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Effect of Needle Length When Immunizing Obese Adolescents With Hepatitis B Vaccine

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WHAT'S KNOWN ON THIS SUBJECT: Obese youth achieve lower titers than average-weight peers in response to hepatitis B vaccine when a 1-inch needle is used.

WHAT THIS STUDY ADDS: Using a longer needle results in significantly higher titers in response to HBV vaccine among obese adolescents.

abstract

OBJECTIVE: Several studies have noted that obese adolescents and adults achieve lower titers of antibody in response to vaccines such as hepatitis B virus (HBV) vaccine. The objective of this study was to determine whether use of a longer (1.5-in) rather than a standard (1-in) needle to penetrate the thicker deltoid fat pad among obese youth would result in higher antibody titers after immunization against HBV.

METHODS: Obese adolescents from a large metropolitan area who had not previously received the HBV vaccine were randomly assigned to be immunized with HBV vaccine by using either a 1-inch or a 1.5-inch needle.

RESULTS: Those who were immunized with a 1.5-inch needle achieved significantly higher antibody titers to hepatitis B surface antigen (median titers: 1-inch = 189.8 mIU/mL, 1.5-inch = 345.4 mIU/mL; $P = .03$).

CONCLUSIONS: This finding supports the hypothesis that needle length accounts for a significant portion of the discrepancy in immune response to HBV vaccine that is seen among those with obesity. *Pediatrics* 2010;125:e508–e512

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KEY WORDS
adolescent immunization, obesity, needle length, hepatitis B vaccine, immunogenicity

ABBREVIATIONS
HBV— hepatitis B virus
anti-HBs— antibody to hepatitis B surface antigen

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Multiple studies have demonstrated that adolescents and adults with a high BMI experience lower antibody titers after receiving the hepatitis B virus (HBV) vaccination series.[1–4] This finding has gained import with the increasing number of vaccines that target an adolescent population experiencing rising rates of obesity. Data from 2003 to 2006 indicate that the BMI of 2- to 19-year-olds in the United States classify 31.9% of youth as overweight; 16.3% are further categorized as obese.[5]

Multiple hypotheses have been offered for disparity in vaccine immune response on the basis of BMI, including the possibility that standard needle length recommendations do not account for the increased length needed to penetrate the deltoid fat pad and into the muscle of obese adolescents and adults. The less abundant blood supply in adipose tissue results in a potential delay in vaccine antigen presentation to the B and T cells that are responsible for immune response; this delay may allow the protein antigens to be denatured by enzymes, resulting in a diminished immune response to vaccination.[6] Older studies among adult populations in which HBV vaccine was administered into the gluteal muscle versus the deltoid muscle support this hypothesis; data revealed inferior immunogenicity after injection into the gluteal site, likely as a result of the increased fat tissue and probable decreased muscle penetration in the area.[7–10] A more recent randomized, controlled trial noted that, although not statistically significant, longer needle length resulted in higher antibody titers among infants who were immunized in the thigh.[11] No data are available regarding adolescent immune response to vaccination with varying needle lengths.

Much has been written about the effect of needle length on vaccine reactogenicity, taking into account bunching/flattening techniques and angle of needle administration.[12–15] Less has been written about needle length and its specific association with immunogenicity. Imaging studies have been conducted to research the needle lengths that will ensure deposition of vaccine antigens into recipients' muscle versus fat pad among infants and toddlers[16–19] as well as adolescents and young adults.[19–21] By using ultrasonography, Poland et al[20] found that among adults aged ≥18 years, women who weighed >90 kg would require a 1.5-in needle to penetrate 5 mm of muscle when the needle was inserted over the deltoid muscle at a 90° angle with 2 to 3 mm of needle visible near the hub after insertion; a 1-in needle was sufficient for all men who were studied (all weighed ≤118 kg). The General Recommendations on Immunizations published by the Centers for Disease Control and Prevention have integrated these data into their recommendations on needle length.[22] To date, however, no data specifically address the hypothesis that immunizing obese adolescents and young adults with HBV vaccine, an intramuscular vaccine, by using a longer needle results in a more vigorous immune response. The hypothesis for this study was that overweight youth who receive HBV vaccine administered with longer (1.5 in) needles will achieve higher antibody titers than those who are immunized with shorter (1 in) needles.

METHODS

Study Population

Patients who were aged 14 to 24 years; weighed >90 and 120 kg for females and males, respectively; and had never received an HBV vaccination series were eligible for enrollment. Enrollment occurred between December 2001 and October 2004 at city clinics, a health fair, and a high school in Houston, Texas. Patients were not eligible to participate when they had an immune system illness, chronic disease, or long-term steroid use; were pregnant; or planned significant weight loss. Risk for pregnancy was determined by last menstrual period at enrollment; a urine pregnancy test was performed when indicated.

Methods

Informed consent (and assent from all minor participants) was obtained in either English or Spanish. Demographic data including race/ethnicity were collected; anthropometric measures, including height and weight, deltoid and triceps skinfold measures, and arm circumference, were obtained by using standard methods. By using a random-numbers table, those who were paired with an odd number received the HBV vaccination series (Engerix B [GlaxoSmithKline Biologicals, Rixensart, Belgium]) by using a 1-in needle and those with an even number with a 1.5-in needle. Because the outcome was biologically determined, there was no blinding associated with group assignment. Participants who were younger than 19 years received 0.5 mL and those who were aged ≥19 years received 1 mL. Injections were given at a 90° angle to the deltoid muscle, leaving 2 to 3 mm of needle visible between the arm and the hub. Patients were vaccinated on a 0-, 1-, 4-month schedule; investigators vaccinated patients either at the clinic site or, when patients indicated that they could not come to clinic, in their homes. Weight was measured again at the time of the third vaccination to assess any changes in weight from enrollment. Blood was obtained at baseline and 2 months after the third vaccination. Presence of antibody to hepatitis B surface antigen (anti-HBs) was determined qualitatively at baseline to rule out previous immunization and quantitatively after vaccination by using the AUSAB kit (ABBOTT Laboratories, North Chicago, IL); results for anti-HBs

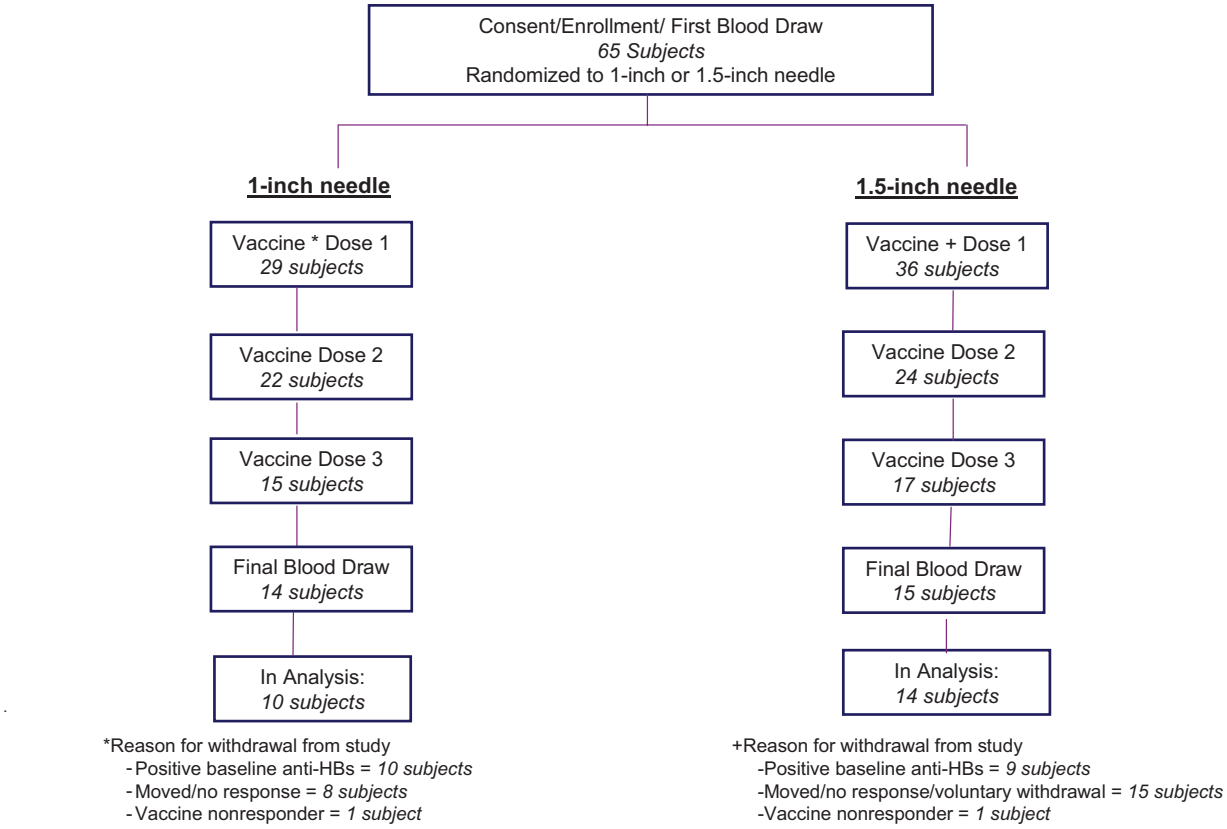

FIGURE 1
Participation of study subjects.

are expressed in milli-international units per milliliter, and levels <1.5 mIU/mL are considered negative. Antibody to core antigen was assessed by using ORTHO HBc ELISA (ABBOTT Laboratories, North Chicago, IL) before and after vaccination to assess for infection that was acquired before or during the study period.

Sample Size

On the basis of data from previous studies, assuming use of the Mann-Whitney test for nonparametrically distributed data, 40 patients per group were required to detect a 15% difference between groups in titer levels with 80% power. Assuming an attrition rate of 30%, 60 participants per group were targeted for enrollment.

Statistical Analysis

The primary outcome variable was anti-HBs titers achieved in each group. χ^2 and Mann-Whitney tests were used to analyze group characteristics for parity; Mann-Whitney test was used to compare titer data between groups.

RESULTS

Sixty-five individuals initially enrolled in the study. Despite specific verbal screening of patients and often their parents, 17 of the 65 participants had evidence of previous immunization with HBV vaccine (baseline serology was anti-HBs–positive and anti–hepatitis B core antigen–negative) and were ineligible to continue (Fig 1). Twenty-four (36.9%) participants moved, withdrew from the study, or did not respond to follow-up communication. Twenty-six participants completed the study; 2 of these (1 from each study group) did not respond to the 3-dose vaccination series and received fourth doses per the study protocol. The remaining 24 participants, 10 in the 1-in

TABLE 1 Description of Groups 1 (1-in Needle) and 2 (1.5-inch Needle)

Variable	1-in Needle (n = 10), Median (Minimum, Maximum)	1.5-inch Needle (n = 14), Median (Minimum, Maximum)
Age at enrollment, y	21.1 (14.1, 24.7)	20.8 (14.1, 23.6)
BMI, kg/m^2	42.1 (31.1, 49.5)	38.6 (33.1, 48.7)
Average deltoid skinfold, mm	40.8 (34.7, 49.3)	41.3 (32.7, 48.7)
Average triceps skinfold, mm	38.8 (33.7, 50.0)	41.0 (32.0, 42.7)
Time from vaccines 1 to 3, d	136 (119, 177)	130 (123, 156)
Time from vaccine 3 to titer assessment, d	64 (57, 72)	66 (59, 76)

No significant differences between groups.

TABLE 2 Quantitative Anti-HBs Titer Data

Group[a]	Participant Titers, mIU/mL													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1 (1-in needle)	51.6	87.4	143.6	144.6	189.7	189.8	208.9	324.7[b]	368.0	383.9				
2 (1.5-in needle)	28.0	181.6	203.9	243.0	249.6	274.3	341.2	349.6	393.0	429.2	464.2	473.1	492.9	6471.0[b]

[a] Difference in titers between groups using Mann-Whitney test: $P = .03$ all participants and $P = .035$ with female participants only.
[b] Male participant.

needle group and 14 in 1.5-in needle group, were included in the analyses.

No significant differences were found between groups 1 and 2 (Table 1) for age at enrollment, weight and BMI at enrollment (all participants with BMI >30 kg/m^2), arm circumference, deltoid or triceps skinfold measures, race/ethnicity (primarily Hispanic), gender (there was 1 male per group), time from vaccinations 1 to 3, and time from vaccination 3 to final blood draw. There were no significant weight fluctuations among participants during the course of the study. Two participants in group 1 received the series with a 0.5-mL dose; 5 participants in group 2 received the 0.5-mL dose.

The titer data for each group are provided in Table 2. There is 1 notable outlier in group 2: titer of 6471 (male participant).

Because only 1 male remained in the data set when the outlier was excluded, the analysis was performed by using 3 sample populations. The titer levels were statistically significantly different for each of the 3 analyses: when the study population included all study participants, $P = .03$ (median titers: 1-in needle = 189.8 mIU/mL, 1.5-in needle = 345.4 mIU/mL); when excluding the outlier from group 2, $P = .047$; and when excluding both male subjects, $P = .035$ (median titers: 1-in needle = 189.7 mIU/mL, 1.5-in needle = 341.2 mIU/mL). A scatter plot of the data depicting the titer levels of the 22 females in groups 1 and 2 is shown in Fig 2.

DISCUSSION

Despite the small sample size, obese adolescents and young adults achieved significantly higher titers of anti-HBs after HBV vaccine when a 1.5-in needle was used for administration rather than a 1-in needle. This supports the hypothesis that inadequate muscle penetration is responsible, at least in part, for lower immune response to HBV vaccine among obese adolescent and adult vaccine recipients. In 1 previous study,[3] the mean titer level achieved among those with BMIs between 17 and 21 kg/m^2 versus those with BMIs >26 kg/m^2 were $\sim$400 and 300 mIU/mL, respectively, after HBV vaccination with a 1-in needle (data not previously published in this format). Many of our participants had difficulty determining whether they had previously received the HBV vaccine (17 of 65 participants had evidence of previous vaccination). It is possible that the male subject whose titer served as an outlier had also received the vaccine in the past and his titer reflected an anamnestic response to the vaccination series. This indicates a need for careful validation of survey data that pertain to vaccination adherence among this age group.

There are some limitations to this study. Sample size was smaller than planned, and there were few male participants. Sample size affected the analysis; because the number of participants was lower than desired, geometric mean titer determinations were not appropriate and nonparametric tests were used. The ability to enroll patients who had not yet received vaccine was limited; in addition, our participants were from a lower socioeconomic stratum and were more transient and less invested in the project than anticipated. There was also little variability in race and ethnicity (most participants were Hispanic). Finally, because of small sample size, the different doses administered (0.5 mL for those who were younger than 19 years) may have introduced potential confounding; however, group 2 had

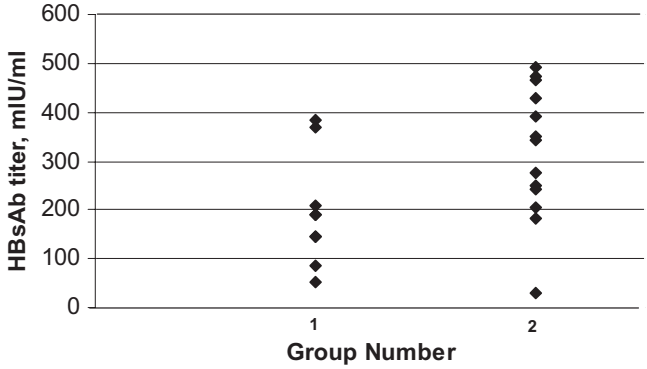

FIGURE 2
Scatter plot for titer data: females in groups 1 (1-in needle) and 2 (1.5-in needle).

a larger number of participants receiving the lower dose despite no significant difference in the average age of participants in each group, so any bias would have blunted the difference in titers between groups rather than increased the difference, further supporting the findings of this study.

As we continue to experience high rates of obesity in the United States and throughout the world, additional evidence-based research on optimizing the effective delivery of immunizations to adolescents and young adults will be critical. Following updated needle length recommendations will be a first step toward improving the health of our youth and young adults by preventing vaccine-preventable diseases.

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