ORIGINAL ARTICLE

Serologic Testing for Protection against Hepatitis B Virus Infection among Students at a Health Sciences University in the United States

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OBJECTIVE. To evaluate hepatitis B vaccination coverage and documentation of vaccine-induced immunity.

DESIGN. Retrospective cohort analysis.

SETTING. Graduate school in the United States with programs in osteopathic medicine, dentistry, and allied health.

METHODS. Data collected included demographics, dates of hepatitis B vaccine doses, and postvaccination concentrations of antibody to hepatitis B surface antigen (anti-HBs), with dates. The proportions of students with anti-HBs of 10 IU/L or more by demographics, age at vaccination, interval since completion of the primary series, and response to additional vaccine doses were compared.

RESULTS. Of 3,452 students who matriculated during 2004–2009, 2,643 had complete data; 2,481 (93.9%) received 3 primary doses. Most were women (64.6%), US-born (85.6%), and white (63.2%); median age at receipt of the primary series was 14.5 years (interquartile range, 11.6–20.2 years) and at postvaccination testing was 23.2 years (interquartile range, 22.1–24.8 years). Of those who received 3 primary doses, 2,306 (92.9%) had an anti-HBs postvaccination concentration of 10 IU/L or more. Younger age at vaccination and longer time interval from vaccination to anti-HBs testing were associated with a postvaccination concentration of less than 10 IU/L ($P < .001$ and $P = .0185$, respectively, Cochran-Armitage test for trend). Almost all students (98.2%) who initially had less than 10 IU/L of anti-HBs, but then received at least 1 additional dose, had a follow-up anti-HBs concentration of 10 IU/L or more.

CONCLUSIONS. Almost all students had serologic evidence of protection against hepatitis B virus infection; most were vaccinated as adolescents and were tested more than 10 years after vaccination. Among students with anti-HBs concentrations of less than 10 IU/L, nearly all had 10 IU/L or more after at least 1 additional vaccine dose.

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The US Centers for Disease Control and Prevention's (CDC) Advisory Committee for Immunization Practices recommends hepatitis B vaccination for adults at high risk for infection, which includes healthcare personnel (eg, employees, students, contractors, attending clinicians, public-safety workers, or volunteers) whose activities involve contact with patients or with blood or other body fluids from patients in a healthcare, laboratory, or public-safety setting.[1] For healthcare personnel, postvaccination testing for serum concentration of antibody to hepatitis B surface antigen (anti-HBs) is recommended 1–2 months after administration of the last dose of the vaccine series, and persons determined to have anti-HBs concentrations of less than 10 IU/L after receipt of the primary vaccine series should be revaccinated.[2]

After primary immunization with hepatitis B vaccine, anti-HBs concentrations decline over time. Among healthy persons who respond to a complete primary 3-dose vaccination series, 15%–50% have low or undetectable concentrations of anti-HBs 5–15 years after the start of the vaccination series.[3] However, immunity to infection persists in many previously vaccinated persons despite a decline in anti-HBs concentration to below 10 IU/L, indicated by a rapid, anamnestic increase in anti-HBs after receipt of a single additional dose of hepatitis B vaccine.[3] Therefore, an anti-HBs concentration found to be below 10 IU/L among persons vaccinated years earlier does not necessarily indicate susceptibility to infection.

For the general US population, universal infant hepatitis B vaccination was recommended in 1991, expanded to include previously unvaccinated children aged 11–12 years in 1995, and expanded again to include previously unvaccinated persons aged younger than 19 years of age in 1999.[4] Therefore, persons who received hepatitis B vaccine in infancy and childhood are approaching the age of employment in health-related fields or of entry into health professional training schools and programs,

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where documentation of prior vaccination and of immunity to hepatitis B virus (HBV) infection is typically required.[5]

Our objective in this retrospective study was to examine postvaccination anti-HBs concentrations among a cohort of US healthcare students with a history of completion of a primary hepatitis B vaccine series and to identify factors associated with a subsequent anti-HBs concentration of less than 10 IU/L. Among students found to have a postvaccination anti-HBs concentration of less than 10 IU/L, we evaluated the response to 1 or more additional doses of vaccine.

METHODS

Study Population and Data Collection

In December 2009, we conducted a retrospective cohort study at a private graduate school in Illinois with programs in osteopathic medicine, dentistry, and allied health. Eligible persons were health science students who matriculated from 2004 to 2009. Data collected through abstraction of student medical records included demographic information (date of birth, sex, birthplace, race, ethnicity), dates of administered hepatitis B vaccine doses, postvaccination anti-HBs results with dates, and hepatitis B surface antigen status. All personal identifying information was removed from the analytic data set. The institutional review boards at Midwestern University and CDC approved the study protocol.

MWU Hepatitis B Immunization Policy

Upon matriculation (and no later than the start of a clinical rotation), students were required to submit a quantitative anti-HBs titer. According to school policy, the result of a postvaccination test performed anytime after the primary series was acceptable. Documentation of hepatitis B vaccination was preferred but not required by the institution. The student health clinic policy regarding interpretation of a postvaccination anti-HBs result and the need for hepatitis B vaccine booster doses was based on the designation of the anti-HBs result provided by the laboratory that performed the test (ie, "immune" [10 IU/L or more], "borderline/intermediate" [1–9 IU/L], and "nonimmune" [0 IU/L]). If the result was "immune" (ie, 10 IU/L or more), then no further testing or vaccination was done; if "indeterminate/borderline," 1 or 2 additional vaccine doses were administered; if "nonimmune," 3 additional vaccine doses were administered. For students who received additional doses, postvaccination testing was performed 6 weeks after the administration of the final dose. A full vaccine series was repeated if a student remained "nonimmune" after receipt of the additional doses. Students found to have a positive HBsAg, indicative of chronic HBV infection, were referred to a gastroenterologist for further evaluation.

We plotted frequencies of year of birth, year of hepatitis B vaccination, and year of postvaccination testing among students who matriculated during 2004–2009 to examine the relationship among these time points and the release of initial and updated hepatitis B vaccination guidelines.

Statistical Methods

The association of seroprotection (anti-HBs greater than 10 IU/L) and student characteristics was assessed by χ^2 test and the percentage of students with an anti-HBs concentration 10 IU/L or more according to age at vaccination and time

TABLE 1. Number and Percentage of Health Professional Students Who Matriculated during 2004–2009 with Postvaccination Anti-HBs ≥10 IU/L, by Demographic Characteristics

Characteristic	Total no. (%)	Anti-HBs ≥10 IU/L, no. (%)	Relative risk	95% CI
Total[a]	2,481	2,306 (92.9)		
Sex				
Female	1,603 (64.6)	1,492 (93.1)		
Male	878 (35.4)	814 (92.7)	1.05	(.78–1.42)
Country of birth				
United States	1,533 (85.6)	1,421 (92.7)		
Other	258 (14.4)	238 (92.3)	1.06	(.67–1.68)
Race/ethnicity				
White, non-Hispanic	1,569 (63.2)	1,462 (93.2)	Ref	...
Black, non-Hispanic	28 (1.1)	23 (82.1)	2.62	(1.16–5.92)
Asian/Pacific Islander	417 (16.8)	383 (91.9)	1.2	(.83–1.73)
Hispanic	44 (1.8)	40 (90.9)	1.33	(.51–3.45)
American Indian/Alaska Native	2 (0.08)	2 (100)	Und	...
Other/unknown	421 (17.0)	396 (94.1)	.87	(.57–1.32)

NOTE. Postvaccination testing performed anytime after the primary series was permissible by school policy. Anti-HBs, antibody to hepatitis B surface antigen; CI, confidence interval; Ref, reference; Und, undetermined.

[a] All 2,481 students had confirmed receipt of 3 primary hepatitis B vaccine doses.

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interval between vaccination and postvaccination testing was assessed by the Cochran-Armitage test for trend. The *Z*-test statistic was used to compare the median age at vaccination between students with and without an anti-HBs postvaccination concentration of 10 IU/L or more. *P* values less than .05 were considered significant. Analyses were conducted using SAS version 9.2.

RESULTS

During 2004–2009, 3,452 health science students matriculated and all had a student health clinic record. Of these, 802 student records were missing data of documented vaccination or serologic testing dates, 6 had a documented history of chronic HBV infection (2 were US-born and of Asian descent and 4 were foreign-born); 1 student reported an allergy to vaccine. Of the remaining 2,643 students (76.6% of all records) with available postvaccination testing results, 2,481 (93.9%) had received 3 primary doses and 162 (6.1%) had received only 1 or 2 primary doses. The demographic characteristics of excluded students were similar to those of study participants (data not shown).

Among the 2,643 students with complete hepatitis B vaccination data, 123 of 162 (75.9%) who received 1 or 2 primary doses and 2,306 of 2,481 (92.9%) who received 3 primary doses had an anti-HBs postvaccination concentration of 10 IU/L or more. Median age at receipt of the primary series was 14.5 years (interquartile range, 11.6–20.2 years) and at postvaccination testing was 23.2 years (interquartile range, 22.1–24.8 years). The characteristics of students who received 3 primary doses are shown in Table 1. Regardless of demographic characteristics, the majority of students had an anti-HBs concentration of 10 IU/L or more. Black students were less likely to have a concentration 10 IU/L or more, relative to white students (relative risk, 2.62; 95% confidence interval, 1.16–5.92); however, black students constituted a small portion of the total sample (approximately 2%).

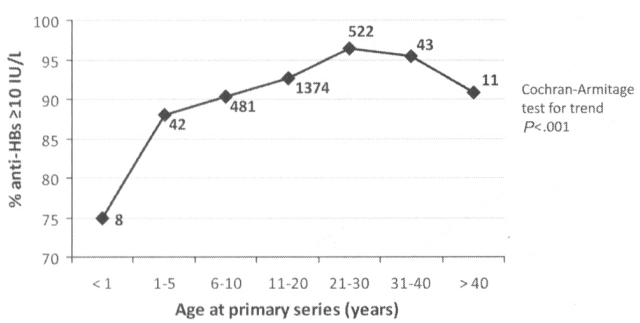

FIGURE 1. Percentage of 2,481 health professional students matriculating during 2004–2009 with postvaccination antibody to hepatitis B surface antigen (anti-HBs) ≥10 IU/L, by age at receipt of the primary hepatitis B vaccine series (no. of students in each age group is shown for each data point). Postvaccination testing performed anytime after the primary series was permissible by school policy.

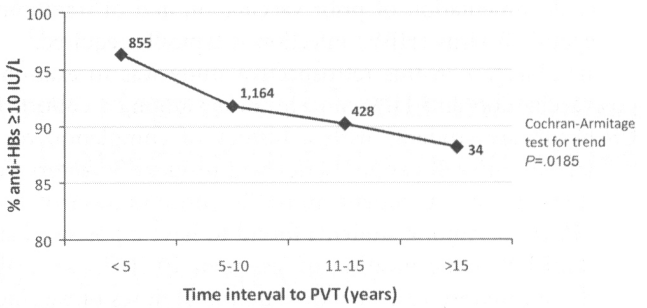

FIGURE 2. Percentage of 2,481 health professional students matriculating during 2004–2009 with postvaccination antibody to hepatitis B surface antigen (anti-HBs) ≥10 IU/L, by time interval from primary hepatitis B vaccine series to postvaccination testing (PVT; no. of students in each time interval category are shown for each data point). PVT performed anytime after the primary series was permissible by school policy.

Postvaccination anti-HBs concentrations are shown for the 2,481 students who received 3 primary doses by age at receipt of the primary series (Figure 1) and by the time interval in years between completion of the primary series and anti-HBs postvaccination testing (Figure 2). The older the age at vaccination, the more likely a matriculating student had an anti-HBs postvaccination concentration of 10 IU/L or more ($P < .001$, Cochran-Armitage test for trend). Of students vaccinated after the age of 5 years, 93.3% had an anti-HBs of 10 IU/L or more. The shorter the time interval from vaccination to postvaccination testing, the more likely a matriculating student had a postvaccination concentration of anti-HBs of 10 IU/L or more ($P = .0185$, Cochran-Armitage test for trend). Of those with a time interval of 15 years or less since completion of the primary series, 92.7% had a postvaccination anti-HBs of 10 IU/L or more.

As per school policy, students with a postvaccination anti-HBs concentration of less than 10 IU/L received 1–3 additional doses. Of 175 students with a postvaccination anti-HBs concentration less than 10 IU/L, 17 did not receive an additional dose, 31 received 1 dose, 46 received 2 doses, and 81 students received 3 doses. Almost all (98.2%) students who received at least 1 additional dose had a postbooster anti-HBs of 10 IU/L or more. Only 2 students failed to achieve a postbooster anti-HBs of 10 IU/L or more; both had received 3 booster doses (neither was positive for HBsAg).

Frequencies of year of birth, year of hepatitis B vaccination, and year of postvaccination testing among students who matriculated during 2004–2009 are shown in Figure 3. Most students in the cohort were born in the mid-1980s, before universal hepatitis B vaccination of infants was recommended in 1991, and were vaccinated in the late-1990s, when catch-up hepatitis B vaccination was recommended for children aged 11–12 years in 1995 and persons less than 19 years of

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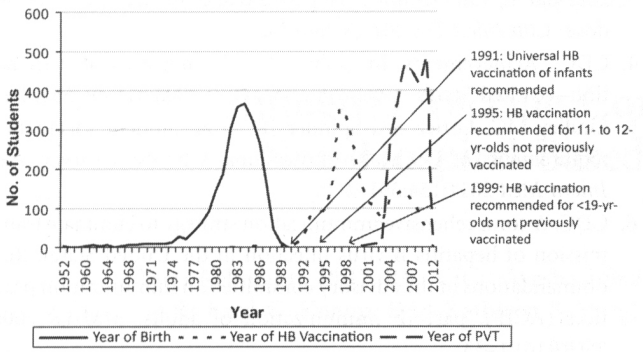

FIGURE 3. Frequency of year of birth, year of hepatitis B (HB) vaccination, and year of postvaccination testing (PVT) among students at a US health professional school who matriculated during 2004–2009.

age in 1999. Almost all students had postvaccination testing in the mid-2000s, corresponding to the time of entry into health professional school.

DISCUSSION

In this retrospective review of student health clinic vaccination records among students who matriculated during 2004–2009, we found that over 90% of students had a postvaccination concentration of anti-HBs of 10 IU/L or more, and all but 2 students with levels less than 10 IU/L adequately responded to at least 1 booster dose of vaccine. Younger age at vaccination and longer time interval from vaccination to anti-HBs testing were associated with a greater likelihood of a postvaccination anti-HBs concentration less than 10 IU/L.

According to 2011 CDC/ACIP guidelines, serologic testing for immunity is not necessary after routine vaccination of adults. Healthcare and public safety workers who "have written documentation of a complete vaccine series but who have never had postvaccination testing do not need serologic testing for anti-HBs unless they have a percutaneous or mucosal exposure to blood or body fluids."[6(p28)] However, "persons found to have anti-HBs concentrations of <10 mIU/mL after the primary vaccine series should be revaccinated."[6(p29)] A recent survey of more than 500 health professional schools found that more than one-half of MD-granting and DO-granting schools require anti-HBs titer measurement from all entering students. Nearly all schools that required anti-HBs titer measurement required at least 1 additional dose of hepatitis B vaccine for students lacking detectable anti-HBs titers.[5] Among students in our study population, most had been vaccinated for hepatitis B within 10 years of matriculation and still had anti-HBs concentrations of 10 IU/L or more. However, in the coming years, most students entering professional health schools will have been vaccinated for hepatitis B as newborns or infants. Therefore, a higher proportion will likely be found to have an anti-HBs concentration less than 10 IU/L when antibody testing is performed many years later.

There were limitations to this study. This study was retrospective and observational. Dates of vaccination and time points for postvaccination testing were highly variable, and there were no data available on primary vaccine formulation or dosage. We could not with certainty exclude the possibility of additional hepatitis B vaccine doses not listed in the student health clinic record. Such omissions could account for the overall high proportion of students with concentrations of anti-HBs of 10 IU/L or more and of students who reportedly were 10 IU/L or more after only 1 or 2 primary vaccine doses. The differences in postvaccination test results noted between black students and those of other races should be viewed with caution, as black students were underrepresented in our study sample. Postvaccination test results of anti-HBs provided by the students were obtained from various laboratories, and no information was available on the quantitative assays used. Therefore, these results may not be generalizable to other healthcare students, other settings, or nonstudents of similar age.

In summary, we found that almost all students in this professional school cohort who matriculated during 2004–2009 had serologic evidence of protection against HBV infection. Younger age at vaccination and longer time interval from vaccination to anti-HBs testing were associated with a greater likelihood of a postvaccination anti-HBs concentration less than 10 IU/L. In the coming years, a growing proportion of incoming professional health students and healthcare personnel will have been vaccinated in infancy or early childhood. Healthcare employers and training institutions have a duty to provide a safe environment, to educate all employees and students regarding the risk of infections, and to encourage reporting of all incidents including mucocutaneous exposure to body fluids. However, to avoid the unnecessary expenditure of healthcare resources, studies that continue to examine the duration of immunity from hepatitis B vaccine, surveillance systems that monitor for breakthrough infections among previously vaccinated persons, and studies examining the cost-effectiveness of current policies regarding serologic monitoring and additional doses are needed.

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