FIELD PERFORMANCE OF VAQTA™ (INACTIVATED, PURIFIED HEPATITIS A VACCINE) IN CHINESE CHILDREN IN JIANGSU

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Abstract. In Jiangsu, 30% of children between the ages of 5 and 8 years test seropositive for hepatitis A. The safety, tolerability, and immunogenicity of a 2-dose regimen (0, 6 months) of VAQTA™ (0.5 ml of 25U) administered IM in 50 healthy children aged 5 to 8 years without prior serological screening was evaluated. Blood samples were collected prior to the first dose and after each additional dose of VAQTA™ to determine the initial anti-HAV serostatus and response rates to the vaccine. Twelve children (24%) were initially seropositive and 38 (76%) were initially seronegative. Four weeks after the primary dose of VAQTA™, 34 of the 38 subjects (89.5%, 95% CI 75 to 97) were anti-HAV seropositive. The geometric mean titer was 33.1 mIU/ml (95% CI 22.4 to 49.0). After the booster dose at 6 months, all the subjects were seropositive (37/37), giving a seroconversion of 100% (95% CI: 90, 100). The geometric mean titer was 7,585.8 mIU/ml (95% CI: 5,623.4 to 10,471.3). Adverse experiences were generally mild and transient. Results of this study are consistent with results from a previous double-blind randomized trial of this vaccine and confirm that VAQTA™ is highly immunogenic, and generally well-tolerated.

INTRODUCTION

Hepatitis A virus (HAV) infection is still endemic in China, but where living conditions are comparable to those of developed countries and affluence has increased, especially in urban areas, a shift in the age when infection commonly occurs has been observed (Barzaga, 2000; Wang *et al*, 2001). Infections of susceptible individuals can occur at any age, with inapparent subclinical or unrecognized infections in young children, but greater morbidity is reported in older individuals. In the last decade of the 20th century, various Asian countries showed a dramatic reduction in anti-HAV prevalence to 0.9-15% in their pediatric population under 10 years of age (Yap and Guan,1993; Kalayanarooj *et al*, 1995; Sohn *et al*, 2000). Prior to the socio-economic progress in Asia, HAV infections occurred universally before 12 years of age. Increased prosperity and improved sanitation has resulted in a decrease in the seroprevalence from 16 to 48% in adults <50 years of age and in adolescents. In less affluent areas of China, the seroprevalence in children under 15 years of age varies from 25 to 80%(Chin *et al*, 1991; Sinlaparatsamee *et al*, 1995; Li *et al*, 1998). A recent study in Wuhan with a single dose live attenuated vaccine has shown the cost-effectiveness of implementing vaccination against hepatitis A in a susceptible urban population 3-19 years of age in China (Wei *et al*, 1998). For the purpose of prevention, single-dose, locally manufactured, live, attenuated vaccines and foreign manufactured, inactivated, attenuated hepatitis A vaccines, such as VAQTA™, are available. The field performance of VAQTA™ was evaluated at a Center for Disease Control Field station in Jiangsu, which is in an area of intermediate endemicity.

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MATERIALS AND METHODS

This study was conducted at a single center in China to evaluate the immune response in the

Chinese population. The study protocol was approved by the Ethical Review Board of Zhang Jia Gang Feng Huang Hospital and the trial was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki.

After parental consent, children aged 2 to 17 years old were eligible. Subjects were enrolled from schoolchildren attending the Jiangsu and Zhang Jia Gang Antiepidemiology Station. Children were excluded if they had a previous history of hepatitis A, hepatitis A vaccination, receipt of blood products, immunosuppressive therapy or any condition that might interfere with the study objective.

Local reactions and oral temperature were recorded for four days following each vaccination. All adverse experiences were reported for 14 days following each vaccination. All prescriptions, medications and therapies received during this period, and the reason for therapy, also were recorded.

A commercially available lot of VAQTA™ (1448H) was used in this study. VAQTA™ is a highly purified, inactivated, whole virus vaccine derived from the hepatitis A CR 326F strain. It contains no thimerosal or other preservatives. Eligible subjects received a single 0.5 ml (~25U) dose of vaccine intramuscularly in the deltoid muscle at an elected date and a booster dose 6 months later. Subjects were not required to be seronegative to HAV prior to study enrollment. Sera were collected prior to the first dose and four weeks after each dose of VAQTA™ for evaluation of the immune response with a modified version of the commercially available HAVAB® assay kit from ABBOTT. Testing was performed at Merck Research Laboratories. The modified HAVAB® assay detects antibody (IgM and IgG) by comparing the competitive binding of anti-HAV (hepatitis A virus) in serum with a radioiodinated standard anti-HAV, using HAV coated on a solid phase. In order to make the HAVAB® test quantitative, a standard curve was constructed using dilutions of a WHO standard. Test samples were compared to the standard curve and the titers of anti-HAV in milli-international unit per milliliter (mIU/ml) were determined. Samples ≥10 mIU/ml were considered positive and those <10 mIU/ml were considered negative (Miller *et al*, 1993).

The primary variable/timepoint of interest was the proportion of subjects who developed anti-HAV titers ≥10 mIU/ml 1 month after the second injection of VAQTA®. The expected response rate from the historical database of the vaccine manufacturer in children and adolescents 2 to 17 years of age was >99% after the second dose. For purposes of power calculations, we assumed an initial seropositivity rate of 10-15% and intended to enroll 50 subjects, expecting 43 subjects to be initially seronegative. Estimating an evaluability rate of 90%, 38 subjects were expected to be available for immunogenicity summaries, giving 94% power to detect a reduction of 15 percentage points or greater after dose 2 compared to the historical response rate. If the observed seropositivity rate post-injection 2 was ≥97%, then the lower bound of the 95% confidence interval on the observed rate would be 86.2%. Power was calculated using exact methods. All subjects with follow-up for safety were summarized for safety and tolerability. All immunogenicity analyses and summaries were prepared on a per-protocol basis, *ie*, those who were seronegative at baseline (<10 mIU/ml) and had valid serological measurements post-vaccination.

RESULTS

Subjects

A total of 50 healthy children, all of them primary one students from Jiangsu and Zhang Jia Gang, were enrolled and vaccinated. Twenty-four (48%) of the enrolled subjects were male and 26 (52%) were female. The mean age was 6.1 years (SD 0.79 year) and the age range was five to eight years. The mean weight was 20.4 kg (SD 2.78 kg) and the mean height was 116.6 cm (SD 5.5 cm) of which both were in a normal range. Forty-eight subjects received both doses of vaccine and had a serology sample at all specified time-points. Two subjects withdrew one after the primary dose, the other after the booster dose).

Immunogenicity

After anti-HAV testing, 12 subjects (24%) were found to be seropositive prior to dose one and were excluded from the analysis. Serological results were available for 38 baseline serone-

Table 1
Serum result 4 weeks and 28 weeks after vaccination.

Time point	Seropositivity rate (SPR)			Geometric mean titer	
	n/N	SPR (%)	95% CI	mIU/ml	95% CI
4 weeks PD1	34/38	89.5	75,97	33.1	(22.4, 49.0)
4 weeks PD2	37/37	100.0	90,100	7,585.8	(5,623.4, 10,471.3)

n = number of subjects with ≥10 mIU/ml anti-HAV antibody; PD1 = post-dose 1
N= number of initially seronegative subjects with valid serology results at the indicated time point.

gative subjects post-dose one and 37 subjects post dose two. Four weeks after the primary dose, 34 out of 38 subjects (89.5%) were seropositive. The geometric mean titer was 33.1 mIU/ml. Four weeks after the booster dose, all subjects (37/37) showed a strong immune response. The seropositivity rate was 100% and the geometric mean titer was 7,585.8 mIU/ml (Table 1).

Safety and tolerability

No subject died. There was one serious adverse event reported (head trauma), which was judged unrelated to vaccination by the investigators and did not cause the subject to be discontinued from the study. No subject discontinued due to an adverse event. Within four days after injecting the vaccine, injection-site complaints were reported by eight subjects (16.0%) post dose one and seven subjects (14.6%) post dose two, After the first dose of vaccine, five subjects (10.0%) reported pain and six subjects (12.0%) reported tenderness. After the second injection, five subjects reported pain (10.4%), four reported tenderness (8.3%), and one reported swelling (2.1%). All these experiences were of a transient nature and resolved uneventfully (Table 2).

Within the 14-day observation period after each injection, 34 of the 50 vaccinees (68.0%) had no adverse experiences after the first dose and 42 of 48 vaccinees (87.5%) had no adverse experiences after the booster dose (Table 3). After the first injection, fever (n=5) and upper respiratory tract infection (n=5) were the most commonly reported systemic adverse experiences. After the booster injection, fever (n=2) and upper respiratory tract infection (n=3) were again the most commonly reported adverse experiences. Side-effects which were determined by the investigator to be possibly vaccine-related, were reported in a total of three subjects (3.06%); two (4.0%) after the first dose (acute tonsillitis and common cold) and one (2.1%) after dose two (fever).

Table 2
Local and systemic experiences 4 days post-vaccination on a vaccination report card.

Vaccine dose/N	Dose 1/N=50	Dose 2/N=48
Local injection-site reactions:		
Pain	5 (10)	5 (10.4)
Tenderness	6 (12)	4 (8.3)
Swelling	0	1(2.1)
Warmth	0	0
Erythema	0	0
Body as a whole: fever (oral)		
<38.3ºC.	4 (8)	2 (4.2)
>38.4-39ºC.	1 (2)	0
≥39.1	0	0

Table 3
Summary of all adverse experiences reported (Days 0 to 14 post-vaccination).

	Dose 1	Dose 2
Subjects	N=50 (%)	N=48 (%)
No adverse experiences (AE)	34 (68.0)	42 (87.5)
One or more AE:	16 (32.0)	8 (16.7)
Injection site AE[a]	8 (16.0)	7 (14.6)
Systemic AE	10 (20.0)	8 (16.7)
Serious AE	1 (2.0)	0 (0.0)
Discontinuation due to SAE	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)

[a]measured for four days only

DISCUSSION

In areas with an intermediate level of risk, hepatitis A infection circulates and immunity is low. However, epidemiological patterns are dynamic and can vary considerably even within one district. As infection rates in children decrease, adolescents and adults are at risk, and the potential for outbreaks increase, as was demonstrated by the outbreak of 292,301 cases of hepatitis A in Shanghai in 1988 (Tang *et al,* 1991). Vaccination programs have been shown to be cost-effective in selected populations in China and elsewhere (Fitzner *et al,* 1994; Smith *et al,* 1997; Buma *et al,* 1998; Fenn *et al,* 1998; Lee *et al,* 2000).

Hepatitis A shares many similarities with polio. Initially it was thought that an oral live hepatitis A virus vaccine could be developed. However, all vaccine candidates attenuated so rapidly that oral immunization was unsuccessful (Midthun *et al,* 1991; Sjogren *et al,* 1992). Parenteral single dose live attenuated vaccine candidates were developed in the US and China, but needed an inoculum dose of greater than 10^6 tissue culture infective doses to induce an antibody response (Adler and Shouval, 1996). The largest trial of a live HAV vaccine was conducted in China on 3,089 subjects using the H2-strain. The seroconversion rate after ~4 weeks was 95.6% (Mao *et al,* 1997; 1985). Four vaccinees were tested for excretion of virus in the stool by tissue culture techniques and virus was detected in three, but no transmission of vaccine virus to non-vaccinees was observed. The concern, that a live attenuated viral HA-strain could mutate back to a more pathogenic form, like oral polio strain with vaccine induced flaccid paralysis, was never proved, because the only evidence was seroconversion, which could have been induced by the antigenic mass contained in the vaccine rather than new antigen produced by replication. This concern of the possible emergence of virulent revertants that may be excreted in the stool, and subsequently in the public sewage system, eliminated the development of a live viral HA-strain in the Western hemisphere and focused instead on inactivated attenuated HA vaccines (Adler and Shouval, 1996).

The principle of vaccination is to first show safety, then immunogenicity, then protective efficacy upon challenge, and lastly, duration of the protection. Only two efficacy trials have been conducted for an inactivated hepatitis A vaccine, one for VAQTA™ and one for HAVRIX™ (GlaxoSmithKline). Both vaccines have been shown to be highly efficacious, VAQTA™ after one dose and HAVRIX™ after two doses (Innis *et al,* 1994; Werzberger *et al,* 1998).

Prior to endorsing vaccination with an imported vaccine, Chinese health professionals were interested in the field performance of an attenuated hepatitis A vaccine in a setting where screening was either not possible or cost-effective. This was a small safety and immunogenicity trial, the observed findings are consistent with those of two immunogenicity studies with VAQTA™ in 99 Chinese and 88 Korean children that showed 100% seroconversion after dose 2 (Wan, 2000; Sohn *et al,* 2001). Findings are also consistent with those of a large-scale, double-blind randomized trial with VAQTA™ in a pediatric population reported in the literature (Werzberger *et al,* 1998). Since the immunogenicity results found in our trial are similar to those in a trial of VAQTA™ in Monroe, NY and in a recent evaluation of routine hepatitis A immunization among children residing in large populations where the disease is recurrent, the vaccine is expected to be equally efficacious (Averhoff *et al,* 2001) in a Chinese population at risk of infection.

In conclusion, a pediatric two-dose regimen of VAQTA™ was found to be highly immunogenic and generally well-tolerated in children in Jiangsu, China.

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REFERENCES

Adler R, Shouval D. Hepatitis A prophylaxis. Vaccine or immunoglobulin. *Clin Immunother* 1996; 6: 261-72.

Adler R, Shouval D. Disease management: hepatitis A prophylaxis vaccine or immunoglobulin? *Clin Immunother* 1996; 6: 261-72.

Averhoff F, Shapiro CN, Deladisma A, Kuter B, Nalin

D. Control of hepatitis A through routine vaccination of children. *J Am Med Assoc* 2001; 19: 286.

Barzaga NG. Hepatitis A shifting epidemiology in South-East Asia and China. *Vaccine* 2000; 18: S61-S64.

Buma AH, Tormans G, Beutels P, vanDoorslaer E, Damme P, Leentvaar-Kuijpers A. An economic evaluation of hepatitis A vaccination in Dutch military personnel. *Milit Med* 1998; 163: 564-7.

Chin KP, Lok ASF, Wong LSK, *et al*. Current seroepidemiology of hepatitis A in Hong Kong. *J Med Virol* 1991; 34: 191-3.

Fenn P, McGuire A, Gray A. An economic evaluation of vaccination against hepatitis A for frequent travelers. *J Infect* 1998; 36: 17-22.

Fitzner KA, Handmaker KE, Wong K. Hepatitis A vaccination: A cost-benefit study in Hong Kong. Hong Kong Practitioner, 1994: 16.

Innis BL, Snitbhan R, Kunasol P, *et al*. Protection against hepatitis A by an inactivated vaccine. *J Am Med Assoc* 1994; 271: 1328-34.

Kalayanarooj S, Vaugn DW, Smitbhan R, *et al*. Age-specific prevalence of hepatitis A antibody in Thai children. *Southeast Asian J Trop Med Public Health* 1995; 26: 709-11.

Lee A, Cheng F, Lau L, Lo A, Fabb WE. Should adolescents be vaccinated against hepatitis A: the Hong Kong experience. *Vaccine* 2000; 18: 941-6.

Li X, Xu Z, Hoffman A. Epidemiology and cost-effectiveness analysis of hepatitis A vaccination in Liuzhou City. *Chin J Epidemiol* 1998; 19.

Mao JS, Chai SA, Xie RY, *et al.* Further evaluation of the safety and protective efficacy of live attenuated hepatitis A vaccine (H2-strain) in humans. *Vaccine* 1997; 15: 944-7.

Mao JS, Dong DX, Zhang HY, *et al.* Primary study of attenuated live hepatitis A vaccine (H2 strain) in humans. *J Infect Dis* 1989; 59: 621-4.

Miller WJ, Clark W, Hurni W, Kuter B, Schofield T, Nalin D. Sensitive assays for hepatitis A antibodies. *J Med Virol* 1993; 41: 201-4.

Midthun K, Ellerbeck E, Gershman K, *et al.* Safety and immunogenicity of a live attenuated hepatitis A virus vaccine in seronegative volunteers. *J Infect Dis* 1991; 163: 735-9.

Sinlaparatsamee S, Nuniem J, Kankao J, *et al.* An outbreak of hepatitis A in schoolchildren at Nakhon Si Thammarat, Southern Thailand. *Southeast Asian J Trop Med Public Health* 1995; 26: 104-8.

Sjogren MH, Purcell RH, McKee K, *et al.* Clinical and laboratory observations following oral or intramuscular administration of a live attenuated hepatitis A vaccine candidate. *Vaccine* 1992; 10 (suppl 1): S135-137.

Smith S, Weber S, Wiblin T, Nettleman M. Cost effectiveness of hepatitis A vaccination in healthcare workers. *Infect Control Hosp Epidemiol* 1997; 18: 688-91.

Sohn YM, Rho HO, Park MS, Choi BY, Ki M, Jang WI. The changing epidemiology of hepatitis A in children and the consideration of active immunization in Korea. *Yonsei Med J* 2000; 41: 34-9.

Sohn YM, Lee JS, *et al.* Immunogenicity of a pediatric formulation of VAQTA in Korea. Beijing, China: 23rd International Congress of Pediatrics, Sept 10-14, 2001: OP-F5-15.

Tang YW, Wang JX, Xu ZY, Guo YF, Qian WH, Xu JX. A serologically confirmed, case-control study, of a large outbreak of hepatitis A in China, associated with consumption of clams. *Epidemiol Infect* 1991; 107: 651-7.

Wang SM, Liu CC, Huang YS, Yan YJ, Lei HY. Change in hepatitis A virus seroepidemiology in Southern Taiwan: a large percentage of the population lack protective antibody. *J Med Virol* 2001; 64: 104-8.

Wei SB, Li SP, Gao L. Herd immunity of 400,000 against hepatitis A: the analysis of costs and benefits. Boston, USA: 8th International Congress of Infectious Diseases. May 15-18, 1998.

Werzberger A, Mensch B, Kuter B, *et al.* A controlled trial of formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med* 1992; 327: 453-7.

Wan CJ. Description of import registration procedures in China: evaluation of the immunogenicity of a purified, inactivated hepatitis A vaccine. Hong Kong: 7th Western Pacific Congress of Chemotherapy and Infectious Diseases, Dec 10-14, 2000: P2-39.

Werzberger A, Kuter B, Nalin D. Six years' follow-up after hepatitis A vaccination. *N Engl J Med* 1998; 338: 1160.

Yap I, Guan R. Hepatitis A sero-epidemiology in Singapore: a changing pattern. *Trans R Soc Trop Med Hyg* 1993; 87: 22-3.