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Duration of protection against hepatitis A for the current two-dose vaccine compared to a three-dose vaccine schedule in children

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Abstract

Background—Hepatitis A is mostly a self-limiting disease but causes substantial economic burden. Consequently, United States Advisory Committee for Immunization Practices recommends inactivated hepatitis A vaccination for all children beginning at age 1 year and for high risk adults. The hepatitis A vaccine is highly effective but the duration of protection is unknown.

Methods—We examined the proportion of children with protective hepatitis A antibody levels (anti-HAV ≥20 mIU/mL) as well as the geometric mean concentration (GMC) of anti-HAV in a cross sectional convenience sample of individuals aged 12–24 years, who had been vaccinated with a two-dose schedule in childhood, with the initial dose at least 5 years ago. We compared a

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Potential conflicts of interest

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subset of data from persons vaccinated with two-doses (720 EL.U.) at age 3–6 years with a demographically similar prospective cohort that received a three-dose (360 EL.U.) schedule and have been followed for 17 years.

Results—No significant differences were observed when comparing GMC between the two cohorts at 10 ($P = 0.467$), 12 ($P = 0.496$), and 14 ($P = 0.175$) years post-immunization. For the three-dose cohort, protective antibody levels remain for 17 years and have leveled-off over the past 7 years.

Conclusion—The two- and three-dose schedules provide similar protection >14 years after vaccination, indicating a booster dose is not needed at this time. Plateauing anti-HAV GMC levels suggest protective antibody levels may persist long-term.

Keywords

Hepatitis A virus; Inactivated hepatitis A vaccine; RNA viruses; Enterovirus infections

1. Introduction

In the early 1990s, Alaska Native (AN) persons had an annual incidence of hepatitis A virus (HAV) infection that was approximately 40 times higher than that of non-Native Alaska residents, with outbreaks occurring among AN persons approximately every 7–10 years [1,2]. A pre-licensure clinical trial of hepatitis A vaccine was conducted at the time in children 3–6 years of age. This cohort has been followed regularly since then to determine long-term protection. This study used a three-dose regimen consisting of half the antigen (360 EL.U.) in each dose of the current licensed two-dose regimen (720 EL.U.) otherwise the vaccines were similar hepatitis A viral protein adsorbed on similar adjuvant [3]. We reported results from this study showing excellent interim protective levels of antibody to hepatitis A antigen (anti-HAV) at 10, 15 and 17 years [4–6].

To determine if the currently licensed two-dose regimen provides long-term protection comparable to the three-dose regimen, we recruited AN children who participated in a hepatitis B booster dose study and received two doses of hepatitis A vaccine after 1 year of age [7]. Others have reported the long term clinical results of the two-dose vaccination schedule in other geographical areas [8–10], herein we compare two-dose vaccination to the three-dose vaccination which is the longest followed cohort for HAV immunization.

2. Subjects and methods

2.1. Subjects

This study was approved by the Institutional Review Boards of the Alaska Area Native Health Service, Indian Health Service, and Centers for Disease Control and Prevention, as well as by two Alaska Native health organizations, the Southcentral Foundation and the Alaska Native Tribal Health Consortium. Consent to participate was received from one parent or guardian at the start of the study. At the time of recruitment, no participants reported any illness that included jaundice or icterus and none had been diagnosed with acute hepatitis. Medical records on each participant were reviewed and none revealed illness consistent with acute hepatitis A.

2.2. Methods

2.2.1. Two-dose cohort—A cohort of Alaska Native individuals participated in a long-term hepatitis B vaccine protection study. They had received a hepatitis B vaccine series (Recombivax®) starting at birth. From this group, we selected a convenience sample of children who had received hepatitis A vaccine after 1 year of age during a "catch-up" hepatitis A vaccination campaign offered to all children in Alaska. We attempted to obtain 100 participants who met our criteria for timely vaccination, a second dose within 6–12 months of the first dose, and recruit an equal number of children who received their first dose between 1–4, 5–9 and above 10 years of age. All participants were consented at the time of blood draw. Participants had received two doses of hepatitis A vaccine either HAVRIX™ (GlaxoSmithKline Biologicals, Rixenart, Belgium) or VAQTA ® (Merck, New Jersey, USA). Both vaccine doses contained 720 ELISA units [EL.U.] of hepatitis A viral protein adsorbed on aluminum hydroxide adjuvant, volunteers were vaccinated with the second dose between 6 and 12 months after the initial dose. The majority received the first dose of hepatitis A vaccine between 1–4 years (50.5%) of age followed by ages 5–9 (31.7%) and over 10 years of age (17.8%). We used the mean value of years since last vaccination to categorize the follow-up groups: specifically, the group evaluated 7.5 to <9 (mean: 8.2) years after second vaccination is designated the 8-year follow-up, the group evaluated 9 to <11 (mean: 10.2) years after second vaccination is designated the 10-year follow-up, the group evaluated 11 to <13 (mean: 12.4) years after second vaccination is designated the 12-year follow-up, and the group evaluated 13 to <15 (mean: 14.2) years after second vaccination is designated the 14-year follow-up.

2.2.2. Three-dose cohort—The original prospective three-dose cohort was comprised of 144 Alaska Native children (age 3–6 years) recruited for long-term follow-up and invited to be tested yearly for the first 5 years then approximately every 2 years thereafter. These volunteers were randomized to receive the inactivated hepatitis A vaccine, HAVRIX™ (360 EL.U. of hepatitis A viral protein adsorbed on aluminum hydroxide adjuvant with 0.5% w/v 2-phenoxyethanol as preservative, GlaxoSmithKline Biologicals, Rixenart, Belgium) on one of three schedules: "A" (0, 1, 2 months, $n = 51$), "B" (0, 1, 6 months, $n = 46$), or "C" (0, 1, 12 months, $n = 47$). For this analysis, we combined the three-dose cohorts (A, B, and C) into a single data set because at 10, 12, or 14 year follow-up periods after second vaccine dose these groups did not have statistically different anti-HAV GMC [4–6]. In addition, we recruited as many participants as possible for each time point. Not all volunteers could be reached or could participate at each time point; however, only those volunteers that received additional doses of HAV (more than three) were excluded from participating in future time points.

2.3. Laboratory methods

Sera were tested for anti-HAV using a modified ELISA (DiaSorin) assay. The results are quantitatively expressed in milli-international units (mIU) per milliliter (mL) with anti-HAV concentrations ≥20 mIU/mL, the lower limit of detection of the assay, were considered protective and this limit has been used in previous publications as the standard for protective anti-HAV. The methodology for this assay was the same as used in the long-term three-dose study [4–6].

2.4. Statistical analysis

All anti-HAV levels were log-transformed and analyzed using simple (two-dose schedule, cross-sectional convenience cohort) and repeated measures (three-dose schedule, prospective longitudinal cohort) analysis of variance (ANOVA). Data are reported as geometric mean concentrations (GMC) by vaccination schedule. Participants were stratified by age when the first vaccination dose was administered and time of follow-up since completing the last dose for the two-dose schedule. We compare anti-HAV GMC of demographically similar cohorts (age, ethnicity, gender) who received the two-dose to those who received the earlier three-dose vaccine; both of these cohorts represent volunteers that received their first dose of vaccine at 3–6 years of age.

3. Results

3.1. Effect of primary vaccination with a two dose schedule

The participants in this study (n = 101) had an average age of 17.6 years (min: 12.7 years, max: 23.4 years) and the time elapsed since the second dose of vaccine was an average of 11.1 years (range: 3.5–15.1 years; Table 1). When comparing groups who received the first vaccination at different ages (1–2, 3–6, and ≥7 years), the anti-HAV GMC levels were not statistically different ($P > 0.05$) at the 8, 10, 12, or 14 year follow-up after second vaccine dose (Table 2), although those vaccinated at 1–2 years consistently had the lowest average GMC levels at each time point. Five (5%) of the 101 participants, all ≥11 years after the second dose, had anti-HAV GMC < 20 mIU/ml, below the seroprotective level.

3.2. Comparison of primary vaccination with a two dose schedule versus a three dose schedule

We compare children in the two-dose cohort with those in the three-dose cohort who received the first vaccination dose between 3 to 6 years of age (Table 1). For any given follow-up time period, GMC levels were not statistically different ($P > 0.05$) comparing the three-dose to the two-dose vaccine schedule (Table 3). Additionally, comparing the anti-HAV GMCs at the 10, 12, 14, and ≥15 year follow up periods within the two-dose (GMC: 160, 298, 80, 43 mIU/mL) or within the three-dose vaccine schedule (GMC: 232, 201, 183, 210 mIU/mL), there were no statistically significant differences in GMCs over the 5 year time span ($P = 0.836$ and $P = 0.300$, respectively). Nearly every person immunized between 3–6 years of age on the two-dose or three-dose schedules demonstrated anti-HAV seroprotective levels (Table 4).

4. Discussion

Prior to 1996, Alaska Native people had the highest incidence of acute hepatitis A in the United States. A pre-licensure clinical trial of inactivated hepatitis A vaccine using a three-dose schedule was conducted in Alaska Native children ages 3–6 that found that the vaccine was 100% immunogenic and safe [4,5]. Initially the three-dose schedule was licensed and later the dosing regimen was modified to a two-dose that was found to be equally protective. Alaska became the first US state to institute universal hepatitis A vaccination for all children in 1996 and is required for school entry. Compliance is excellent with 93% of Alaska

adolescents having a complete hepatitis A vaccination schedule [11]. As a result, within a very short time span after universal vaccination was begun, the annual incidence of hepatitis A is now <1/100,000; the lowest in the world [12]. Thus, we believe there is no reservoir of HAV present to result in natural boosting in this population. Albeit, Alaska has isolated rural communities including some without a consistent source of treated water or sewer service and conditions exist that favor the return of hepatitis A outbreaks. Thus, it is crucial to keep vaccination a priority and demonstrate the long-term immunogenicity for both the two- and three-dose regimens to determine if booster doses are needed for protection.

The data presented in this report demonstrate that the currently licensed two-dose regimen of hepatitis A vaccine given in childhood is able to provide serologic levels of protection for at least 14 years in a geographically distinct cohort. Our data are unique in that we can compare them to a demographically similar cohort that has been followed for a longer period of time. Data from our study demonstrate that GMC values of the three-dose immunization cohort and the 14 year two-dose immunization cohort are not statistically different. Regardless of vaccine manufacturer (Merck or GlaxoSmithKline) that was used, the long-term immunogenicity is excellent. Thus, we predict the two-dose schedule will follow the same trend as the three-dose study and immunogenicity will persist at similar levels until at least 17 years. Two previous studies on the long-term immunogenicity of hepatitis A vaccine using the 2 dose schedule in children and adolescence have shown excellent long-term immunogenicity at 10 years [8,10]. Another study compared a two- and three-dose schedule using a combination hepatitis A and B vaccine with the same amount of antigen as in our study and demonstrated good immunogenicity at 10 years and the vaccination schedules elicit immune responses that are not statistically different [9].

Our comparative study has limitations. The numbers of participants in the cohorts are relatively small and data obtained on the two-dose cohort is cross-sectional whereas the three-dose study is a longitudinal follow-up of the same individuals tested over time.

Our group and others have used repeated measures log-linear mathematical models in the past to predict how long protective anti-HAV GMCs should remain above the minimum seroprotective level of 20 mIU/mL. These models predicted rates of decline for anti-HAV GMCs to persist above seroprotective levels for 15–32 years [4,5,13–16]. However, we observed no statistically significant difference between anti-HAV GMCs recorded between 10 and 14 years in this two-dose vaccine regimen and we have reported that they are also not different between 10 and 17 years for the three-dose immunization schedule [6]. Therefore the previously predicted rates of decline for anti-HAV GMC may significantly underestimate the longevity of seroprotective levels.

In order to show long-term protection beyond 14 or 17 years, continued observation of these cohorts and testing is required to determine whether booster doses are indicated. Now that we have shown no difference in the long-term immunogenicity between these cohorts, we plan to continue to follow only the three-dose cohort since we feel that the longitudinal data obtained will be the most valuable in determining how long protection will last and if booster doses are needed in this population. Our data support the conclusion that protective levels of anti-HAV persist and that observed levels of anti-HAV are not artificially elevated

by natural boosting (i.e. participants being exposed to infected persons) due to the high vaccination rates in children and fall in acute HAV incidence [12,17,18]. We speculate that in areas of high or intermediate endemicity, the GMC years after primary vaccination could be higher due to "natural boosting." In these areas it is possible that just one dose of hepatitis A may be sufficient to provide prolonged protection. We have found in previous studies this population that almost 100% achieve protective levels of anti-HAV after just one dose of vaccine [19] and that even when the second dose of vaccine was delayed up to 30 months, all persons had a booster response to the second dose. [20]

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Abbreviations

GMC	geometric mean concentration
anti-HAV	hepatitis A antibody
AN	Alaska Native persons
HAV	hepatitis A virus

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Table 1

Demographic characteristics of participants.

Schedule	Characteristics, all participants			
	Total (*n*)	**Age at first dose, mean (range), years**	**Female sex, *n* (%)**	**Alaska Native/American Indian, *n* (%)**
Two-dose	101	5.4 (1.0–16.7)	54 (53%)	101 (100%)
Three-dose	81	4.5 (3.1–6.1)	45 (56%)	81 (100%)
	Characteristics, children immunized with first dose between ages 3–6 years			
Two-dose	24	5.1 (3.1–6.9)	13 (54%)	24 (100%)
Three-dose	81	4.5 (3.1–6.1)	45 (56%)	81 (100%)

Table 2

Geometric mean concentrations (GMC) and 95% Confidence Intervals (CI) of antibody to hepatitis A virus (Anti-HAV) by follow up period after completing primary vaccination schedule and by age at first dose among a cohort of Alaska Native children who received two doses of vaccine.

Follow-up since second dose of HAV (years)	Age at first dose (years)			*P* value comparing three age groups
	1–2	3–6	≥7	
	Anti-HAV GMC (mIU/mL) (95% CI)	Anti-HAV GMC (mIU/mL) (95% CI)	Anti-HAV GMC (mIU/mL) (95% CI)	
< 7.5	none	none	148 (*n* = 1) (N/A)	N/A
≥ 7.5 to < 9	48 (*n* = 1) (N/A)	115 (*n* = 3) (12, 1114)	125 (*n* = 3) (11, 1358)	0.688
≥ 9 to < 11	144 (*n* = 10) (78, 263)	160 (*n* = 7) (94, 271)	201 (*n* = 17) (117, 343)	0.634
≥ 11 to < 13	98 (*n* = 26) (66, 147)	298 (*n* = 8) (51, 1749)	211 (*n* = 11) (112, 397)	0.054
≥ 13 to < 15	21 (*n* = 5) (6, 77)	80 (*n* = 5) (40, 159)	81 (*n* = 1) (N/A)	0.081
≥ 15	none	43 (*n* = 1) (N/A)	none	N/A

Table 3

Geometric mean concentrations (GMC) and 95% Confidence Intervals (CI) of hepatitis A virus (Anti-HAV) antibody by follow up time period after completing primary vaccination schedule and vaccination schedule used in Alaska Native children initially immunized between 3–6 years.

Follow-up since second dose of HAV (years)	**Vaccination Schedule**		***P* value comparing 3 and 2 dose schedules**
	3 Dose	**2 Dose**	
	Anti-HAV GMC (mIU/mL) (95% CI)	**Anti-HAV GMC (mIU/mL) (95% CI)**	
10	232 (*n* = 62) (165, 327)	160 (*n* = 7) (94, 271)	0.467
12	201 (*n* = 49) (135, 300)	298 (*n* = 8) (51, 1749)	0.496
14	183 (*n* = 56) (128, 261)	80 (*n* = 5) (40, 159)	0.175
≥ 15	210 (*n* = 58) (136, 325)	43 (*n* = 1) (N/A)	N/A
P value comparing each follow-up interval	0.300	0.836	

At each follow up period, we recruited all available participants that had not received additional booster doses of inactivated hepatitis A vaccine. The *P* values listed below the table compare the anti-HAV GMC observed at the listed follow-up interval by the type of vaccination schedule.

Table 4

Proportion with seroprotective antibody levels to hepatitis A virus (≥20 mIU/mL) by follow up time period and vaccination schedule among Alaska Native children initially immunized between 3–6 years of age.

Vaccination Schedule	Follow-up since second dose of HAV (years)			
	10	12	14	≥ 15
two-dose	7 (100%) of 7	8 (100%) of 8	5 (100%) of 5	1 (100%) of 1
three-dose	62 (100%) of 62	46 (94%) of 49	53 (95%) of 56	54 (93%) of 58