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Randomized Trial to Determine Safety and Immunogenicity of Two Strategies for Hepatitis B Vaccination in Healthy Urban Adolescents in the United States

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Abstract

Background—Multiple studies have shown excellent response rates after hepatitis B immunization in youth; however, one previous study conducted in urban youth demonstrated poor responses.

Methods—Urban youth, ages 12–17 years, at participating Adolescent Medicine Trials Network for HIV/AIDS Interventions Clinical/Research (ATN) sites were randomized to receive either two doses of Recombivax HB (10mcg hepatitis B surface antigen) or Twinrix (20mcg hepatitis B surface antigen and 720 EL.U hepatitis A antigen) at 0 and 24 weeks. Safety data were collected and antibody measures performed at 0, 28 and 76 weeks.

Results—123 subjects were enrolled and 102 had week 28 serum samples available for antibody measure. A positive response (serum antibody $\geq 10\text{mIU/mL}$) to hepatitis B antigen was documented in 41/47 (87.2%; 95% confidence interval (CI) 74.3%–95.2%) Recombivax HB recipients and in 52/55 (94.6%; 95% CI 84.9%–98.9%) Twinrix recipients ($p=.295$). In an adjusted analysis, those identified as Hispanic ethnicity ($N=86$) were more likely to have a positive response (odds ratio 7.38, 95% confidence interval 1.56–34.95; $p=0.0018$); whereas those who identified as not heterosexual ($N=9$) were less likely to respond (odds ratio=0.12, 95% CI, 0.02–0.74). The majority of youth in the Twinrix arm were hepatitis A antibody positive at baseline (26/51; 51%); however, 24/25 hepatitis A antibody negative youth responded to the hepatitis A component. Both vaccines were safe.

Conclusions—Response rate to two doses of Recombivax HB in urban youth is lower than previous studies suggest. The factors associated with diminished response are not known.

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Keywords

Adolescents; hepatitis B; Vaccination; Immunogenicity

Introduction

Hepatitis B prophylactic immunization is recommended for infants, children ages 11-12 years, and at-risk adolescents for more than 10 years,^{1,2} but universal coverage has been slow and in some places remains incomplete.^{3,4,5} Antibody response to vaccination in healthy adolescents has generally been reported to be excellent,^{6,7,8} but observational data from the “Reaching for Excellence in Adolescent Care and Health” (REACH) longitudinal cohort of HIV-infected and HIV-uninfected at-risk youth demonstrated only a 70% vaccine response rate in an HIV-uninfected older adolescent population.⁹ There were several limitations to the REACH hepatitis B study design including small sample size, retrospective reporting of immunization status, and site-to-site variability in vaccine product used. However, the low response rate observed in the REACH cohort suggested that the response to hepatitis B immunization among HIV-negative urban youth at Adolescent Medicine Trials Network for HIV/AIDS Interventions Clinical/Research (ATN) sites; an extension of the original REACH trial sites, would be significantly lower than prior published reports in this age group. The present study was designed to determine the response to hepatitis B vaccine in this population and to allow exploratory, secondary analysis to evaluate factors that contribute to vaccine response in this group.

Methods

This study was a Phase II, randomized, single-blinded trial of two hepatitis B immunization regimens planned in 150 healthy youth of both sexes, 12 through 17 years of age. Youth were randomized 1:1 to receive either Recombivax HB (10mcg hepatitis B surface antigen (HbsAg); Merck Vaccine Division, West Point, PA) or Twinrix (20mcg HbsAg and 720 EL.U hepatitis A antigen; GlaxoSmithKline Pharmaceuticals) on a two-dose schedule; 0 and 24 weeks. Subjects were recruited from nine ATN sites. Each site developed its own recruitment program that varied from large scale media efforts to recruitment in youth health clinics. Inclusion criteria were as follows: receipt of no more than one prior hepatitis B immunization, and negative HBV and HIV serology. Participants were excluded if they had a serious underlying illness, immunosuppressive therapy, or pregnancy. The protocol was approved by each unit's Institutional Review Board for Protection of Human Subjects and each participant provided a written, informed assent. In addition, a parent or guardian provided written informed consent.

The primary study endpoint was the post-second dose antibody response at week 28; a positive response was defined as a titer of ≥ 10 mIU/mL. Titers were measured in serum collected pre-immunization, week 28, and week 76 in one central testing laboratory (Abbot EIA or Ortho Vitros ECI performed by Quest Diagnostics, Baltimore, MD). The serologic test method changed during the study; however, sufficient samples were available to provide pre and post immunization test results with the Ortho Vitros ECI test for 198/204 (97%) samples. Six samples had testing only with the Abbot EIA; in these cases, the Abbot EIA results were used in the analysis as the overall agreement between the two tests was 98.2% (Kappa = 97.9%). Youth with a negative response to hepatitis B immunization after two doses received a third immunization of Recombivax HB (10mcg HbsAg).

Vaccine safety was monitored using standardized assessments after each immunization and by collecting specific signs and symptoms during telephone interviews performed 48 hours

and seven days after the immunization. Clinical and laboratory toxicities were graded using the National Institute of Allergy and Infectious Diseases, Division of AIDS standard grading table with events ranging from Grade 1 (mild) to Grade 4 (severe or life-threatening). The protocol was reviewed and monitored by an Independent Data and Safety Monitoring Board.

The study was designed as a Phase II, single blinded (patients), randomized, two-arm trial. Endpoint specimens collected for laboratory measures were masked to the individuals performing assays. The study was designed to provide a reasonable precision for estimating the antibody response rates to the two study vaccines and was not designed to compare the response rates between study arms. The intended sample size of $n=75$ subjects per arm was determined to provide a 95% confidence interval of 0.90 ± 0.070 (i.e., 0.83 to 0.97) for an observed proportion of 90% positive responses assuming a dropout rate of 5% and a sample size inflation factor of 10.8%. Data analysis included chi-square tests and logistic regression. Exact tests were used for small sample sizes. Multivariate models were developed using stepwise methods. Data analysis was performed in SAS and LogXact.

Results

Participants

The study began enrollment in November 2004 and closed to accrual in January 2007 after 123 of the planned 150 subjects were enrolled. The study closed before meeting the planned enrollment of 150 subjects because increasing hepatitis B immunization coverage made identification of eligible, non-vaccinated subjects difficult. In addition, one site with expected high accrual (New Orleans, LA) was closed due to Hurricane Katrina. The 123 youth were enrolled from nine sites with a range of 4-67 subjects enrolled per site; one site where a media and outreach campaign was implemented in the community (Baltimore, MD) accounted for more than half the enrolled subjects. Figure 1 summarizes the final status of all 123 enrolled subjects. All subjects were included in the safety analysis. Baseline characteristics of youth do not differ significantly between the study arms (Table 1; supplemental digital content). Ten of the 21 subjects lost to follow-up prior to the week 28 samples collection were enrolled in New Orleans and were taken off study immediately after Hurricane Katrina. The subjects lost to follow-up did not differ from those who remained on study through week 28 in any of the baseline factors assessed (data not shown).

One hundred six subjects received both scheduled immunizations and 17 subjects discontinued prematurely and did not receive the second immunization. Eight subjects received a third dose due to inadequate response to the initial vaccine series.

Antibody response

The qualitative antibody analysis included all 102 subjects with follow-up serum samples available. In the intent to treat analysis of HBsAb response one month after the second immunization, 41/47 (87.2%; 95% confidence interval (CI) 74.3%-95.2%) had a positive response in the Recombivax HB arm and 52/55 (94.6%; 95% CI 84.9%-98.9%) Twinrix recipients ($p=0.30$) had positive responses. Sensitivity analysis where missing values were assumed to be positive raised the response rate to 90.0% (95% CI 79.5-96.2) and 95.3% (95% CI 86.7-99.0) in the Recombivax HB and Twinrix arms, respectively. The quantitative antibody analysis was limited to the 75 individuals who had the week 28 serum collected within eight weeks of the second immunization. Quantitative titers showed a trend towards lower titers in the Recombivax HB arm with a mean $\log_{10}$ titer of 2.36 (SD ± 0.85) compared to a mean $\log_{10}$ titer of 2.60 (SD ± 0.68) in the Twinrix arm; $p=0.17$; however the difference was not statistically significant.

Serum antibody titers to HBsAg declined during the 12 months of follow-up (Figure 2; supplemental digital content) with 30/37 (81.1%; 95% CI 64.8-92.0%) and 44/50 (88.0%; 95% CI 75.7-95.5%) subjects with titers ≥ 10 mIU/mL at week 76 in the Recombivax and Twinrix arms, respectively ($p=0.38$).

Unadjusted and adjusted analyses were performed to determine predictors for response to immunization. Study arm (Recombivax vs Twinrix) was not significantly correlated with response; therefore, all subjects with follow-up serology were combined for the subsequent analysis. In the unadjusted qualitative response analysis, Hispanic ethnicity was associated with an increase response rate. However, higher baseline body mass index (BMI), sexual identity as gay, bisexual or not sure, or having ≥ 6 lifetime male sexual partners were each associated with inadequate vaccine response (Table 2). In the adjusted analysis the factors which remained significant were Hispanic ethnicity and sexual identity (Table 2).

The relationship between potential impact factors and antibody response was further explored using the quantitative antibody results with the analysis limited to the 75 subjects who had the post immunization serology within the specified study window. In the univariate analysis, significantly lower antibody titers were noted in males ($p=0.01$), those with higher BMI ($p=0.01$), and those with ≥ 6 lifetime male sex partners ($p<0.001$). A trend for lower titers was seen in those not heterosexual ($p=0.06$). When the quantitative analysis was adjusted for all potential factors, the factors that remained significant were male gender ($p<0.005$) and more than 6 lifetime male partners ($p<0.0001$). Of the 63 subjects enrolled in the Twinrix arm, 51 had baseline and at least one post-immunization hepatitis A serology result; 26 were negative at baseline and all but one of these subjects seroconverted.

Safety

Both vaccines were safe and well tolerated. Adverse events were infrequent and generally mild, not associated with immunization, and evenly distributed across both arms of the study (data not shown).

Discussion

The main purpose of this study was to estimate response rates to two vaccines, Twinrix and Recombivax HB, with sufficient precision to determine if they were markedly lower than those seen in the general literature^{6,7,8,10,11,12,13} and in the range that was previously seen in the REACH study.⁹ We found the response rate to Twinrix to be 94.6% (95% CI 84.9%-98.9%), which is quite similar to that reported in the literature. The response rate to a two-dose Recombivax schedule is lower than that reported in most prior studies, including those trials that supported licensure of the 2-dose schedule,^{6,7,8,10,11} but is clearly higher than the extremely low response rates previously demonstrated in the REACH study.⁹ The lower than expected response rate for Recombivax support the need for testing vaccines in all populations where they will be administered.

The response rates in the Recombivax and Twinrix arms were not significantly different, but the study was not designed to detect a difference between arms. The present study explored some of the factors that might account for reduced responses. In much of the literature, favorable response to hepatitis B vaccine is reported to be almost universal among immunized youth;^{6,7,8,10,12,13} hence, analysis of risk factors for reduced response is difficult but obesity has been identified as a risk factor for reduced response.^{14,15} In adults beyond adolescence, favorable immune response is not nearly as frequent and numerous factors are reported to correlate with poor response including female gender, increased BMI, older age, cigarette smoking and chronic disease.^{16,17,18,19} Among earlier adolescent studies, detailed demographic information and BMI for the populations studied has

generally not been reported; however, several of the studies enrolled predominantly white youth.^{8, 15} The youth in the REACH study are well described: 40% had a BMI greater than the 75th percentile and 85% were black or Hispanic and included a relatively high proportion of youth who smoked cigarettes and used alcohol and/or other drugs.⁹ The population for the present study, while not identical to those enrolled in REACH, included 20% with BMI greater than 30 and an additional 24% with a BMI greater than 25 and included primarily subjects who self-identified as Hispanic and/or Black. A trend for diminished immune response was seen in those who were overweight or obese but this difference did not remain after adjusting for other factors. The factors that remained significant in the multivariable analysis were Hispanic ethnicity (improved response compared with those not Hispanic) and sexual identity; youth who identified as heterosexual were more likely to respond with a protective antibody response. Future studies should evaluate which genetic and environmental factors impact on vaccine responsiveness. The number of youth identifying as “not heterosexual” was small and included “gay”, “bi-sexual”, and “questioning” youth; therefore, these findings must be interpreted with caution. Nevertheless, two early studies of hepatitis B immunization using a serum-derived hepatitis B product described reduced response rates in men having sex with men (MSM) compared with a similar population where sexual orientation was not specified.^{20,21} Further study is necessary to determine if MSM or increased number of male sex partners are truly risk factors for reduced response to immunization.

A titer of ≥ 10 mIU/mL is considered an indication of a “response”. Previous studies have shown decline over time^{14,16,21} and suggest that if titers drop below 10 mIU/mL, the individual is at risk of acquiring hepatitis B infection.²⁰ These data suggest that titer is important for durability of protection.

The frequency and durability of the antibody response to the hepatitis A component in those randomized to Twinrix are excellent and similar to previous studies of Twinrix vaccine.¹³

The limitations of the study include a relatively small sample size, a disproportionate number enrolled at one site, and a significant rate of loss to follow-up. The single site with very high accrual was in a state that did not require hepatitis B vaccine for high school entry, hence the availability of more eligible subjects. Analysis showed that study site did not correlate with vaccine response. The significant rate of loss to follow-up is likely due to two factors. Hurricane Katrina hit New Orleans after 10 subjects were enrolled at that site but before any completed a 28 week visit, resulting in those 10 subjects being lost to follow-up. In addition, urban youth enrolled in the study proved to be very challenging to follow as there was a high rate of relocation and disappearance from medical contact. Study of such youth populations require extensive resources for education of the youth and their families and to support staff to find and keep subjects on study once enrolled.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow of participants through each stage of the study.

Table 1

Demographic characteristics by study arm for all subjects enrolled.

	Total (N=123)	Recombivax HB (N=60)	Twinrix (N=63)	p-value ¹
Age years (±SD)				0.3444
Mean	15.12 (±1.58)	15.02 (±1.43)	15.22 (±1.71)	
Age # (%)				0.4441
12-14	41 (33.3)	18 (30.0)	23 (36.5)	
15-17	82 (66.7)	42 (70.0)	40 (63.5)	
Gender # (%)				0.1998
Male	77 (62.6)	41 (68.3)	36 (57.1)	
Female	46 (37.4)	19 (31.7)	27 (42.9)	
Race/Ethnicity				
Non-Hispanic white	2 (1.6)	1 (1.7)	1 (1.6)	0.1815
Non-Hispanic black	33 (26.8)	20 (33.3)	13 (20.6)	
Hispanic	86 (69.9)	39 (65.0)	47 (74.6)	
Other	2 (1.6)	0 (0.0)	2 (3.2)	
Tanner stage for males				0.7569
Stage 1-3	13 (0)	7 (0)	6(0)	
Stage 4	37 (48.1)	21 (51.2)	16 (44.4)	
Stage 5	27 (35.1)	13 (31.7)	14 (38.9)	
Tanner stage for females ²				0.2862
Stage 1-3	1 (0)	1 (0)	0 (0.0)	
Stage 4	23 (50.0)	11 (57.9)	12 (44.4)	
Stage 5	22 (47.8)	7 (36.8)	15 (55.6)	
Smoking History				1.0000
Yes	13 (68.4)	6 (75.0)	7 (63.6)	
In past 3 months, smoked every day	5 (38.5)	1 (16.7)	4 (57.1)	
Height (cm; mean (±SD))	164.2 (±10.0)	165.8 (±8.8)	162.6 (±10.9)	
Weight (kg; mean (±SD))	67.2 (±21.5)	67.7 (21.6)	66.7 (21.7)	0.9839
BMI (kg/m ² mean (±SD))	24.7 (6.9)	24.4 (6.5)	25.1 (7.38)	0.3629
BMI Classification # (%)				0.2658
Underweight (BMI<18.5)	6 (4.9)	2 (3.3)	4 (6.3)	
Normal (BMI: 18.5-24.9)	73 (59.3)	40 (66.7)	33 (52.4)	
Overweight (BMI: 25.0-29.9)	24 (19.5)	8 (13.3)	16 (25.4)	
Obese (BMI: ≥30.0)	20 (16.3)	10 (16.7)	10 (15.9)	
Sexual identity				1.0000
Straight (heterosexual)	113 (91.9)	55 (91.7)	58 (92.1)	
Gay (homosexual), Bi (bisexual) and not sure or undecided	10 (8.1)	5 (8.3)	5 (7.9)	
Total lifetime male sex partners				
0 partner (include never had sex)	101 (83.5)	49 (84.5)	52 (82.5)	0.6811
1-5 partners	15 (12.4)	6 (10.3)	9 (14.3)	
≥ 6 partners	5 (4.1)	3 (5.2)	2 (3.2)	

	Total (N=123)	Recombivax HB (N=60)	Twinrix (N=63)	p-value ¹
Ever drank alcohol				0.4519
Yes # (%)	44 (35.8)	19 (31.7)	25 (39.7)	
Ever smoked marijuana				1.0000
Yes # (%)	22 (17.9)	11 (18.3)	11 (17.5)	
Ever used drug not prescribed				0.4321
Yes # (%)	6 (4.9)	4 (6.7)	2 (3.2)	

¹ p-value is from t-test (or Wilcoxon's two-sample test if normality assumption doesn't hold) for continuous variable, Chi-square (or Fisher's exact) test for categorical variables to compare the differences between two study arms.

² The value shown for female Tanner stage is a composite stage calculated as the higher value between breast and hair Tanner stage. For example, if a subject has a breast Tanner stage of 4 and a hair Tanner stage of 3, then her Tanner stage of 4 will be used.

Table 2
Relationship between vaccine response (responder/non-responder) and potential impact factors

Impact factors	Responder (N=93) n (%)	Non-Responder (N=9) n (%)	Total (N=102) n	Unadjusted ¹		Adjusted ^{1,2}	
				OR (95% CI)	p-value	OR (95% CI)	p-value
Study Arm						--	
Recombivax	41 (87.23)	6 (12.77)	47	1.00			
Twinrix	52 (94.55)	3 (5.45)	55	2.54 (0.60-10.76)	0.2068		
Hispanic							
No	21 (77.78)	6 (22.22)	27	1.00		1.00	
Yes	72 (96.00)	3 (4.00)	75	6.86 (1.58-29.78)	0.0102	7.38 (1.56-34.95)	0.0118
BMI at baseline (Continuous)						--	
BMI				0.91 (0.84- 0.99)	0.0225		
Sexual identity							
Straight (heterosexual)	87 (93.55)	6 (6.45)	93	1.00		1.00	
Gay (homosexual), bi(bisexual) and not sure or undecided	6 (66.67)	3 (33.33)	9	0.14 (0.03- 0.69)	0.0161	0.12 (0.02- 0.74)	0.0222
Total Lifetime Sex Partners ³						--	
0 partners	59 (95.16)	3 (4.84)	62	1.00			
1-5 partners	26 (100.0)	0 (0.00)	26	1.65 (0.17 -∞)	0.6893		
≥6 partners	7 (58.33)	5 (41.67)	12	0.08 (0.01 - 0.48)	0.0042		
Total Lifetime Male Sex Partners (includes never had sex) ³						--	
0 partners	78 (95.12)	4 (4.88)	82	1.00			
1-5 partners	13 (100.0)	0 (0.00)	13	0.85 (0.10 -∞)	1.0000		
≥6 partners	1 (20.00)	4 (80.00)	5	0.02 (0.0003 - 0.19)	0.0003		
Ever Smoked Marijuana						--	
No	78 (93.98)	5 (6.02)	83	1.00			
Yes	15 (78.95)	4 (21.05)	19	0.24 (0.06- 1.00)	0.0501		

¹ The probability modeled is 'Responder' for Hepatitis B antibody results. The OR, 95% CI, and p-value are from PROC LOGISTIC. A normal or lower risk group is used as the reference group with a value of 1.00. The OR is the odds of responding to Hepatitis B vaccine for subjects in a specific group compared to the reference group. For example, an OR of 6.86 for Hispanic subjects indicates that the odds of responding to vaccine are 6.86 times greater than non-Hispanic subjects (p=0.0102).

² Indicates the variable is not statistically significant at alpha 0.05 and excluded from the final multivariate model.

³ Due to the zero cell frequency for 1-5 sex partners, the estimates for these models were generated using exact logistic regression (Log-act). The upper confidence bounds for the 1-5 sex partners groups are infinite.