

Randomized, Double-Blind Study in Healthy Adults to Assess the Boosting Effect of Vaqta or Havrix after a Single Dose of Havrix

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A randomized, double-blind, multicenter study was conducted to investigate the boosting effect of Vaqta or Havrix in 537 healthy adults 18–53 years of age who had received a single dose of Havrix either 24 or 52 weeks earlier. Subjects were randomized in a 2 : 1 ratio to receive either Vaqta or Havrix for their second dose of vaccine and followed for clinical reactions for 14 days after dose 2 was administered. Serum samples were collected immediately before dose 2 was administered and again 4 weeks later and evaluated for hepatitis A antibody (modified hepatitis A virus antibody assay). The booster response rate after administration of the second dose of either vaccine was similar (86.1% for Vaqta vs. 80.1% for Havrix). The geometric mean titers were also similar: 3274 mIU/mL (95% confidence interval [CI], 2776–3858) for Vaqta versus 2423 mIU/mL (95% CI, 1911–3074) for Havrix. The proportion of subjects who reported ≥ 1 injection-site adverse experiences was lower in the patients receiving Vaqta than in those receiving Havrix (36.6% vs. 59.7%; $P < .001$). The results of this study indicate that a regimen of Havrix followed by Vaqta is generally well tolerated and highly immunogenic.

Hepatitis A disease may now be prevented by vaccination. Two inactivated hepatitis A vaccines, Vaqta (Merck) and Havrix (SmithKline Beecham), are currently licensed in the United States [1, 2]. Both vaccines are formaldehyde-inactivated preparations of hepatitis A virus grown on MRC-5 human diploid cell lines. Inactivated virus strain HM175 is used for production of Havrix and inactivated strain CR326F strain is used for production of Vaqta [3–5]. Both vaccines have been

shown to be well tolerated, immunogenic, and efficacious [6–9]. Each vaccine is administered as a 2-dose series with a primary dose at time 0 and a booster dose 6–12 months later. The standard adult dose for Havrix is 1440 ELISA units; the standard adult dose for Vaqta is 50 U [1–2].

The ability to interchange the 2 vaccines is a practical concern for health care personnel, the military, and vaccine recipients. Health care personnel may have access to >1 brand of hepatitis A vaccine or switch brands because of supply or price. Because of travel, patients may need to begin the vaccine series in one locale and receive the booster dose in another. Because Havrix was licensed ~ 1 year before Vaqta, the goal of this study was to compare the immunogenicity and safety of a mixed regimen of Havrix followed by Vaqta to a standard regimen of 2 doses of Havrix.

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Informed consent was obtained from the patients. Guidelines for human experimentation of the US Department of Health and Human Services and those of the authors' institutions were followed in the conduct of the clinical research.

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Table 1. Immunogenicity summary of seropositivity rates (SPR), booster response rates (BRR), and geometric mean titers (GMT) before booster and 4 weeks after booster, by treatment group.

Time	50 U booster of Vacta (n = 356)			1440 ELISA units booster of Havrix (n = 181)						
	SPR	BRR		SPR	BRR					
	n ^a	% (95% CI)	n ^a	% (95% CI)	n ^a	% (95% CI)				
Before booster	277/310	89.4 (85.4–92.6)	---	71.0 (56.4–89.4)	136/151	90.1 (84.1–94.3)	---			
After booster	312/313	99.7 (98.2–100)	267/310	86.1 (81.3–89.8)	3274 (2775.5–3858.4)	150/151	99.3 (96.4–100)	121/151	80.1 (72.9–86.2)	2422.8 (1911.3–3071.1)

NOTE. Booster response was defined as ≥ 10 -fold increase from prebooster to postbooster titer and postbooster titer ≥ 100 mIU/mL. Seropositivity for hepatitis A vaccine was defined as a positive result from the modified hepatitis A virus antibody assay (titer ≥ 10 mIU/mL). GMTs and their 95% CIs were computed from the analysis of variance model without adjustment.

^a No. of subjects positive for hepatitis A antibody/no. tested.

Table 2. Results of the statistical analyses of similarity (noninferiority) of booster response rates (BRR) and geometric mean titers (GMT) at 4 weeks after booster.

Parameter	Treatment group		Comparison	Estimated difference/fold difference (95% CI)	Individual P^a	Conclusion
	50 U booster of Vaqta (no. of patients tested)	1440 ELISA unit booster of Havrix (no. of patients tested)				
BRR ^b	86.2% (310)	80.2% (151)	$P_{\text{Vaqta}} - P_{\text{Havrix}}$	6.0% (-1.0 to 13.9)	<.001	Similar
GMT ^c	4228.7 (313)	3052.6 (151)	$\text{GMT}_{\text{Vaqta}} / \text{GMT}_{\text{Havrix}}$	1.4 (1.0 to 1.8)	<.001	Similar

^a An individual 1-sided P value of $\leq .025$ implies that the difference of the proportions or the ratio of the GMTs is statistically significantly higher than the prescribed difference (-0.10) or ratio (1/4) of interest and allows for a conclusion of similarity.

^b The measures presented in this table, including BRR, difference in BRRs, and 95% CI, and the associated 1-sided P value were computed from a statistical model that adjusts for time of booster and age category.

^c GMT, fold difference in GMTs, 95% CI, and the associated 1-sided P values were computed from an analysis of variance model that adjusted for study center, time of booster, age category, and weight category; all interaction effects were excluded from the model.

PATIENTS AND METHODS

Vaccines. In this study, all participants had received an initial dose of Havrix before enrollment and were randomized to receive either Vaqta or Havrix as the booster dose. The standard dose and volume for healthy adults was used (1440 ELISA units per 1.0 mL dose for Havrix and 50 U per 1.0 mL dose for Vaqta). The composition of each vaccine has been previously published [10]. Each vaccine was shipped and stored at 2°C–8°C. All vaccines were administered in a blinded fashion.

Study design. The study was double-blind, multicenter, and randomized. Healthy adults were eligible to receive a booster of either Havrix or Vaqta in this study if they met all of the following criteria: they had written confirmation that they had received only the primary dose of Havrix ~24 weeks (range, 22–30 weeks) or ~52 weeks (range, 46–54 weeks) before enrollment; they were ≥ 18 years of age; they signed an informed consent form before receipt of the booster dose; they had no active liver disease, systemic illness, or active infection; they were not pregnant, expecting to conceive, or nursing; they were not allergic to any vaccine component; they had a temperature $< 37.8^\circ\text{C}$ oral equivalent; they had received no immunoglobulin or blood-derived product within the 12 months before the booster injection; they were not receiving any immunosuppressive therapy; they had no history of severe thrombocytopenia or any coagulation disorder; they had no other vaccinations planned during the study period; and they had no other condition that might interfere with the evaluation of the study objectives.

Subjects were stratified by age (18–29 years and ≥ 30 years), weight (< 77.3 kg and ≥ 77.3 kg), and time of booster (22–30 weeks or 46–54 weeks), and then randomized in a 2 : 1 ratio to receive either Vaqta or Havrix. All vaccines were administered in the deltoid of the right arm.

All subjects received a vaccination report card at the time of the booster dose and were instructed to record on the card their daily temperature and any injection-site complaints for the first 5 days after vaccination and any systemic reactions for

14 days after vaccination. The report card only requested temperature data and injection-site complaints. Participants were instructed to immediately report any serious or unusual reactions to study personnel.

A blood specimen was collected from each subject immediately before the booster dose and 4 weeks after the booster dose. All serum samples were tested in a blinded fashion at Merck Research Laboratories, West Point, Pennsylvania, for hepatitis A antibody by use of the modified hepatitis A virus antibody assay [11]. The testing laboratory was blinded as to which of the 2 vaccines each subject received. A titer of ≥ 10 mIU/mL was considered positive in this assay.

Statistical methods. Primary immunogenicity analyses were performed with a per-protocol method. The 2 primary immunogenicity hypotheses tested in this study were that the booster response rates (BRRs) and geometric mean titers (GMTs) of subjects who received a booster dose of Vaqta or Havrix, after an initial dose of Havrix, would be similar (noninferior). The BRR was defined as ≥ 10 -fold rise from pre-booster to postbooster titer ≥ 100 mIU/mL. The statistical criteria for similarity (noninferiority) was based on ruling out a difference in BRRs of 10 percentage points (using a 95% CI) and ruling out a 4-fold difference in GMTs (with 95% CI) between the treatment groups comprising patients receiving Vaqta or Havrix.

Essentially, this approach compares the BRRs by a statistical test to reject a nonzero difference in proportions at the $\alpha = 0.025$, 1-sided level, adjusting for time of booster and age category. The test statistic used was based on an expansion of the equivalence testing methodology proposed by Farrington and Manning [12] to a stratified design. For the GMT comparisons, an analysis of variance test (1-sided with $\alpha = 0.025$), including the effects of study center, time of booster, age category, and weight category, was used to confirm a < 4 -fold difference in GMTs. A significant 1-sided P value ($P \leq .025$) for both comparisons supported a conclusion that the immune responses between the 2 treatment groups were similar (noninferior).

Table 3. Summary of clinical safety data after a booster dose of Vqta or Havrix.

Event	Treatment group				P ^c
	50 U Booster of Vqta (n = 356) ^a		1440 ELISA units booster of Havrix (n = 181) ^b		
	n	%	n	%	
Days 0–14 after visit 1					
≥1 clinical adverse experience	212	60.2 ^d	124	70.5	.022
Vaccine-related systemic adverse experience ^e	63	17.9	34	19.3	.721
Serious vaccine related adverse experience	0	0.0	0	0.0	1.000
Days 0–4 after visit 1					
≥1 injection-site adverse experiences ^f	129	36.6	105	59.7	<.001
Ecchymosis	4	1.1	2	1.1	1.000
Erythema	13	3.7	15	8.5	.024
Pain	69	19.6	59	33.5	<.001
Pruritus	2	0.6	2	1.1	.604
Swelling	11	3.1	15	8.5	.010
Tenderness	79	22.4	80	45.5	<.001
Warmth	24	6.8	12	6.8	1.000
Maximum temperature ≥38.3°C (oral equivalent) or abnormal	0	0.0	0	0.0	1.000

^a Groups 2a and 2b.^b Groups 1a and 1b.^c Two-sided P values were computed using Fisher's exact test.^d Percentages are calculated on the basis of the number of subjects with follow-up after each visit.^e A vaccine-related adverse experience is one that was determined by the investigator to be possibly, probably, or definitely related to the vaccine.^f Although a subject may have had ≥2 injection-site adverse experiences, the subject is counted only once.

Success was required for both end points; therefore, no multiplicity adjustment was made to the overall error rate of $\alpha = 0.025$. This study had 96% power to rule out a BRR lower by 10 percentage points and had >99% power to rule out GMT 4-fold lower in the treatment group that received a booster dose of Vqta compared with the treatment group that received the booster dose of Havrix. Assuming independence of the 2 comparisons, the primary analysis had a 96% overall power. All subjects who were vaccinated and who had safety follow-up contributed to the safety analysis. Two safety parameters were compared between the treatment groups: the incidence of injection-site adverse experiences and elevated temperatures on days 0–4 after injection, and the incidence of specific systemic clinical adverse experiences that were reported from days 0–14 by at least 1% of subjects in either treatment group. These safety parameters were compared by means of Fisher's exact test [13].

RESULTS

The study was initiated on 15 December 1996. A total of 536 adults who had previously received only a single dose of Havrix ~24 or 52 weeks earlier were enrolled at 1 of 5 study sites. Three hundred fifty-six subjects received Vqta for the

booster dose. Fifty-five percent (296 of 537) of the subjects were women, the median age was 44 years (range, 18–83 years), the median weight was 72.7 kg (range, 45.4–136.4 kg), and >85% of participants were white. There were no apparent differences among the 4 treatment groups with respect to sex, age, weight, or race/ethnicity.

A summary of the immune responses in each group, including the BRRs and GMTs and seropositivity rates along with 95% CIs, is shown by treatment group in table 1. The ability of each vaccine to boost the immune response 4 weeks after a booster dose was similar.

The results of the statistical analysis of the comparison of BRRs and GMTs at 4 weeks after the booster are shown in table 2. On the basis of the statistical model, the 4-week postvaccination BRRs were similar (noninferior within 10 percentage points) between the recipients of Vqta and the recipients of Havrix (86.2% and 80.2%, respectively). The 4-week postvaccination GMTs calculated from the statistical model also were similar (noninferior within a 4-fold difference) between the recipients of Vqta (4228.7 mIU/mL) and the recipients of Havrix (3052.6 mIU/mL). The 95% CIs on the difference in the immune response rates (BRR and GMT) support the conclusion of similarity.

Ninety-eight percent (528 of 537) of the subjects completed

all safety follow-up after receiving the booster dose. In general, both vaccines were well tolerated; no serious vaccine-related adverse experiences were reported. A summary of the clinical data after the booster dose is shown in table 3. No subjects in either group experienced fever or any unusual reactions after vaccination. The percentage of subjects who reported ≥ 1 injection-site complaint days 0–4 after vaccination was significantly higher ($P < .001$) among the adults who received Havrix for their booster dose than among those adults who received Vaqta for their booster dose (59.7% vs. 36.6%, respectively). The proportion of subjects reporting pain, tenderness, erythema, and swelling at the injection site was significantly higher in the group that received Havrix than the group that received Vaqta. There was no significant difference in terms of ecchymosis, pruritus, or warmth at the injection site.

DISCUSSION

To our knowledge, this is the first large-scale, double-blind, randomized, controlled study to demonstrate that administration of Vaqta is effective in boosting healthy adults who had previously received a primary dose of Havrix 24–52 weeks earlier. The immune responses (as measured by the BRR and GMT) 4 weeks after the booster dose were similar regardless of whether Vaqta or Havrix was used as the booster.

Analysis of the safety data obtained from this study indicates that administration of a booster dose of either vaccine was generally well tolerated. However, it is interesting to note that the rate of injection-site complaints was significantly higher among the recipients of Havrix than among the recipients of Vaqta. Preliminary data from 3 other studies in which adults received either Vaqta or Havrix in the same study have demonstrated a similar finding with respect to the rate of injection-site complaints [14, 15] (Merck, unpublished data). These differences in the rate of injection-site complaints may be due to the differences in the compositions of the 2 vaccines, the most notable of which was the lower amounts of MRC-5 cell proteins and formaldehyde in Vaqta compared with Havrix [10]. Further study of this phenomenon is needed to determine if this pattern continues.

The findings from this study support the safety and immunogenicity results from 2 earlier studies that addressed whether inactivated hepatitis A vaccines could be switched. In a small, noncontrolled trial involving 43 subjects who received Vaqta after an initial dose of Havrix, the immune responses were compared to historical data for healthy adults who received 2 doses of Vaqta [16]. In a randomized, single-blind trial, Avaxim (an inactivated hepatitis A vaccine currently licensed in Europe) was used as the booster for Havrix and responses were compared to 2 doses of Havrix [17]. Both studies showed that one vaccine could effectively boost another without untoward side effects.

The data from this study are particularly useful to physicians, public health personnel, the military, and patients themselves in addressing the practical question of whether individuals can switch from one vaccine to another. These findings support the recent recommendations, made by both the Advisory Committee on Immunization Practices and the Armed Forces Epidemiology Board, that subjects who begin their hepatitis A vaccine series with Havrix may complete the series with Vaqta [18] (Armed Forces Epidemiological Board, personal communication).

Further study is needed to determine whether all inactivated hepatitis A vaccines may be interchanged with each other in any order. Additional studies to address this issue are in progress.

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