg group had anti-HBs levels at or greater than 10mUI/ml. None of the individuals under study became HBV infected.

In France a Hevac B study was performed by Couronce et al. (9) to evaluate anti-HBs levels among health care workers. These individuals received a booster immunization 17 months after their primary vaccination; 101 individuals were followed for five years. Approximately 93% had protective levels (10mIU/ml or greater) and 85% had levels greater than or equal to 50mIU/ml. Four individuals developed HBV infections during the study. All four were characterized by seroconversion to anti HBc with increased anti-HBs levels. None had detectable HBsAg, a rise in hepatic transaminases, or clinically significant hepatitis B infection.

A study using Heptavax-B vaccine was conducted in the Netherlands by Wismans et al. (10), following 38 adults, all considered healthy documented vaccine responders, for 2.5 years. Subjects received 20ug doses IM at 0, 1, and 6 months and a booster dose at 30 months. At 30 months, prior to the booster injection, 87% had anti-HBs levels above 10mIU/ml. One month after the booster injection all subjects had protective anti-HBs (10mIU/ml or greater). The decline in anti-HBs was proportional the antibody titer originally obtained. A 10 to 100 fold increase in anti-HBs occurred after the booster injection and it too was proportional to the antibody titer originally obtained.

In Wisconsin, a study conducted by Horowitz and colleagues (11) evaluated 245 hospital employees 3 years post-vaccination. The subjects received 3 doses of 20µg of Heptavax-B. At follow-up, 62% were found to have anti-HBs levels above 10mIU/ml. When results were adjusted for potential non-responders post-vaccination, this rose to 71%. The incidence of HBV infection among the study group was not evaluated.

Street and colleagues at Duke University (7) conducted a study among 82 health care workers five years after completion of the HBV vaccine series. The Heptavax-B vaccine had been administered in 20µg doses at 0, 1, and 6 months. Protective antibody levels were defined as greater than or equal to 10 S/N (sample counts/negative control counts) radioimmunoassay units. Hospital employees were stratified according to risk factors that could affect anti-HBs levels, creating 108 different categories. Individuals were then requested to participate from each of the categories. The investigators considered these individuals to be representative of the Duke University Medical Center health care workers and made estimations of the duration of anti-HBs levels for all employees based on the sample results. The investigators estimated that only 30% of the hospital health care workers had anti-HBs levels above 10S/N units after 5 years.

Gibas et al. (12) conducted a study among 32 health care workers; followed for 5 years. Subjects had been vaccinated with the Heptavax-B vaccine and all 32 were

documented vaccine responders. All individuals received the vaccine in the deltoid in 20 µg doses per the usual 0, 1, and 6 month schedule. Ninety-seven percent of the subjects had detectable anti-HBs, however, only 76% had protective levels after five years.

A study of the Heptavax-B vaccine in Alaska among the Yupik Eskimo population by Wainwright et al. (13) also evaluated antibody response at five years. They immunized adults and children including infants. They used the recommended, standard dosing schedule with the dose adjusted for age. Of those who initially responded to vaccine, 81% maintained anti-HBs levels in the protective range. The same cohort at eight years after completion of HBV vaccination (14) had 74% of those immunized with protective levels of antibody.

Age

Most of the studies that have evaluated the effect of age on the immunogenicity of the HB vaccination do so at the time of initial vaccination. These studies include both plasma derived and recombinant vaccines. In the study conducted among the Yupik Eskimo population, Wainwright et al. (13) found a lower initial response to the vaccine with increasing age, especially among those over 49 years of age. This lower level of protective antibody in an older age group was again observed among the Yupik Eskimo population at the eight year follow up point (14).

Wood et al. (15) found age was a risk factor for lack of detectable antibody three months after completion of the vaccination series. The mean age for those who lacked anti-HBs was 42.9 years of age vs. 39.3 years for those with detectable anti-HBs ($p=.01$).

In a study of public safety personnel by Roome et al. (16), age was also shown to be related to anti-HBs levels one to six months post-vaccination. Measurable anti-HBs levels below 10mIU/ml were found in 3% of individuals younger than 30 years and 42% of those greater than 60 years of age ($p<0.0001$).

Horowitz et al. (11) reported that 3 years following vaccination, the group with low levels of anti-HBs were significantly older than those with protective levels of anti-HBs, 42 years of age vs. 36 years of age ($p<0.002$).

Sex

Wood et al. (15) found an association between the development of low levels of anti-HBs for the recombinant vaccine and sex. With univariate and multivariate analysis, male gender was significantly associated with low anti-HBs levels. Eighteen (18%) of 98 men lacked detectable anti-HBs compared with 45 (9%) of 497 women ($p=0.006$). The study by Street et al. (7) evaluated sex as a variable that could affect anti-HBs levels but found no independent association with protective antibody levels at five years. The Yupik Eskimo study by Wainwright et al. (13) evaluated the effect of sex on initial anti HBs levels following vaccination; there was no significant difference between men and women, controlling for age.

Body Mass Index

Body mass index (BMI) is defined in two ways, the Quetelet index (weight in pounds/height in inches^2 X 100) and body mass index (weight in kilograms/height in meters^2). The higher the BMI or Quetelet indices, the more obese the individual.

The study by Street et al. (7) found that individuals with higher Quetelet indices tended to have higher initial anti-HBs levels but a more rapid antibody decline over time after immunization. Horowitz et al. (11) used body mass index when considering factors that could effect anti-HBs levels. They reported that individuals (population 81% female) with a BMI greater than 25 had a relative risk of 1.4 to have anti-HBs levels lower than 10mIU/ml ($p<0.02$) when compared to individuals with a BMI of 25 or less. The public safety personnel study by Roome et al. (16) (population 97% male) also evaluated BMI as

a factor effecting anti-HBs levels. Anti HBs levels were below 10mIU/ml in 8.6% of individuals with a BMI of less than 25; 11% of those with a BMI of 25-29; 11.5% of those with a BMI of 30-35; and 61.5% of those with a BMI of greater than 35. Wood et al. (15) evaluated body mass index and found that the mean BMI for those who lacked anti-HBs was 28.6 vs. 25.6 for those with detectable anti-HBs ($p<.001$).

Race

In the studies published to date, the race of the populations has been fairly homogeneous among the subjects, (Chinese (8), Eskimo (13, 14), White (11, 16)). In general, race has not been evaluated as a variable effecting anti-HBs levels. Street et al. (7) did find a greater decline in anti-HBs levels among African Americans; however, this difference was accounted for by BMI. Among public safety personnel in the study by Roome et al. (16), 13% of whites, 7% of African Americans, and 9% of Hispanics did not have protective levels of antibody. Although these differences were not significant, the study lacked adequate power to address this issue.

Smoking Status

Smoking status was evaluated as a risk factor for insufficient protective antibody levels in three of the ten studies reviewed. Horowitz et al. (11) studied a population of which 19% were classified as smokers. Subjects with low anti-HBs levels were more likely to smoke cigarettes (23% compared with 14%, $p<0.01$). The study by Roome et al. of public safety personnel (16) found 7% of individuals who never smoked and 21% of individuals who ever smoked to have anti-HBs levels below the protective level, a significant difference ($p<0.05$). Wood et al. (15) found an association between smoking and lower anti-HBs levels in their study of Minnesota health care workers. Nineteen

percent of smokers lacked detectable anti-HBs compared with 9% of nonsmokers (p=0.001).

Vaccine Type

No study compared the plasma derived vaccine to the recombinant vaccines. Only one study considered the two different brands of recombinant vaccine. The study by Wood et al. (15) compared the two recombinant vaccines, Recombivax HB and Engerix-B, in Minnesota health care workers. A total of 595 health care workers, at 10 different hospitals, 426 of whom had received Recombivax HB and 169 whom had received Engerix-B were evaluated. Even after controlling for age, sex, body mass index, and smoking status, recipients of Recombivax HB were more likely to lack anti-HBs than recipients of Engerix-B (p=0.02).

CHAPTER III

METHODOLOGY

Research Design

This study was designed to determine the proportion of employees vaccinated prior to an exposure, the proportion with protective (immune) anti-HBs blood levels over time, and to assess independent risk factors associated with the absence of protective anti-HBs levels during follow-up.

Study Population

The study population includes all employees of the University of Iowa Hospital and Clinics (UIHC) who had serologic testing for anti-HBs between January 1, 1988 and December 31, 1992. Six hundred and ten employees had serologic testing done during this time period. Table 1 provides the reasons for elimination from the study population and the number of subjects eliminated. Data were available and obtained by chart review and employee survey on 587 of the 610 health care workers. Of the 587 individuals on whom data were collected 160 were excluded; vaccine status was unknown on 10 (2%); 15 (3%) had not been vaccinated; 41 (7%) had received fewer than 3 vaccine doses; 80 (15%) had their only serology levels drawn before receiving the third vaccine dose; and 14 (2%) were classified as initial non responders to the vaccine. Individuals who had serology drawn within one year of their third vaccine and had results of negative or equivocal were considered initial non responders to the vaccine. Since initial non responders can not provide information on the duration of vaccine immunity, those

Table 1
Reasons for Elimination From the Initial Study Population of 610

Reason	No. Eliminated	Cumulative Total
Data not available from medical record or survey	23	587
Vaccine status unknown	10	577
Not vaccinated	15	562
Fewer than 3 vaccine doses	41	521
Serology only before 3rd vaccine dose	80	441
Initial non-responders	14	427
Serology drawn only before one year after 3rd vaccine dose	138	289

individuals who had serology drawn only within the first year of the third vaccine were excluded from further analysis, (138 responders (23%) plus 14 non responders). Therefore a total of 298 (51%) subjects were excluded from further analysis leaving 289 (49%) for the study population.

These individuals were divided into three groups, based on when serology was drawn in relationship to the date of the third vaccine dose, to evaluate the effect of time. Because an individual may have had more than one serology level drawn over time an individual may contribute data to more than one of these groups. Each individual contributes only once to a group, with the latest serology result drawn for that time period. Therefore the number of serology results analyzed ,317, does not equal the number of individuals contributing data, 289.

Dependent Variable

The dependent variable considered in this study is the anti-HBs serum level. The level was determined at the UHIC laboratory using the Abbott AUSAB EIA immunoassay for the detection of hepatitis B surface antibody. Immunity was determined qualitatively; individual specimens were designated either positive immune, positive equivocal, or negative nonimmune. The testing method included the running of positive and negative controls along with the specimen. The mean of the negative controls was used to determine an immune cut off point. An equivocal range was determined by taking the mean of the negative controls and adding 0.05 to determine the lower limit of the range. The upper limit of the range was the lower limit multiplied by 1.4. Any specimen value below the equivocal range was considered negative nonimmune. Any specimen value above the equivocal range was considered positive immune. For data analysis the six serology results from the study population that were in the equivocal range were considered negative nonimmune.

Independent Variables

Based on studies concerning factors that may have affected the initial and duration of immunity provided by the HB vaccine, body mass index (BMI), smoking status, race, sex, age, site of immunization and vaccine type are considered for their potential effect on anti-HBs levels (7, 8, 9, 12, 14, 15, 16). Time and the persistence of anti-HBs levels was also evaluated.

Data Collection

All UHIC employees who had anti-HBs serologic testing done by the UHIC laboratory during the study period (January 1, 1988 to December 31, 1992) were randomly assigned a subject number. Anti-HBs serology levels for each subject were obtained from UHIC virology laboratory records. A data base was created containing name, subject number, birthdate, sex, hospital number, and serology results including immune cut off points. A second data base was created containing further data collected (by one individual) from reviewing hospital occupational health records using a data collection form designed for this study (Appendix A). Hospital medical records were reviewed for those who did not have occupational health records available. All post-vaccination serology results (other than those already collected from virology laboratory records) were collected from health records. These data were transferred to a data entry form to facilitate data entry (Appendix B). Subject sex and birthdate were verified and updated in the original data base from health record review data and not reentered into the second data base.

A survey instrument was developed, after data collection from health records, to obtain the information most frequently missing from the health record as well as estimates of the frequency of occupational blood contact (Appendix C). A survey, with return envelope, was sent to each of the 610 individuals who had serologic testing during

the study period. Of the 610 subjects, 417 were still hospital employees and surveys were sent to them via the hospital mail system; 193 subjects had left the hospital and were mailed the survey at their most recent home address. Overall response to the survey was 37% (228/610); 18% (34/193) of those contacted at their home address and 47% (194/417) of those contacted via the hospital mail system. Forty-six percent (133/289) of those individuals on whom final data analysis was done responded to the survey.

After data collection and initial data entry it was realized that the serology data from the virology laboratory was qualitative and required coding. Using the immune cut off points and serology data from the first data set the serology data was re coded as positive immune, positive equivocal or negative nonimmune (Appendix D).

Data Analysis

The number of employees who were vaccinated against HBV prior to sustaining an exposure is expressed as a simple proportion. The number of employees with protective antibody levels at specific time intervals is also expressed as a simple proportion. The Fisher's Exact test was used for categorical data and the Wilcoxon rank sum test for continuous variables to compare associations of age, sex, body mass index, smoking status, and type of immunization to the presence of protective antibody levels within the specific year groups. The risk factors of race and site of immunization were excluded from further analysis because of lack of variability among the subjects and the large proportion of unknown; race 85% white and 14% unknown; site of immunization 57% unknown and 40% IM deltoid. Statistical analysis was performed using the SAS (SAS Institute, Cary, North Carolina) software program by the University of Iowa Biostatistics Consulting Center.

Immunity survival curves were plotted using the Nonparametric Estimation of a Distribution Function for Interval Censored Data method. This method was developed by

Bruce W. Turnbul and published in 1976 in the Journal of the Royal Statistical Society B (p. 290-295). The method is used for interval data that can be both right and left censored. The starting point for the data analyzed is one year after the third vaccine; the outcome point is the loss of immunity; the left censored point is the first titer drawn that shows loss of immunity; the right censored point is the last titer drawn that shows immunity. A loss of immunity window is created by the left censored point of an individual and the start point or date of titer last showing immunity, whichever is later. This window reflects the time period during which immunity was lost. The immunity survival curves reflect left censored data. Those individuals that are right censored only, do not contribute to the left censored data, and contribute information for analysis only to the point of right censor.

CHAPTER IV

RESULTS

Demographics

The 441 employees who had received 3 or more doses of vaccine and had serology drawn after the third dose were primarily white (84%) and female (71%) with a mean age of 31 years. Seventy-three percent were non smokers and 19% were ever smokers. The category of ever smoker includes current and previous smokers. The mean body mass index (weight in kilograms/height in meters^2) was 25, with a range of 17 to 53. The site of hepatitis B immunization was unknown for 58% and IM deltoid for 40%. The type of vaccine given was recombinant for 54% and plasma derived for 11%, with 33% unknown. Table 2 gives complete demographic information for this group.

The 289 employees considered for the final analysis (included also in the above group) were primarily white (85%) and female (74%) with a mean age of 30.5 years. Seventy-five percent were non smokers and 19% were classified as ever smokers. The mean body mass index for this group was 24.5, with a range of 17 to 54. The site of immunization was unknown for 57% and IM deltoid for 40%. The vaccine type was 16% plasma derived; 49% recombinant and 3% unknown. Table 3 provides a summary of all the demographic information for this group. The two groups did not differ greatly from each other. The second group excludes the 298 individuals who had serology drawn only within the first year of the third vaccine or were not vaccinated.

Table 2
Demographics of Individuals Who Received Three or More Vaccine Doses (Serology Drawn After the Third Dose)

	N = 441	
Sex	Frequency	Percent
Female	315	71
Male	126	29
Race		
White	370	83.9
African-American	2	0.5
Hispanic	2	0.5
Asian	1	0.2
Other	1	0.2
Unknown	65	14.7
Smoking Status		
Non-smoker	323	73.2
Ever-smoker	85	19.3
Unknown	33	7.5
Site of Immunization		
IM Deltoid	176	40
Subcutaneous	7	2
IM Gluteal	4	1
Unknown	254	57
Vaccine Type		
Recombinant	239	54
Plasma Derived	47	11
Mix of Types	11	2
Unknown	144	33

	No.	Mean	Median	Range
Age (at 3rd vaccine)	431	30.9	28.5	18.4 - 62.7
Body Mass Index	369	24.8	23.5	17.0 - 53.5

Table 3
Demographics of Vaccine Responders (Serology Drawn
One Year or More After Third Vaccine Dose)

	N = 289	
Sex	Frequency	Percent
Female	214	74
Male	75	26
Race		
White	245	85
African-American	1	0.3
Hispanic	2	0.7
Asian	1	0.3
Unknown	40	14
Smoking Status		
Non-smoker	217	75
Ever-smoker	54	19
Unknown	18	6
Site of Immunization		
IM Deltoid	117	41
Subcutaneous	4	1.4
IM Gluteal	2	0.7
Unknown	166	57
Vaccine Type		
Recombinant	140	48
Plasma Derived	45	16
Mix of Types	9	3
Unknown	95	33

	No.	Mean	Median	Range
Age (at 3rd vaccine)	287	30.5	28.3	18.4 - 55.4
Body Mass Index	242	24.5	23.3	17.0 - 53.5

Research Questions

Question One

The first question asked was, "What proportion of employees *sustaining a sharps* injury or exposure were previously vaccinated?". This question was asked to determine the number of people who had started their vaccination series before they experienced an injury that placed them at a higher than their usual risk for hepatitis B exposure. We wanted to ascertain how many individuals took advantage of the hepatitis B vaccination prophylacticly. This question also identifies those individuals who have never been vaccinated against the hepatitis B virus.

We found that 81% (448/551) of individuals on whom vaccine date was known had started their vaccination series prior to a sharps injury or exposure to blood or body fluids. Nineteen percent (103/551)of these individuals started their vaccination series after an injury or exposure. Fifteen individuals had not been vaccinated at all. Of the fifteen individuals who had not been vaccinated, 10 (75%) had positive immune serology results indicating previous contact with the hepatitis B virus and antibody production. One individual had a *positive serology* level in May of 1982 and a subsequent negative noninmmune serology level in February 1992, indicating a loss of immunity that was acquired naturally. Four individuals had negative noninmmune serology results. Thus of the 15 individuals who had never received hepatitis B vaccination only five (25%) would benefit from it.

Question Two

The second question asked was "What proportion of health care workers have protective levels of anti-HBs post-vaccination at specific time intervals?". To evaluate the effect of time the serology results analyzed (from the 289 subjects who had three or

more vaccine doses) were divided into three groups. Group One included those serology results obtained between one year and less than three years; Group Two included results from between 3 years and less than 5 years; Group Three included results from 5 years or more. Group Three had 25 serology's drawn between 5 years and less than six years; 21 serology's drawn between six years and less than 7 years; 17 serology's drawn between 7 years and less than 8 years; 14 serology's drawn between 8 years and less than 9 years; 5 serology's drawn at more than 9 years. The last observations for Group Three were two individuals who had serology drawn at 9.3 years.

Immunity results were; overall 85% (245/289) immune and 15% (44/289) nonimmune; Group One 86% (133/155) immune and 14% (22/155) nonimmune; Group Two 81% (64/79) immune and 19% (15/79) nonimmune; Group Three 89% (73/82) immune and 11% (9/82) nonimmune. Figure 1 illustrates the immunity survival curve for all of the groups combined. Three months after the 1 year from third vaccine start point 9% were nonimmune; 16% were nonimmune at three years from the third vaccine; 17% were nonimmune at 5 years from the third vaccine; and 19% were nonimmune at 7 years from the third vaccine.

Question Three

The third and final question considered was "What are the independent risk factors for absence of protective anti-HBs immunity over time post-vaccination?". As stated in the methodology section, the risk factors of race and site of vaccination were not considered because of the lack of variability among the subjects and the large proportion of missing data. The risk factors that were considered were sex, smoking status, type of vaccine, age (at the time of the third vaccine) and body mass index.

The effects of the risk factors were considered on the entire group of 289 and by the groups described above under question two. Risk factors were analyzed by groups to

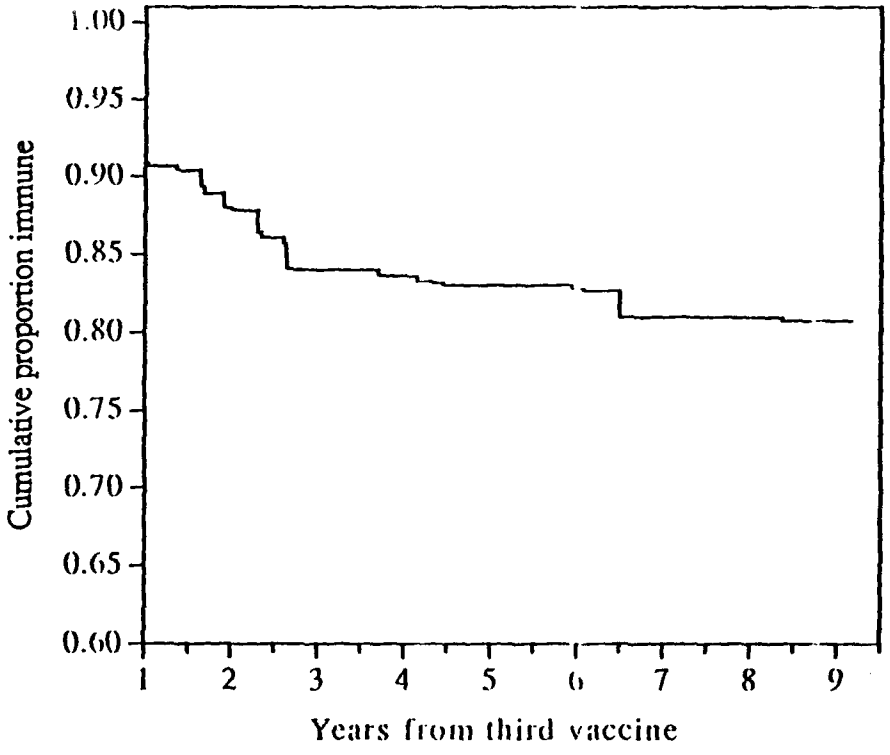

Figure 1
Immunity Survival Curve

reflect the different time periods. As described in the methodology section, Fisher's Exact test was used to compare associations for categorical data and the Wilcoxon rank sum test for continuous data. Results have been summarized in Table 4 for all subjects regardless of time; Table 5 for Group One; Table 6 for Group Two; and Table 7 for Group Three.

Sex

When analyzed for the whole group of 289 sex did not show a significant association with loss of immunity (p=0.3). A one tail test for significance was used because a previous study had suggested lower anti-HBs levels associated with male sex (7). Group One did show a significant association between being male (p=0.03) and lack of protective immunity with a one-tail Fisher's Exact test. The p-value changed from p=0.03 to p=0.06 when a two-tail test for significance was used, reducing the significance to a trend. Groups Two and Three did not show a significant association between sex and lack of immunity, p=0.8 and p=0.9 respectively. See Figure 2 for the immunity survival curve by sex for the entire study population. Seventeen percent of the males were nonimmune at 1 year and 1 month after their third vaccine and this did not increase more than 0.5 of a percentage point over time. In contrast approximately 4% of females were nonimmune at 1 year and 1 month after their third vaccine and immunity dropped off gradually overtime; 11% nonimmune at 2 years; 17% nonimmune at 4 years; 19% nonimmune at 6 years.

Smoking Status

Smoking has been associated with an increased risk for the loss of protective levels of immunity in previous studies (11, 15, 16). For this reason a one-tail test for significance was used to evaluate the data. When analyzed as a whole group of 289 there was a significant association between smoking status and loss of immunity, p=0.02.

Table 4
Risk Factor Analysis for Non protective Anti-HBs
Regardless of Time

N = 289					
	Frequency		Percent		
Immune	245		85		
Nonimmune	44		15		
Sex	Immune No. (%)		Nonimmune No.(%)		P Value+
Female	183 (86)		31 (14)		
Male	32 (76)		10 (24)		0.03+
Smoking Status					
Non-smoker	198 (88)		26 (12)		
Ever-smoker	41 (76)		13 (24)		0.02+
Unknown = 8					
Vaccine Type					
Recombinant	117 (84)		23 (16)		
Plasma Derived	43 (96)		2 (4)		
Mix of Types	4 (44)		5 (56)		
Unknown = 95					0.002++
Age	No.	Mean	Median	Range	P Value**
Immune	243	30	27	18 - 55	
Nonimmune	44	34	31	23-53	0.002
Body Mass Index	No.	Mean	Median	Range	P Value**
Immune	202	24	23	17-44	
Nonimmune	40	25	23	19-53	0.48
Unknown = 47					

*P value calculated using Fisher's Exact Test, 0.05 significance

**P value calculated using Wilcoxon Rank Sum Test, 0.05 significance

+one-tail test

++two-tail test

Table 5
Group 1 (One Year to < Three Years) Risk Factor Analysis
for Non-protective Levels Anti-HBs

	N = 155		
	Frequency	Percent	
Immune	133	86	
Nonimmune	22	14	
Sex	**Immune No. (%)**	**Nonimmune No.(%)**	**P Value+**
Female	101 (89)	12 (11)	
Male	32 (76)	10 (24)	0.03+
Smoking Status			
Non-smoker	102 (89)	13 (11)	
Ever-smoker	24 (75)	8 (25)	0.05+
Unknown = 8			
Vaccine Type			
Recombinant	92 (86)	15 (14)	
Plasma Derived	9 (90)	1 (10)	
Mix of Types	1 (50)	1 (50)	
Unknown = 36			0.38++

Age	No.	Mean	Median	Range	P Value**
Immune	133	30	27	18 - 55	
Nonimmune	22	35	32	25-53	0.002

Body Mass Index	No.	Mean	Median	Range	P Value**
Immune	110	24	23	18-35	
Nonimmune	19	26	24	19-53	0.73
Unknown = 23					

*P value calculated using Fisher's Exact Test, 0.05 significance

**P value calculated using Wilcoxon Rank Sum Test, 0.05 significance

+one-tail test

++two-tail test

Table 6
Group 2 (Three Years to < Five Years) Risk Factor
Analysis for Non-protective Levels Anti-HBs

N = 79

	Frequency	Percent
Immune	64	81
Nonimmune	15	19

Sex	Immune No. (%)	Nonimmune No.(%)	P Value[+]
Female	47 (80)	12 (20)	
Male	17 (85)	3 (3)	0.80[+]

Smoking Status			
Non-smoker	54 (84)	10 (16)	
Ever-smoker	9 (64)	5 (36)	0.09[+]
Unknown = 1			

Vaccine Type			
Recombinant	21 (72)	8 (28)	
Plasma Derived	9 (100)	0 (0)	
Mix of Types	4 (80)	1 (20)	
Unknown = 36			0.24[++]

Age	No.	Mean	Median	Range	P Value**
Immune	64	29	26	19-54	
Nonimmune	15	29	28	24-39	0.33

Body Mass Index	No.	Mean	Median	Range	P Value**
Immune	56	25	24	17-44	
Nonimmune	15	25	23	19-35	0.82
Unknown = 8					

*P value calculated using Fisher's Exact Test, 0.05 significance

**P value calculated using Wilcoxon Rank Sum Test, 0.05 significance

[+]one-tail test

[++]two-tail test

Table 7
Group 3 (Five Years or More) Risk Factor Analysis for
Non-protective Levels Anti-HBs

N = 82		
	Frequency	Percent
Immune	73	89
Nonimmune	9	11

Sex	Immune No. (%)	Nonimmune No.(%)	P Value*
Female	53 (87)	8 (13)	
Male	20 (95)	1 (5)	0.94+

Smoking Status			
Non-smoker	54 (92)	5 (8)	
Ever-smoker	14 (100)	0 (0)	1.00+
Unknown = 9			

Vaccine Type			
Recombinant	6 (100)	0 (0)	
Plasma Derived	32 (97)	1 (3)	
Mix of Types	0 (0)	3 (100)	
Unknown = 40			0.38++

Age	No.	Mean	Median	Range	P Value**
Immune	71	30	28	19-48	
Nonimmune	9	36	31	23-47	0.14

Body Mass Index	No.	Mean	Median	Range	P Value**
Immune	58	23	23	18-42	
Nonimmune	8	26	23	20-35	0.27
Unknown = 16					

*P value calculated using Fisher's Exact Test, 0.05 significance

**P value calculated using Wilcoxon Rank Sum Test, 0.05 significance

+one-tail test

++two-tail test

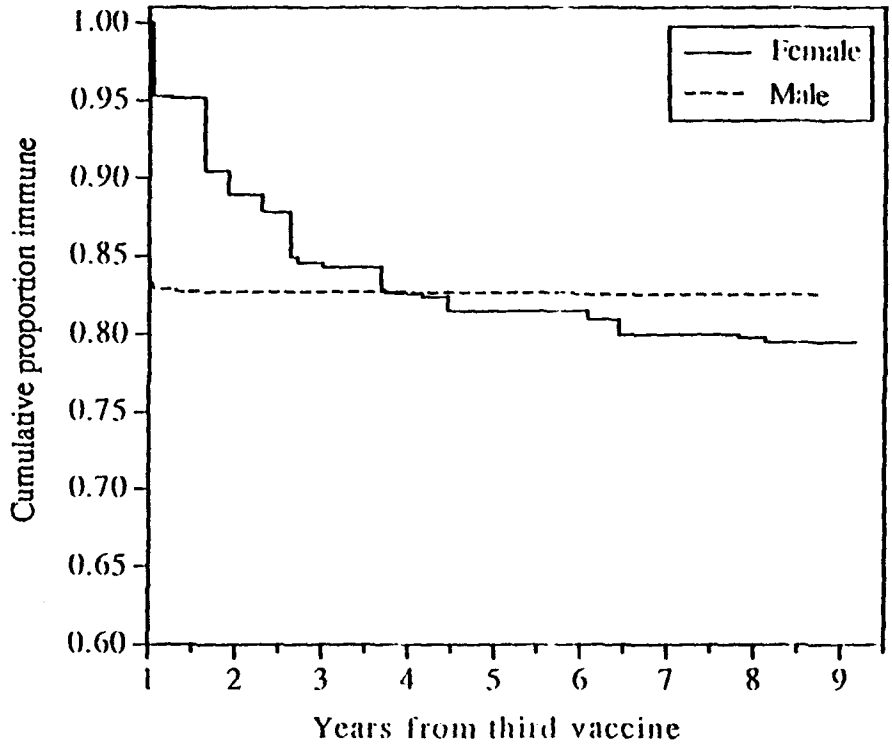

Figure 2
Immunity Survival Curve by Sex

When a two-tail test for significance was done the significance remained, p=0.03. Group One showed a significant association between smoking and loss of immunity, p= 0.05. When a two-tail test for significance is done for the Group One data the significance is reduced (p=0.08) to a trend. Groups Two and Three did not show a significant association, p=0.9 and p=1.0 respectively. See Figure 3 for the immunity survival curve by smoking status for the entire study population. Ever smokers immunity dropped off rapidly when compared to never smokers; 9% nonimmune at 1 year and 1 month after the third vaccine; 21% nonimmune at 2 years; and 29% nonimmune at 3 years and beyond. Immunity for never smokers was 7% nonimmune at 1 year and 1 month after third vaccine; 12% nonimmune at 2 years to 6 years; 16% nonimmune at 6.5 years; and 18% nonimmune at 7.8 years and beyond.

Vaccine Type

The entire study population of 289 showed a significant association between the different types of vaccine and loss of immunity, p= 0.001. This association completely disappeared when the data were re-analyzed using only plasma derived and recombinant vaccines, eliminating mix of types from analysis, p=1.0. This significant difference was due to the mix of types category where five out of nine were nonimmune. Groups One and Two did not show a significant association between the different types of vaccine (p=0.4 and p=0.2 respectively) and loss of immunity. Group Three did show a significant association of vaccine type and loss of immunity, p=.0004. This association completely disappeared when the data were re-analyzed using only plasma derived and recombinant vaccines, eliminating mix of types from analysis, p=1.0. This significant difference was due to the small number in mix of types, 3, and the fact that all results for mix of types were nonimmune.

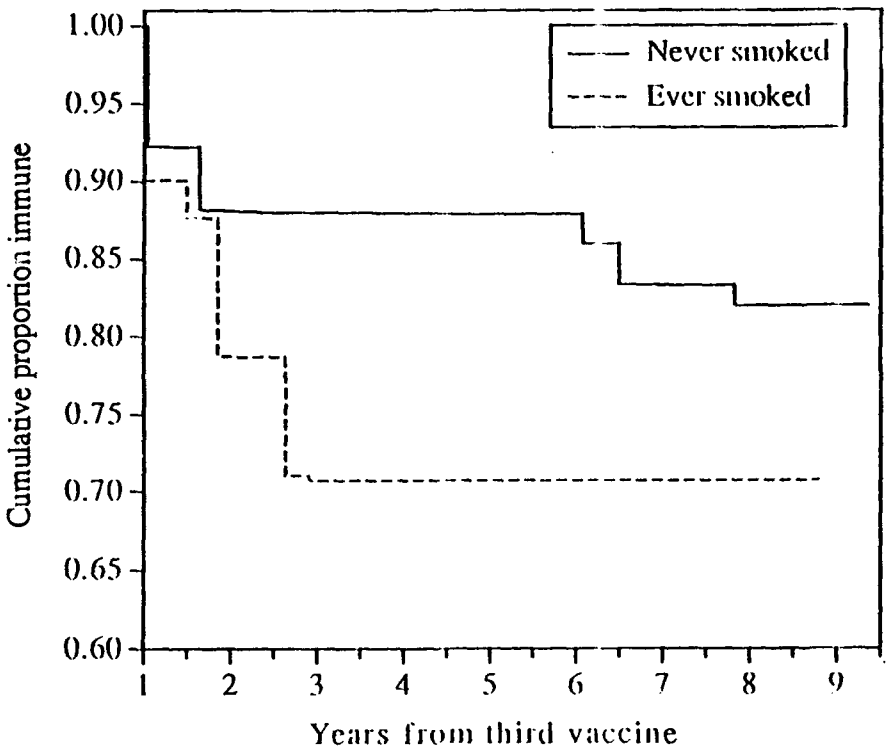

Figure 3
Immunity Survival Curve by Smoking Status

Age

Overall the study population of 289 showed a significant association between age and loss of immunity, p=0.002. The mean age (at third vaccine dose), for those immune, was 30 years; median 27 years; range 18 to 55 years. The mean age for those nonimmune was 34 years; median 31 years; range 23 to 53 years. Group One also showed a significant association between age and loss of immunity, p=0.002. The mean age (at third vaccine dose), for those immune, in Group One was 30 years; median 27 years; range 18 to 55 years. The mean age for those nonimmune in Group One was 35 years; median 32 years; range 25 to 53 years. Groups Two and Three did not show an association between age and loss of immunity, p=0.3 and p=0.1 respectively. In Group Two, for those immune, mean age was 29 years; median 26 years; range 19 to 54 years. Those nonimmune in Group Two had a mean age of 29 years; median 28 years; range 24 to 39 years. Among those immune in Group Three the mean age was 30 years; median 28 years; range 19 to 48 years. Among those nonimmune in Group Three mean age was 36 years; median 31 years; range 23 to 47 years. See Figure 4 for the immunity survival curve by age for the entire study population. It was found that those older than the median age of 28 years showed a significant association of age with loss of immunity, p=0.009 (Fischer's Exact test, two-tail). For this reason 28 years of age was used as the cut off point to diagram the curve. For those 28 years old or greater 16% were nonimmune at 1 year and 1 month after the third vaccine; 21% were nonimmune at 2.6 years; 25% were nonimmune at 6.5 years; 28% nonimmune at 8.3 years. For those younger than 28 years 5% were nonimmune at 1.6 years; 10% were nonimmune at 3 years; 13% were nonimmune at 6.9 years.

Body Mass Index

The study population overall did not show a significant association between body mass index and loss of immunity, p=0.4. Among the immune the mean body mass index was 24; median 23; range 17 to 44. Among the nonimmune the mean body mass index was 25; median 23; range 19 to 53. None of the groups when considered separately showed a significant association between body mass index and loss of protective immunity, p=0.7, p=0.8 and p=0.3 consecutively. In Group One, among the immune, body mass index mean was 24, median 23 and range 18 to 35; among the nonimmune the mean was 26, median 24 and range 19 to 53. In Group Two, among the immune, body mass index mean was 25, median 24 and range 17 to 44; among the nonimmune the mean was 25, median 23 and range 19 to 35. In Group Three, among the immune, body mass index mean was 23, median 23 and range 18 to 42; among the nonimmune the mean was 26, median 23 and range 20 to 35.

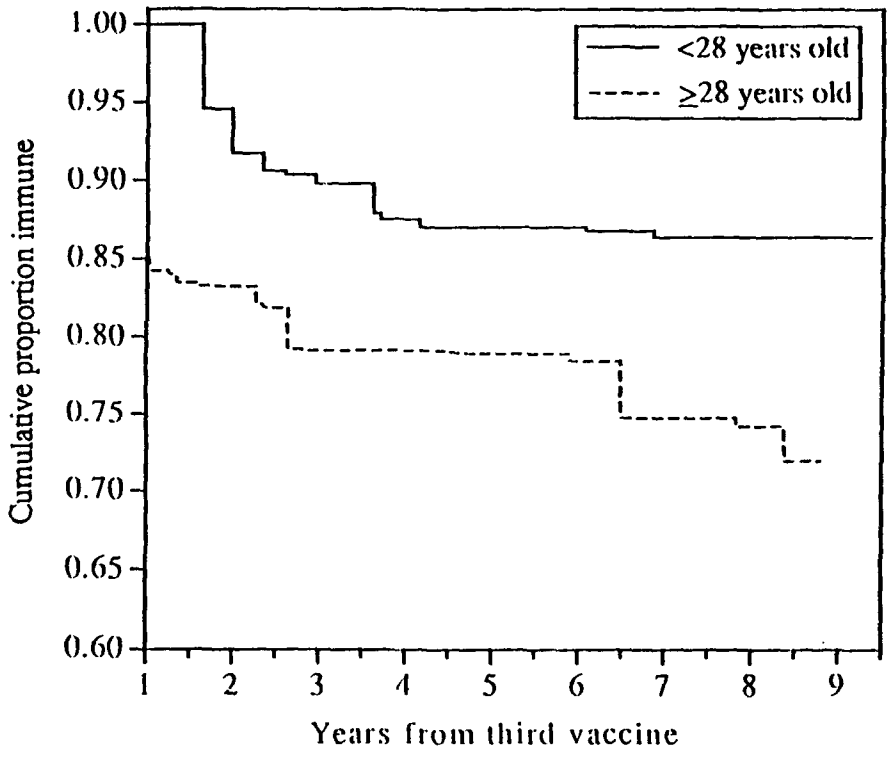

Figure 4
Immunity Survival Curve by Age

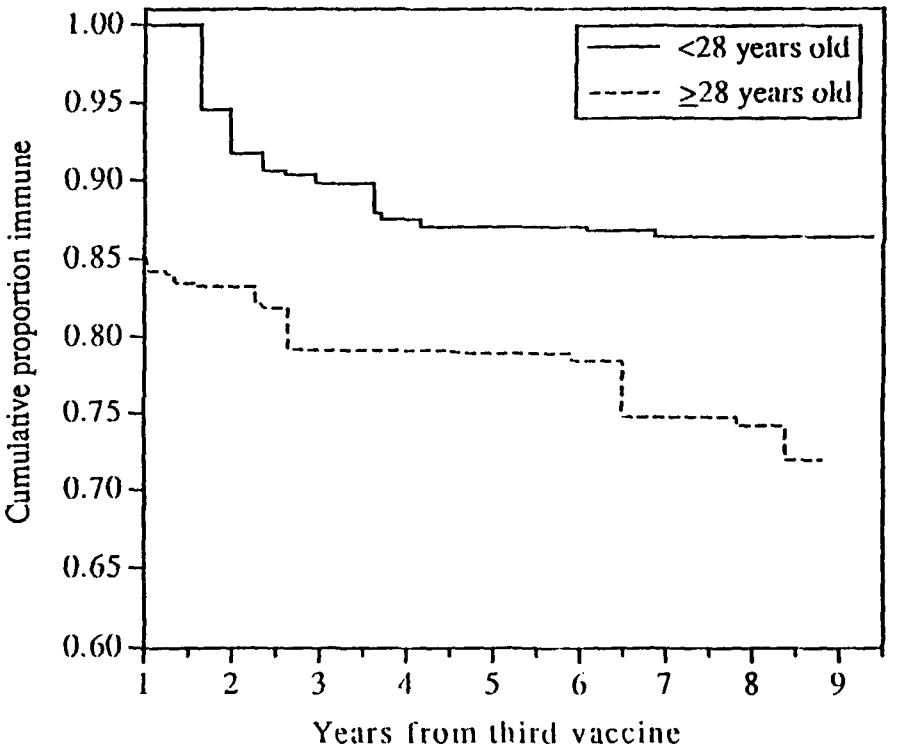

Figure 4
Immunity Survival Curve by Age

CHAPTER V

DISCUSSION

This study assessed the prevalence of immune anti-HBs levels among UHC health care workers who had been previously vaccinated against the hepatitis B virus. The prevalence of the initiation of the vaccine series prior to a sharps injury or exposure to blood or body fluids was also determined. Associations between suspected risk factors of age, race, sex, body mass index, smoking status, vaccine type and site of immunization and loss of immune status were also assessed.

Study Limitations

The study was unable to assess the association of race on anti-HBs levels because the study population was predominately white (85%). Therefore, in addition to not being able to assess race as a risk factor to loss of immunity the applicability of the study findings to other than whites must be carefully considered.

The site of immunization was unknown for over 57% of the population and IM deltoid for another 40% of the population. This eliminated the ability to make any associations between immunization site and anti-HBs levels.

The study population used to consider the association of risk factors to anti-HBs levels was predominately female (74%). This is, I feel, a reflection of the large proportion of nurses among health care workers. Results for males were not considered separately in this study. This study did find, in the one year to less than three years post vaccination group, a significant association between age, male sex, smoking status and loss of anti-HBs. In comparison the one study reviewed that was predominately male

(16) found significant associations for age, obesity, smoking status and lack of immunity in recently vaccinated subjects. Because this study did show an association in one group between male sex and loss of immunity, application of the results of this study to predominately male populations should be done with care.

Sources of Bias

There are several opportunities for misclassification bias both in the medical record and the employee survey. Race was most likely misclassified on occasion by health care providers recording in the subjects medical record. It was noted in at least one chart that an individual had been recorded as being white and Asian on different occasions by different health care providers. There were several charts with patient names that were distinctly Asian, Eastern Indian or Hispanic in origin and these individuals were classified as white. Most likely a portion of these individuals would have been more accurately classified as other than white. Because of this, information on race from returned surveys took precedence over information found on chart review. It is unlikely that the misclassification contributed significantly to the lack of variability among race and the inability to evaluate race as a risk factor to loss of immunity. The misclassification of race is a nondifferential bias; if race had been evaluated, any results would have been biased towards the null.

Among survey responders there was the potential for recall bias which would lead to the misclassification of the site of immunization, the type of vaccine given and the date of third vaccination. Because of this, information from the survey was only used if the medical record did not indicate the type and site of vaccination and the date of the third vaccine dose. Information from the chart, if recorded at the time of vaccination, was felt to be accurate and took precedence. Of those responding to the survey, correlation with information found in the medical record was poor. Many individuals put question marks

beside their data or wrote "I'm not sure." This recall bias is most likely nondifferential in nature; there is the possibility that it may be differential. Those individuals who had been told in the past that they no longer had immunity may have researched the type, site and date of vaccination and be more aware of the information now; thus improving recall among those without immunity. This would have only had an impact for those individuals who did not have this information recorded in their medical record, since medical record information took precedence over the survey information. If the recall bias had been differential, one can not predict if it would have increased or decreased the significance of the findings.

Confounders

There are no known confounders associated with the risk factors studied and anti-HBs levels.

Results

When risk factors were analyzed for the study population of 289, significant associations were found between age, smoking status and loss of protective levels of anti-HBs ($p=0.002$ and $p=0.02$, respectively. Odds ratios and 95% confidence intervals (95% CI) were calculated for these two risk factors. It was found that ever smokers had a 1.8 odds ratio for loss of immunity when compared to never smokers (95% CI 0.87, 4.03. It was found that age greater than or equal to 25 years of age had a 2.97 odds ratio for loss of immunity when compared to those less than 25 years of age (95% CI 1.18, 7.49).

Group One (one year to less than three years post-vaccination, n=155) also showed significant associations between risk factors and anti-HBs levels. There was a significant association between male sex ($p=0.03$), smoking ($p=0.05$) and age ($p=0.002$). Group Two (three years to less than five years post-vaccination, n=79) showed a trend

toward significance in relation to smoking status. Group Three (five or more years post-vaccination, n=82) showed no significant associations or trends.

One of the primary limitations for the groups, especially Group One and Two, was sample size and therefore lack of power to show significance. Groups Two and Three each contained only 14 smokers versus 78 and 73 known non-smokers respectively. Group Two had only one person over the age of 45 years; Group Three had six individuals over the age of 45 years.

The findings of this study are consistent with the findings of previously conducted studies. Of those studies that evaluated risk factors, the risk factors that were found to be significant were sex, age, body mass index, and smoking (7, 11, 13, 15, 16). This study found age and smoking to be significant among the entire study population of 289; sex, age and smoking to be significant among Group One; and a trend towards significance in Group Two for smoking.

The findings on the duration of immunity among those vaccinated were also consistent with previous studies. With the exception of the study conducted by Street et al. (7), 71% to 95% of those vaccinated were still immune in the three to five year time period (8, 9, 10, 11, 12, 13, 14). This is comparable with the 81% still immune in the three to five year time period from this study. Only one study of the Yupik Eskimo population (14) by Wainwright et al. considered immunity beyond five years. They found 74% of their population to be still immune at the 8 year point. This is consistent with our findings of 89% immune among the group tested five or more years post-vaccination (91% immune among those 7 or more years post-vaccination, 33/36).

Conclusions

When considering the question of whether or not routine booster immunizations are needed for those who have been vaccinated against hepatitis B, several factors must

be considered. First, the risk for clinically significant disease, then population risk for loss of immunity, and finally the cost of a booster program.

Although this study did not determine if any individual vaccinated later contracted disease, other studies have assessed this (7, 8, 9, 12, 13, 14). What they found was that few people developed signs of hepatitis B infection after vaccination. Of those who did, all were clinically asymptomatic with no detectable HBsAg or rise in serum alanine aminotransferase levels. The only sign of infection was the appearance of anti-HBc and a natural increase in anti-HBs levels.

My study provided information on the health care worker populations risk for loss of immunity over time. My findings are consistent with previous studies; overall immunity was maintained in the three to five year time frame for greater than 71-95% of those who responded to vaccination. My study also showed 89% immune in the five to nine year time period which exceeds the 74% found immune at the eight year point among the Yupik Eskimo population (14).

The costs for administering a routine booster vaccination program would be great. There would be administration and documentation costs for tracking individuals; notifying them of the need for booster; following them up to assure they have received their booster; in addition to the cost of the vaccine and its administration.

In view of the fact that; clinically significant disease has not been identified among those who previously responded to initial hepatitis B vaccination; and the majority of those vaccinated maintain their immunity; I would not recommend a routine booster program at this time. Individuals who have anti-HBs titers drawn, for whatever reason, and are found to have lost immunity should be evaluated on a case by case basis and a booster injection may be indicated. If a clinically significant hepatitis B infection should occur in an individual who had previously responded to vaccination the need for routine booster vaccination programs must be reconsidered.

APPENDIX A

DATA COLLECTION FORM:

HBV SEROLOGY FOLLOW-UP STUDY

1) Subject #: _____

2) Sex: F = 1 M = 2

3) Birthdate: __ _____

4) Race: White, not Hispanic = 1 African-America = 2 Hispanic = 3 Asian = 4 Other = 5 Unknown = 0

5) Smoking status: Smoker (currently) = 3 Smoker (previously) = 2 Non-smoker = 1 Unknown = 0

6) Ht: _____cm 7) Wt: _____kg

8) Vaccinated: Yes = 1 No = 2 Unknown = 0

9) Vaccine type: Combination = 5 Engerix = 4 Heptavax = 3 Recombivax = 2 Plasma-derived = 1

10) Dates doses received: 1___ ___ ___ 2___ ___ ___ 3___ ___ ___ 4___ ___ ___ 5___ ___ ___ 6___ ___ ___

11) Site of immunization: SQ = 1 IM deltoid = 2 IM gluteal = 3 IM other = 4 Unknown = 0

12) Percutaneous injury dates: 1___ ___ ___ 2___ ___ ___ 3___ ___ ___ 4___ ___ ___ 5___ ___ ___ 6___ ___ ___ 7___ ___ ___

13) Serology level dates: 1___ ___ ___ 2___ ___ ___ 3___ ___ ___ 4___ ___ ___ 5___ ___ ___ 6___ ___ ___

14) Serology results: 1_____ 2_____ 3_____ 4_____ 5_____ 6_____ (Actual serology results from lab log or coded as: Positive immune = 100 Positive = 200 Positive equiv. = 300 Negative = 400

15) Vaccine year: _____ (The year of 2 or more vaccinations or the year started.)

APPENDIX B

DATA ENTRY FORM HBV SEROLOGY FOLLOW-UP STUDY

1. SUBJECT #:_____
2. RACE:_____
3. SMOKING:_____
4. HT:_____
5. WT:_____
6. VACTYPE:_____
7. SITEIMM:_____
8. DATEVAC1:_____
9. DATEVAC2:_____
10. DATEVAC3:_____
11. DATEVAC4:_____
12. DATEVAC5:_____
13. DATEVAC6:_____
14. DATEINJ1:_____
15. DATEINJ2:_____
16. DATEINJ3:_____
17. DATEINJ4:_____
18. DATEINJ5:_____
19. DATEINJ6:_____
20. DATETR1:_____
21. DATETR2:_____
22. DATETR3:_____
23. DATETR4:_____
24. DATETR5:_____
25. DATETR6:_____
26. TITELVL1:_____
27. TITELVL2:_____
28. TITELVL3:_____
29. TITELVL4:_____
30. TITELVL5:_____
31. TITELVL6:_____
32. VACYR:_____
33. VACCINE:_____

APPENDIX C

OCCUPATIONAL BLOOD CONTACT SURVEY:

HEPATITIS B VIRUS SEROLOGY FOLLOW-UP STUDY

Dear Health Care Worker:

Frequent contact with blood has been identified as a risk factor highly correlated with hepatitis B virus (HBV) infection in health care workers. The more frequent the contact with blood the greater the likelihood of coming in contact with HBV infected blood. Some researchers feel that this frequent blood contact may also act as a "booster" to the health care workers' HBV vaccine immunity. You have had HBV antibody titers drawn at UIHC and we would like you to agree to participate in our HBV serology follow-up study. We are interested in evaluating the duration of protective antibody after HBV vaccination. This study may help determine vaccine protection over time and if there is a need for a routine booster dose of the HBV vaccine. In order to measure the effect of occupational blood contact on HBV antibody serology, it is necessary to collect data regarding routine daily blood contact. Your cooperation in the completion of this form is essential to measure this effect. Please complete this form and return to us in the envelope provided. Your responses will be assigned a code number for the purposes of data entry and analysis. All individual results will be kept strictly confidential and identified in the study data base by number only. Any questions you may have may be directed to Peggy Leopardi, RN at 354-0117 or Brad Doebbeling, MD at 6-8556. Thank you for your assistance.

SITE OF HEPATITIS B VACCINE IMMUNIZATION: (circle all that apply)

1 Subcutaneous (between skin and muscle)

2 Intramuscular deltoid (arm muscle)

3 Intramuscular gluteal (hip)

4 Intramuscular other (thigh etc.)

0 Unknown

RACE: 1 White, not Hispanic **2** African-American **3** Hispanic **4** Asian **5** Others

VACCINE TYPE: 0 Unknown **1** Plasma-derived **2** Recombivax (recombinant) **3** Heptavax

4 Engerix-B (recombinant) **5** Mix of types (recombinant and plasma-derived)

SMOKING STATUS (at the time of vaccination): 1 Non-smoker **2** Smoker (previously)

3 Smoker (currently)

MONTH AND YEAR OF 3rd VACCINE DOSE: MONTH ___ ___ **YEAR** ___ ___

CONTINUED ON OTHER SIDE

PLEASE INDICATE ALL AREAS OF EMPLOYMENT IN HEALTH CARE AND ESTIMATE DIRECT CONTACT WITH BLOOD DURING THAT TIME PERIOD USING THE FOLLOWING CODE

0 No Blood Contact **1** Once a month **2** 2-3 times a month **3** Once a week (4 times a month)

4 2-4 times a week **5** Once a day **6** 2-4 times a day **7** 5 or more times a day

HOSPITAL AREA (ICU, CLINIC, etc.)	NUMBER YEARS AND MONTHS		BLOOD CONTACT CODE

PLEASE RETURN COMPLETED SURVEY TO: BRAD DOEBBELING M.D.
DEPT. OF EPIDEMIOLOGY
C-41 L GH

APPENDIX D

DATA CODES

SEX: 1 = FEMALE 2 = MALE

RACE: 1 = WHITE, not Hispanic 2 AFRICAN AMERICAN

3 = HISPANIC 4 = ASIAN 5 = OTHERS 0 = UNKNOWN

SMOKING STATUS: 1 = NONSMOKER 2 = PREVIOUS SMOKER

3 = CURRENT SMOKER 0 = UNKNOWN

SITEIMM: 1 = SUBCUTANEOUS 2 = IM DELTOID 3 = IM GLUTEAL

4 = IM OTHER 0 = UNKNOWN

VACTYPE: 1 = PLASMA DERIVED 2 = RECOMBIVAX 3 = HEPTAVAX

4 = ENGERIX 5 = MIX OF TYPES 0 = UNKNOWN

TITELVL: 100 = POSITIVE IMMUNE 200 = POSITIVE

300 = POSITIVE EQUIVOCABLE 400 = NEGATIVE NONIMMUNE

VACCINE: 1 = YES, 3 or more doses 2 = NO 3 = YES, less than 3 doses

0 = UNKNOWN

SEX: 1 = FEMALE 2 = MALE

RACE: 1 = WHITE, not Hispanic 2 = AFRICAN AMERICAN

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