International Journal of Infectious Diseases (2008) **12**, 270—277

http://intl.elsevierhealth.com/journals/ijid

Immunogenicity, safety, and interchangeability of two inactivated hepatitis A vaccines in Chilean children☆

Katia Abarca [a,*], Isabel Ibánez [a], Cecilia Perret [a], Pablo Vial [a], Jean-Antoine Zinsou [b]

[a] *Centro Médico San Joaquín, Pontificia Universidad Católica de Chile, Marcoleta 391, Santiago, Chile*
[b] *Sanofi Pasteur, Lyon, France*

Received 7 February 2007; received in revised form 12 August 2007; accepted 22 August 2007
Corresponding Editor: Jane Zuckerman, London, UK

KEYWORDS
Hepatitis A vaccine;
Children;
Safety;
Immunogenicity;
Interchangeability

Summary
Objectives: To compare the immunogenicity, safety, and interchangeability of two pediatric hepatitis A vaccines, Avaxim 80U-Pediatric® and Havrix 720®, in Chilean children.
Methods: In this randomized trial, 332 hepatitis A virus (HAV) seronegative children from 1 to 15 years of age received two doses of Avaxim, two doses of Havrix, or Havrix followed by Avaxim, 6 months apart. Anti-HAV antibody titers were measured before and 14 days after the first dose of vaccine, and before and 28 days after the second dose of vaccine. Immediate reactions were monitored; reactogenicity was evaluated from parental reports.
Results: Seroconversion rates after the first vaccination were 99.4% and 100% for Avaxim and Havrix, respectively. Anti-HAV geometric mean concentrations (GMCs) were 138 mIU/ml for Havrix (95% confidence interval (CI): 120; 159) and 311 mIU/ml for Avaxim (95% CI: 274; 353). GMCs increased to 4008 mIU/ml after two doses of Havrix, 8537 mIU/ml following two doses of Avaxim, and 7144 mIU/ml in children who received Havrix with Avaxim as the second dose. Following the first injection, 36% of subjects given Avaxim and 44% given Havrix reported local reactions; 38% of subjects in the Avaxim group and 40% in the Havrix group reported systemic reactions related to vaccination. Solicited reactions were less frequent after the second dose of Avaxim or Havrix, occurring in 27% to 37% of subjects.
Conclusions: No significant difference in seroconversion rates was seen 14 days after a single dose of vaccine. A two-dose schedule with either vaccine or with Havrix/Avaxim provided a strong booster response. Both vaccines were well tolerated and can be recommended for routine vaccination of Chilean children. Avaxim 80 may be used to complete a vaccine schedule begun with Havrix 720.

☆ This study was presented in part at the 11th International Congress on Infectious Diseases, Cancun, Mexico, 4—7 March 2004 (Abstract 10.007).

* Corresponding author. Tel.: +56 2 354 6823; fax: +56 2 638 7457.
E-mail address: katia@med.puc.cl (K. Abarca).

1201-9712/$32.00
doi:10.1016/j.ijid.2007.08.006

Introduction

In young children, hepatitis A is usually asymptomatic or mild, but it increases in severity with age, so that in subjects older than 5 years the infection is often clinically significant.[1,2] The epidemiological patterns of hepatitis A virus (HAV) infection correlate with local socioeconomic conditions, and since the most common mode of HAV transmission is by the fecal—oral route, improvements in public health lead to reduced HAV circulation.[3,4] As sanitation improves, decreased circulation of the virus results in groups of older children and adolescents within a population who have not yet been exposed, and remain susceptible to HAV infection. Hepatitis A vaccination of toddlers can thus be a desirable public health measure in countries where hepatitis endemicity is decreasing to intermediate or low levels.

The benefits obtained by universal vaccination of young children have been confirmed in a growing list of countries. Following the institution of universal vaccination of toddlers at 18 and 24 months of age, the overall incidence of hepatitis in Israel decreased from a mean of approximately 50 cases per 100 000 per year from 1993 through 1998 to <2.5 cases per 100 000 in 2002 and 2003.[5] A similar program conducted from 1995 to 2000 in California, USA, in children between 2 and 17 years of age, resulted in a decrease in HAV annual case incidence from 57 to 1.9 per 100 000.[6] Argentina began universal vaccination of toddlers in 2005 following an increase of 23% in the previous year in the number of reported cases of hepatitis A, an overall annual incidence of 171 per 100 000 compared to 139 per 100 000 during the previous year.[7]

Recent epidemiological studies show that there has been a shift from high to intermediate endemicity of HAV infection throughout much of Latin America. Community seroprevalence studies show that as of the year 2000, only 11—12% of Chilean children between 1 and 5 years of age had been exposed to HAV, 25—30% at age 6—10 years, and it was only in a cohort of 20—24 year-olds that the seroprevalence rate reached approximately 70%.[8—10] It is clear, however, that these age-related changes in seroprevalence have not occurred throughout the population, but are associated with communities having a relatively high socioeconomic level.[10] The Chilean data show that the decrease in overall HAV seropositivity has not been associated with a smooth decrease in incidence of clinical disease, but rather with upward displacements in incidence or epidemic cycles, such as occurred in 1994—1995 and the years 2002 and 2003.[11,12] Epidemiologic data from Chile also indicate that the proportion of hepatitis A cases in children younger than 5 years of age has decreased from about 30% of the total in 1975 to 16% in 2006. Over the same period of time, the proportion of hepatitis A cases in adolescents and young adults between the ages of 15 and 24 years has increased from approximately 5% to 18%. The shift in the average age of infection to one when clinically significant illness is more likely has led to an increasing tendency towards immunizing children at a young age.[7]

Inactivated hepatitis A vaccines were first developed for adult administration, to protect travelers to endemic areas. However, extensive experience with inactivated hepatitis A vaccines in prospective efficacy trials[13,14] and intervention studies during outbreaks[15—17] have shown that vaccination could also protect children from infection. The potential for routine vaccination of children to lower the overall incidence of the disease has led to the development of pediatric hepatitis A vaccine formulations containing reduced amounts of hepatitis A viral antigen. The Avaxim pediatric vaccine evaluated in this trial has been shown to be safe and immunogenic in Israeli and Argentinean children aged from 1 to 15 years when given in two doses 6 months apart.[18,19] A study in Thai children confirmed the immunogenicity and safety of the vaccine when the second dose was given at 6, 12, or 18 months after the first one.[20] The safety profile of this vaccine has been evaluated in more than 3000 subjects aged from 12 months to 15 years who received at least one dose of pediatric inactivated hepatitis A vaccine.[21]

Comparative trials of the adult formulations of this vaccine, Avaxim 160® (Sanofi Pasteur, Lyon, France) and Havrix 1440® (GlaxoSmithKline, Rixensart, Belgium), have demonstrated that two doses given 6 months apart are strongly immunogenic and well tolerated.[22,23] Previous studies with the adult formulations have also confirmed the interchangeability of these two vaccines.[24]

We conducted this study to evaluate the immunogenicity and safety of the pediatric formulations of Avaxim and Havrix (Avaxim 80U-Pediatric® and Havrix 720®), and to evaluate the use of Avaxim to complete a vaccination schedule begun with Havrix.

Materials and methods

Study design

This was a monocenter, comparative trial in which healthy, seronegative children were randomized to receive two doses of hepatitis A vaccine 6 months apart. The trial was conducted in accordance with the Edinburgh version of the Declaration of Helsinki. The study was approved by the Ethics Committee of the School of Medicine, Pontificia Universidad Católica de Chile. Parents or legal guardians of all participants gave written informed consent prior to study entry.

Eligible subjects were between 1 and 15 years of age and anti-HAV seronegative. Subjects were excluded if they were enrolled or scheduled to be enrolled in another clinical trial, had an acute febrile illness ($\geq$37.5 °C axillary or $\geq$38.4 °C rectal temperature), had a known history of allergy to any vaccine component, were unable to comply with the visit schedule, had a chronic immunosuppressive disease or had received immunosuppressive treatment within the month prior to inclusion, had uncontrolled coagulopathy or a blood disorder that contraindicates intramuscular injection, had received blood and/or plasma transfusion or received any immunoglobulins within the four months prior to inclusion, had previously been vaccinated against hepatitis A, had a previous history of hepatitis A, had hepatosplenomegaly on the day of pre-selection/inclusion, or had a previous history of treatment with growth hormone.

When enrolled, children were stratified to one of three age groups of equal size (1—5, 6—10, or 11—15 years of age), and then randomized to two equal groups (Figure 1). The first group received two doses of Avaxim. The second group received a first dose of Havrix, and the subjects were then randomized to two subgroups of equal size for the second injection, either Avaxim or a second dose of Havrix. Group

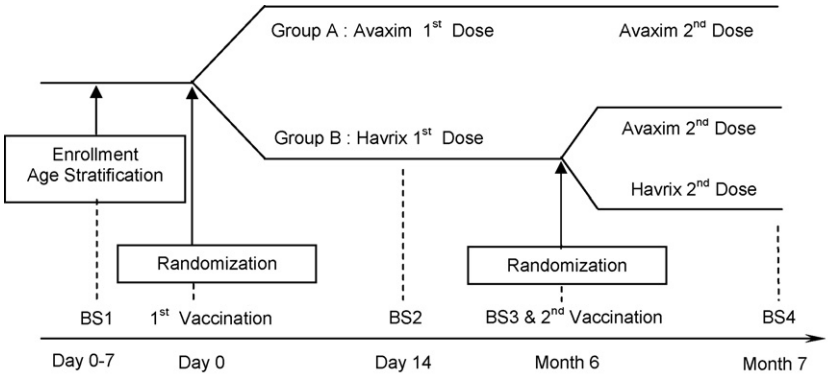

Figure 1 Study design.

allocations were determined using previously generated lists of random numbers. As the two vaccines have different packaging, the study could only be observer-blind.

Vaccines

Avaxim 80U is a formaldehyde-inactivated hepatitis A liquid vaccine adsorbed onto aluminum hydroxide, containing 80 antigen units per 0.5 ml dose (aluminum hydroxide 0.15 mg, 2-phenoxyethanol 2.5 μl, formaldehyde 12.5 μg). Havrix 720 is a formaldehyde-inactivated hepatitis A liquid vaccine adsorbed onto aluminum hydroxide, containing 720 ELISA units per 0.5 ml dose (aluminum hydroxide 0.25 mg, 2-phenoxyethanol 0.5%, formaldehyde 100 μg). The vaccines were administered by intramuscular (IM) injection into the right deltoid.

Serological analysis

Blood samples for determination of anti-HAV antibody and calculation of geometric mean concentrations (GMCs) were obtained at enrollment, at 14 ± 2 days after the first vaccination, at 6 months (−7, +21 days) just prior to second vaccination, and at a month ± 4 days following the second vaccination (Figure 1). Serum anti-HAV antibody concentrations were determined using a commercially available enzyme immunoassay (EIA) (ETI-AB-HAVK PLUS; DiaSorin, Saluggia, Italy). Samples with values below the lowest limit of quantification of 10 mIU/ml were assigned a value of 5 mIU/ml in order to calculate the GMC.

Reactogenicity and safety evaluation

The local and systemic reactogenicity of Avaxim and Havrix were evaluated in all subjects following each injection. Immediate reactions were monitored for 30 minutes. Solicited local (pain, redness, or induration) and systemic (fever: axillary temperature ≥37.5 °C, asthenia, headache, arthralgia, myalgia, gastrointestinal disorders) reactions occurring within 3 days following any injection were recorded on diary cards by parents or guardians. Unsolicited local and systemic reactions and serious adverse events (SAEs) were recorded throughout the study period. Adverse events were classified according to their nature, severity, relationship to vaccination (for systemic reactions and SAEs), time of onset, and duration.

Statistical analysis

The primary study objective was comparison of the seroconversion rates (increase in anti-HAV antibody concentration to ≥20 mIU/ml) for the two study vaccines, 2 weeks after the first dose. The clinically relevant limit for between-group differences in seroconversion rates was set at 10%. A 95% confidence interval (CI) of the difference in rates between Avaxim and Havrix entirely above −10% would then indicate non-inferiority of the response to Avaxim. If the 95% CI of the difference was entirely above zero, the Avaxim seroconversion rate could be considered superior to Havrix. Seroconversion rates and GMCs with 95% CIs were also calculated before and after the second dose of vaccine in each study group. Between-group comparisons of anti-HAV GMCs following each of the two vaccine doses were descriptive only, based on the 95% CI. In addition, reverse cumulative distribution curves (RCDCs) of anti-HAV antibodies were plotted for each study group and each time point. Exploratory analyses were performed in order to find a possible relationship between the age of the subject and response to the vaccination using a logistic regression for seroconversion rates with the treatment group and age as covariates. Descriptive analysis of reactogenicity included the numbers and percentages of children who reported immediate or solicited reactions, with 95% CIs. All statistical analyses were performed by the Biostatistics Platform of Sanofi Pasteur (Lyon, France) using SAS software (SAS Institute, Cary, NC, USA).

Based on expected seroconversion rates of 94% for each vaccine following the first dose, a type I error of 2.5% and a power of 90%, a sample size of 120 subjects per group was required for a non-inferiority test. The final sample size of 132 subjects was determined by assuming that 10% of subjects would be excluded from the analysis, including those lost to follow-up. The study protocol was amended to enroll 68 additional subjects because the batch number of vaccine used was not indicated on the randomization list for 68 subjects who had been included in the trial.

Results

Subjects

A total of 332 seronegative children (anti-HAV concentration <10 mIU/ml) were enrolled. Demographics were similar for

Table 1 Characteristics of the study population[a]

	Group A	Group B	Subgroup B1	Subgroup B2	Total
Number of subjects (*N*)	164	166	84	82	330
Male	80 (49)	77 (46)	38 (45)	39 (48)	157 (48)
Female	84 (51)	89 (54)	46 (55)	43 (52)	173 (52)
Age 1—5 years	54 (33)	54 (32)	26 (31)	28 (34)	108 (33)
Age 6—10 years	58 (35)	59 (36)	31 (37)	28 (34)	117 (35)
Age 11—15 years	52 (32)	53 (32)	27 (32)	26 (32)	105 (32)

[a] Excludes one subject in group A and one in group B who received a first vaccination, but withdrew voluntarily before a post-vaccination serum sample could be obtained at 14 days. Results are *n* (%).

all study treatment groups (Table 1). A total of nine subjects discontinued the study, five in group A and four in group B. Three subjects withdrew voluntarily and one was lost to follow-up. Two subjects were withdrawn by the sponsor because the maximum time allowed between the first and second dose had been exceeded. One subject was withdrawn by the investigator because of hepatitis A infection. This was not considered as a vaccine failure because symptoms appeared 15 days after the first injection, consistent with infection before vaccination. The subject recovered without hospitalization. Another subject was withdrawn by the investigator because the person who signed the consent form was not the parent or legal guardian of the child. One subject received immunotherapy for glomerulonephritis and discontinued the study because of receiving a prohibited treatment. No patient withdrew because of a serious adverse reaction.

Immunogenicity: first vaccine dose

The seroconversion rates in response to Avaxim and Havrix on day 14 were 99.4% and 100%, respectively. The 95% CI of the difference between the seroconversion rates for the two vaccines was −4.3; 2.1. Of the 330 evaluable subjects on day 14, one in the Avaxim group did not have an anti-HAV antibody concentration ≥20 mIU/ml. This subject had seroconverted by the time the second evaluation was done before the second vaccine dose. The GMCs on day 14 were 311 mIU/ml (95% CI: 274; 353) in subjects receiving Avaxim and 138 mIU/ml (95% CI: 120; 159) in those receiving Havrix, and the anti-HAV concentrations are shown in Figure 2 in RCDCs. GMCs for the study vaccines within each age group are shown in Figure 3. A regression analysis with age cohorts and vaccine groups as covariates showed a statistically significant interaction between age and treatment group GMCs in response to the first vaccine dose ($p = 0.04$). The relationship of age and GMCs was statistically significant in the Avaxim group ($p < 0.0001$), but this was not observed in the Havrix group. GMCs decreased with increasing age of the subjects, but still remained numerically higher than the GMCs in the Havrix group.

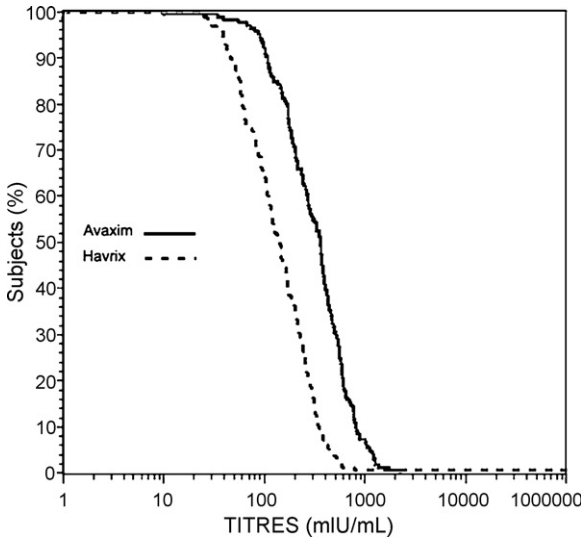

Figure 2 Anti-HAV (mIU/ml) 14 days following the first dose of vaccine.

Immunogenicity: second vaccine dose

GMCs in all groups decreased in the six-month interval before administration of the second dose, but all subjects, except one in the Havrix group, remained seroconverted (Table 2). Post- to pre-second dose GMC ratios (Table 2) show that both Avaxim and Havrix induced a marked booster-like response within a month. The anti-HAV antibody GMCs were 8537 mIU/ml (Avaxim/Avaxim), 7144 mIU/ml (Havrix/Avaxim), and 4008 mIU/ml (Havrix/Havrix) a month after the second dose (Table 2). There were no non-responders to the second vaccine dose. The overall responses to the second injection in each treatment group are illustrated by the RCDCs in Figure 4. Regression analysis showed no age effect on GMC after the second dose in any group for either of the study vaccines ($p = 0.6625$).

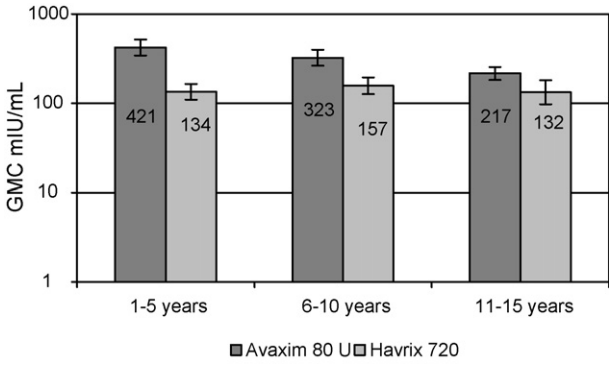

Figure 3 Geometric mean concentrations (mIU/ml) of anti-HAV antibodies 14 days after the first dose of vaccine.

Table 2 Anti-HAV antibody GMC, seroconversion rates (≥20 mIU/ml) pre- and post-second vaccination, and post-/pre-second vaccination GMC ratios

	Avaxim/Avaxim		Havrix/Havrix		Havrix/Avaxim	
	Pre-	Post-	Pre-	Post-	Pre-	Post-
n	159	160	83	83	80	80
GMC (mIU/ml)	273	8537	117	4008	110	7144
95% CI	242; 309	7768; 9382	99.0; 138	3261; 4926	86.8; 138	5907; 8640
% (*n*)	100 (159)	100 (160)	100 (83)	100 (83)	98.8 (79)	100 (80)
(95% CI)	97.7; 100	97.7; 100	95.7; 100	95.7; 100	93.2; 100	95.5; 100
	Post-/pre-		Post-/pre-		Post-/pre-	
n	159		83		80	
GMC ratio	31.1		34.3		65.2	
(95% CI)	28.0; 34.6		28.9; 40.7		53.5; 79.4	

HAV, hepatitis A virus; GMC, geometric mean concentration; CI, confidence interval.

Safety: immediate reactions

Three children given Avaxim (2.3%) and eight subjects receiving Havrix (6%) had immediate reactions following the first dose; all were mild and all resolved within 3 days, except in one child with moderate pain and another with mild induration in the Havrix group, both lasting 4 days. Immediate reactions were experienced by six subjects following a second Avaxim dose (4.8%), four children after a second Havrix dose (6%), and in two given Avaxim after a first dose of Havrix (3.1%). Pain was the most commonly reported reaction: mild, lasting 24 hours in five subjects receiving Avaxim, and severe, lasting one to three days in two subjects given Havrix. Mild redness lasting less than 2 days occurred in two patients given Avaxim and 4 days in one patient receiving Havrix.

Safety: solicited local and systemic reactions

Overall, 36% (95% CI: 27.9; 45) of subjects given Avaxim and 44% (95% CI: 35.5; 52.9) of subjects who received Havrix reported local reactions during the 3 days following the first dose of vaccine. Pain was the most frequent reaction, reported by 31—38% of subjects, followed by induration and redness, which occurred in 9—12% and 5—8% of children, respectively (Table 3). Following the second dose, from 27% (95% CI: 19.5; 35.6) to 37% (95% CI: 24.3; 48.9) of the children experienced a solicited local reaction, and again pain was the most frequently reported (Table 4). Most reactions were of mild or moderate intensity.

Systemic reactions related to vaccination occurred in 38% of subjects in the Avaxim group and 40% in the Havrix group following the first injection. The occurrence of systemic reactions after the second vaccination was slightly lower in both study groups, ranging from 31% to 33%. Most reactions were of mild to moderate intensity and resolved within 3 days. Headache and asthenia were the most common reactions (Table 4).

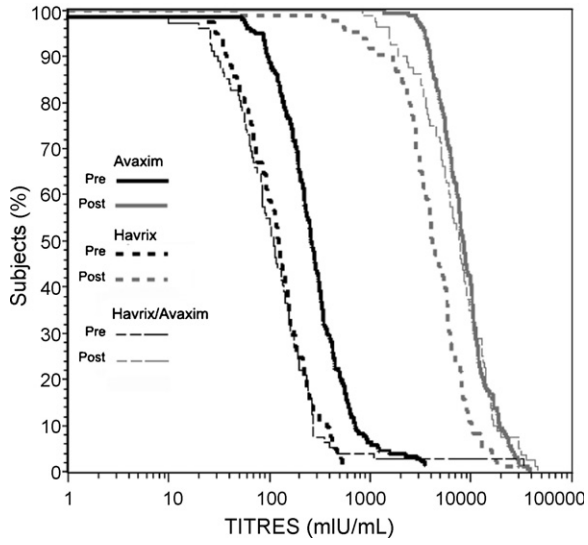

Figure 4 Anti-HAV concentrations (mIU/ml) at the time of (Pre), and one month after (Post) the second dose of vaccine.

Safety: unsolicited local and systemic reactions

Few unsolicited reactions occurred following injection of either vaccine. Three local reactions occurred following the first Avaxim injection (2%) and six occurred following Havrix (4%). The unsolicited reactions included purpura, injection site mass, pruritus, and hematoma. Only one unsolicited systemic reaction occurred — severe somnolence following the first injection of vaccine (Havrix), which resolved in 1 day. There were no unsolicited local or systemic reactions following an Avaxim for the second injection, but one subject had mild injection site pruritus and another had mild ecchymoses after receiving Havrix as a second injection. One subject experienced severe somnolence lasting 1 day concomitant with severe asthenia and mild headache following a Havrix as a second dose. A total of 11 SAEs were reported, none were related to vaccination. These included three upper respiratory disorders, six planned surgeries, a testicular cancer, and a glomerulonephritis. There were no study withdrawals because of SAEs. The subject with glomerulonephritis, reported as an SAE, discontinued the study because she received immunosuppressive therapy, a prohibited treatment.

Discussion

This randomized trial compared the immune response, safety, and tolerability of two pediatric hepatitis A vaccines, Avaxim

Table 3 Incidence of solicited local and systemic adverse reactions within 3 days after the first injection

	Avaxim		Havrix	
	n	%	*n*	%
Vaccinated	130	100	134	100
Any local reaction	47	36	59	44
Pain	40	31	51	38
Induration	12	9	16	12
Redness	7	5	10	8
Any systemic reaction	49	38	54	40
Fever	3	2	5	4
Asthenia	17	13	19	14
Headache	23	18	32	24
Arthralgia	6	4	12	9
Myalgia	9	7	13	10
Gastrointestinal disorders	13	10	14	10

80U-Pediatric and Havrix 720. Both vaccines were highly immunogenic, with all but one study subject in the Avaxim group seroconverting within 14 days of receiving a single dose. As shown by the 95% CI, there was no difference in the seroconversion rates in response to the first dose of these two vaccines. Overall however, GMCs were higher in response to Avaxim: 311 mIU/ml versus 138 mIU/ml, and within each age group the GMCs were higher in response to Avaxim. The kinetics of antibody response after the first dose followed the same pattern as seen in studies of the adult formulations of these vaccines, with higher antibody concentrations observed with Avaxim at week 2 than with Havrix.[22,25] A previous study with Avaxim had shown a trend for higher GMCs in response to vaccination in younger, as compared with older, children.[18] In our study, the GMCs following vaccination with a first dose of Avaxim were higher in the younger subjects ($p < 0.0001$), but this was not the case for Havrix ($p = 0.3699$).

Anti-HAV GMCs decreased in the 6-month interval between injections, but all subjects, except one who had received Havrix, remained seroconverted. The second dose of both vaccines induced a marked response in all children. The observed increases in GMC following the second dose suggest that immunological priming with both vaccines had been adequate. The responses in subjects given Avaxim/Avaxim and Havrix/Avaxim indicate that Avaxim may be used to complete a vaccination series begun with Havrix. The increase in GMCs did not demonstrate an age-related effect in any study group ($p = 0.6625$) in response to the second injection. The responses to the second dose of these pediatric vaccines are consistent with previous trials that confirmed the interchangeability of the adult formulations of these vaccines, using Avaxim to complete a series begun with Havrix.[22–24] Published models of antibody persistence with both Avaxim and Havrix in adults show long-term rates of decline for both vaccines. Projections extrapolating the decreases in anti-HAV antibody concentrations indicate that between 50% and 60% of vaccinees would still be seroprotected 10 years after vaccination, and that antibody persistence could last up to 20 years.[26,27] However, similar analyses are not yet available for two doses of each vaccine in pediatric subjects.

Table 4 Solicited local and systemic adverse events occurring within 3 days after the second vaccination

	Avaxim/Avaxim		Havrix/Havrix		Havrix/Avaxim	
	n	%	*n*	%	*n*	%
Number vaccinated	126	100	67	100	64	100
Any local reaction	34	27	25	37	23	36
Pain	29	23	22	33	20	31
Redness	8	6	3	4	5	8
Induration	9	7	10	15	5	8
Any systemic reaction	41	33	21	31	21	33
Fever	6	5	4	6	5	8
Asthenia	24	19	7	10	9	14
Headache	15	12	10	15	13	20
Arthralgia	6	5	4	6	2	3
Myalgia	6	5	3	4	3	5
Gastrointestinal disorder	13	10	7	10	1	2

The high seroconversion rates seen here for both vaccines make them suitable for universal childhood vaccination. However, increased immune response in children younger than 5 years of age, and high GMCs at 2 weeks following administration of a single dose of vaccine, such as seen with Avaxim, may be particularly useful for control of outbreaks. Vaccination, when used during hepatitis A outbreaks, is consistently followed by a rapid decline in incidence of new cases, most likely related to reductions of secondary transmission and sub-clinical cases that play a role in maintaining the outbreak.[28] Data from randomized trials are limited, but in a study of household contacts of individuals diagnosed with primary hepatitis A infection, vaccination was approximately 80% effective for prevention of secondary infection.[29] The effectiveness may be correlated with the rate at which antibody concentrations rise to protective levels following vaccination, but confirmatory data from clinical trials are lacking.

The overall reactogenicity was somewhat better than that seen in trials of the adult formulations of these vaccines and comparable to other studies that evaluated these pediatric vaccines.[14–19,27,30] The incidence of both solicited local and systemic reactions was somewhat lower in all study groups following the second dose than after the first dose. Immediate reactions were seen in 3–6% of patients, and as in the other studies, injection site pain was the most frequent reaction, followed by redness. Only two reactions were severe, local pain in children receiving Havrix. The local safety profile was satisfactory in both groups, with approximately 8% fewer patients reporting a reaction after receiving Avaxim. Pain was the most frequently solicited local reaction after any injection, and most reactions were of mild or moderate intensity. No SAEs occurred that were related to vaccination.

Experience in Israel and in the Catalonian region of Spain have demonstrated that universal childhood immunization against HAV is feasible and sustainable, and results in a remarkable reduction of HAV disease not only in children but also in other age groups.[5,31] The Advisory Committee on Immunization Practices (ACIP) in the USA recently recommended universal vaccination of children between the ages

of 2 and 18, following confirmation that selective vaccination of children in states with the highest incidence of hepatitis A had reduced the incidence to lower levels than the overall national incidence.[32] A recent health—economic analysis concluded that decreases in the incidence of hepatitis A within all age groups following vaccination of Chilean children would result in reductions in medical costs and lost productivity that would quickly outweigh the costs of vaccination.[33]

The availability of alternative vaccines is likely to facilitate the implementation of a program of universal vaccination of young children. The increasing need for hepatitis A vaccine could easily mean that a single manufacturer could not satisfy demand. Because of potential differences in availability, it is important to show that a schedule begun with a vaccine from one manufacturer can be completed with one obtained from a different provider. In many cases the hepatitis A vaccines administered in one clinic or office practice will be different from those available from others, or it may not be known which product was administered previously. In addition, healthcare systems may change from stocking vaccines from one manufacturer to another. In such circumstances, the physician often has no choice but to switch brands during the series. Thus, for a number of reasons, it may not always be feasible or practical to give children a single manufacturer's vaccine for both of the required vaccinations. Physicians faced with the necessity of giving mixed sequences should know that the mixed schedule would be well tolerated and protective. The immunogenicity and safety results in this study support the use of both vaccines for routine childhood vaccination in Chile, and also show that a vaccination schedule started with Havrix may be completed with Avaxim.

Acknowledgments

The authors wish to acknowledge Andréa Arancibia and Fabrice Guitton for study monitoring, Annick Favier and Christèle Deroche for statistical analyses, and Clement Weinberger for assistance in manuscript preparation. This study was conducted with the support of Sanofi Pasteur, Lyon, France.

Conflict of interest: This study was sponsored and supported financially by Sanofi Pasteur. Dr Zinsou is a member of staff of Sanofi Pasteur, Lyon, France. Dr Abarca has received fees from Sanofi Pasteur and Glaxo SmithKline for speaking at or attending medical meetings and for serving on advisory boards.

References

1. Forbes A, Williams R. Increasing age: an important adverse prognostic factor in hepatitis A infection. *J R Coll Phys (London)* 1988;**22**:237—9.
2. Lieberman JM, Greenberg DP. Hepatitis A and B vaccines in children. *Adv Pediatr Infect Dis* 1996;**11**:333—63.
3. Gust ID. Epidemiological patterns of hepatitis A in different parts of the World. *Vaccine* 1992;**10**(Suppl 1):S56—8.
4. Shapiro CN, Margolis HS. Worldwide epidemiology of hepatitis A virus infection. *J Hepatol* 1993;**18**(Suppl 2):S11—4.
5. Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of Toddlers. *JAMA* 2005;**294**:202—10.
6. Averhoff F, Shapiro CN, Bell BP, Hyams I, Burd L, Deladisma A, et al. Control of hepatitis A through routine vaccination of children. *JAMA* 2001;**286**:2968—73.
7. Ministro de Salud y Ambiente, Argentina. Comenzó la vacunación gratuita contra la hepatitis A en todo el país 20/5/2005. Available at: http://www.msal.gov.ar/htm/site/Noticias_plantilla.asp?Id=569 (accessed September 2007).
8. Tanaka J. Hepatitis A shifting epidemiology in Latin America. *Vaccine* 2000;**18**(Suppl 1):S57—60.
9. Tapia-Conyer R, Santos JI, Cavalcanti AM, Urdaneta E, Rivera L, Manterola A, et al. Hepatitis A in Latin America: a changing epidemiologic pattern. *Am J Trop Med Hyg* 1999;**61**:825—9.
10. Fix AD, Martin OS, Gallicchio L, Vial PA, Lagos R. Age-specific prevalence of antibodies to hepatitis A in Santiago, Chile: risk factors and shift in age of infection among children and young adults. *J Trop Med Hyg* 2002;**66**:628—32.
11. Ministerio de Salud, Chile, Departamento de Epidemiología. Situación de las enfermedades de notificación obligatoria: hepatitis A. Boletín Electrónico Mensual de Vigilancia Epidemiológica No. 43. Publicación 16 de Junio Año 2006. Available at: http://epi.minsal.cl/evigant/Numero43/evigia/index.html (accessed September 2007).
12. Ministerio de Salud, Chile, Departamento de Epidemiología. Hepatitis A y hepatitis sin especificación: Situación 2005. Available at: http://epi.minsal.cl/epi/html/bolets/reportes/hepatitisA.htm (accessed September 2007).
13. Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik C, et al. Protection against hepatitis A by an inactivated vaccine. *JAMA* 1994;**271**:1328—34.
14. Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med* 1992;**327**:453—7.
15. Prikazsky V, Olear V, Cernoch A, Safary A, Andre FE. Interruption of an outbreak of hepatitis A in two villages by vaccination. *J Med Virol* 1994;**44**:457—9.
16. McMahon BJ, Beller M, Williams J, Schloss M, Tanttila H, Bulkow L. A program to control an outbreak of hepatitis A in Alaska by using an inactivated hepatitis A vaccine. *Arch Pediatr Adolesc Med* 1996;**150**:733—9.
17. Sagliocca L, Amoroso P, Stroffolini T, Adamo B, Tosti ME, Lettieri G, et al. Efficacy of hepatitis vaccine in prevention of secondary hepatitis A infection: a randomized trial. *Lancet* 1999;**353**:1136—8.
18. Dagan R, Greenberg D, Goldenberg-Gehtman P, Vidor E, Briantais P, Pinsk V, et al. Safety and immunogenicity of a new formulation of an inactivated hepatitis A vaccine. *Vaccine* 1999;**17**:1919—25.
19. López E, Del Carmen Xifró M, Torrado L, De Rosa F, Gómez R, Dumas R, et al. Safety and immunogenicity of a pediatric formulation of inactivated hepatitis A vaccine in Argentinean children. *Pediatr Infect Dis J* 2000;**20**:48—52.
20. Lolekha S, Pratuangtham S, Punpanich W, Bowonkiratikachorn P, Chimabutra K, Weber F. Immunogenicity and safety of two doses of a paediatric hepatitis A vaccine in Thai children: comparison of three vaccination schedules. *J Trop Pediatr* 2003;**49**:333—9.
21. Vidor E, Dumas R, Porteret V, Bailleux F, Veitch K. Aventis Pasteur vaccines containing inactivated hepatitis A virus: a compilation of immunogenicity data. *Eur J Clin Microbiol Infect Dis* 2004;**23**:300—9.
22. Zuckerman J, Peyron F, Wallon M, Gay F, Delolme H, Briantais P, et al. Comparison of the safety and immunogenicity of two inactivated hepatitis A vaccines. *Adv Ther* 1997;**14**:116—24.
23. Goilav C, Zuckerman J, Lafrenz M, Vidor E, Lauwers S, Ratheau C, et al. Immunogenicity and safety of a new inactivated hepatitis A vaccine in a comparative study. *J Med Virol* 1995;**46**:287—92.
[24] Zuckerman JN, Kirkpatrick CT, Huang M. Immunogenicity and reactogenicity of Avaxim (160AU) as compared with Havrix (1440 EL.U) as a booster following primary immunization with

Havrix (1440 EL.U) against hepatitis A. *J Travel Med* 1998;**5**:18—22.
25. Flehmig B, Staedele H, Xueref C, Vidor E, Zuckerman J, Zuckerman A. Early appearance of neutralizing antibodies after vaccination with an inactivated hepatitis A vaccine. *J Infect* 1997;**35**:37—40.
26. Van Herck K, Beutels P, Van Damme P, Beutels M, Van den Dries J, Briantais P, et al. Mathematical models for assessment of long-term persistence of antibodies after vaccination with two inactivated hepatitis A vaccines. *J Med Virol* 2000;**60**:1—7.
27. Van Damme P, Thoelen S, Cramm M, De Groote K, Safary A, Meheus A. Inactivated hepatitis A vaccine: reactogenicity, immunogenicity, and long-term antibody persistence. *J Med Virol* 1994;**44**:446—51.
28. D'Argenio P, Adamo B, Cirrincione R, Gallo G. The role of vaccine in controlling hepatitis A epidemics. *Vaccine* 2003;**21**:2246—9.
29. Sagliocca L, Amoroso P, Stroffolini T, Adamo B, Tosti ME, Lettieri G, et al. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: a randomized trial. *Lancet* 1999;**353**:1136—9.
30. Abarca K, Ibanez I, Flores J, Vial PA, Safary A, Potin M. Efficacy of hepatitis A vaccination in children aged 12 to 24 months. *Arch Med Res* 2001;**32**:468—72.
31. Dominguez A, Salleras L, Carmona G, Batalla J. Effectiveness of a mass hepatitis A vaccination program in preadolescents. *Vaccine* 2003;**21**:698—701.
32. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;**55**(RR-7):1—23.
33. Valenzuela MT, Jacobs RJ, Arteaga O, Navarrete MS, Meyerhoff AS, Innis BL. Cost-effectiveness of universal childhood hepatitis A vaccination in Chile. *Vaccine* 2005;**23**:4110—9.