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Persistence of Seropositivity Among Persons Vaccinated for Hepatitis A During Infancy by Maternal Antibody Status: 15-Year Follow-up

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Abstract

The effect of passively transferred maternal antibody to hepatitis A virus (anti-HAV) on the duration of seropositivity after hepatitis A vaccination during infancy and early childhood is unclear. We obtained levels of anti-HAV at intervals through age 15–16 years among three groups of Alaskan Native children who initiated a two-dose inactivated hepatitis A vaccination series at ages 6 months (group 1), 12 months (group 2), and 15 months (group 3), each group randomized according to maternal anti-HAV status. Seropositivity (anti-HAV ≥ 20 mIU/mL) 30 years after the second vaccine dose among the three groups was predicted using a random effects model. One hundred eighty-three children participated in the study; follow-up did not differ significantly by vaccine group or maternal anti-HAV status. Although the frequency of seropositivity among all participants through age 10 years was high (100% among groups 2 and 3 and >90% among group 1), there was a decrease thereafter through age 15–16 years among group 1 children, who initiated vaccination at age 6 months (50%–75%), and among maternal anti-HAV-positive children in groups 2 and 3 (67%–87%), who initiated vaccination at ages 12 months and 15 months, respectively. Nonetheless, the model indicated that anti-HAV seropositivity should persist for 30 years after vaccination in 64% of all participants; among those seropositive at age 15–16 years, 84% were predicted to remain so for 30 years. **Conclusion:** Most children vaccinated during early childhood available for sampling maintained seropositivity through age 15–16 years; however, seropositivity was less frequent among those starting vaccination at age 6 months and among maternal antibody-positive participants who started vaccination at age 12 months or 15 months; overall, our findings support current vaccine recommendations and continued follow-up of this cohort.

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Since the introduction of the hepatitis A vaccine in the mid-1990s, hepatitis A incidence in the United States has fallen precipitously. During the prevaccination era (i.e., 1980–1995), approximately 22,000–36,000 cases of hepatitis A were reported annually in the United States.⁽¹⁾ From 1996 through 2006, the Advisory Committee on Immunization Practices incrementally expanded hepatitis A vaccine recommendations from groups at high risk of infection to universal vaccination of children aged ≥12 months.⁽¹⁾ Since then, the number of hepatitis A cases in the United States has decreased approximately 90%, from 13,397 in 2000 to 1781 in 2013; incidence was lowest among persons aged <19 years.⁽²⁾

Two doses of inactivated hepatitis A vaccine are highly immunogenic in virtually all healthy children and adults, resulting in postvaccination concentrations of antibody to hepatitis A virus (anti-HAV) that are likely to persist at protective levels for at least 30 years.⁽³⁾ In contrast, among infants born to anti-HAV-positive mothers (from either natural infection or vaccination), the presence of passively acquired maternal anti-HAV may persist until age 12 months and may substantially reduce hepatitis A vaccine immunogenicity.^(4–6)

Alaska became the first US state to institute universal hepatitis A vaccination for all children in 1996, at which time Alaska Native persons had the highest incidence of acute hepatitis A in the United States. Passively acquired maternal antibody occurs in populations with endemic HAV infection and in whom the majority of infections occur in children. In light of concerns about interference of maternal antibody with hepatitis A vaccine immunogenicity, the Centers for Disease Control and Prevention (CDC) and the Indian Health Service identified a need to determine the optimal immunization schedule for American Indian/Alaska Native infants as well as all other infants and children. In 1997, the Alaska Native Tribal Health Consortium and the CDC began a study in infants and children aged 6–24 months to determine the best age at which to begin to administer this vaccine, the early results of which informed the decision of the US Food and Drug Administration to lower the age of hepatitis A vaccine initiation from 24 months to 12 months [7]. Subsequently, the objective of continued follow-up of the original cohort has been to determine whether administration of hepatitis A vaccine in early childhood will provide long-term protection into adulthood, when clinical icteric hepatitis is a greater risk after exposure. Follow-up of this cohort by testing anti-HAV titer has been conducted through 15 years after the primary immunization series; herein, we describe these most recent findings.

Patients and Methods

STUDY POPULATION AND VACCINATION

Participants included in this follow-up study were adolescents originally enrolled as infants and young children between the ages of 6 months and 15 months in a phase 4 immunogenicity study reported by Bell et al.⁽⁷⁾ In that study, participants were recruited among mothers and their infants who received care in the prenatal and pediatric clinics of the Southcentral Foundation Primary Care Center at the Alaska Native Medical Center in Anchorage, Alaska, and the Anchorage Neighborhood Health Center. Mothers provided informed consent and were tested for total anti-HAV using a standard, commercially available assay (HAVAB; Abbott Laboratories, Abbott Park, North Chicago, IL). Among mothers testing positive for anti-HAV, hepatitis A vaccination status was confirmed by state

vaccine registry. Infants and young children were then randomized to receive two doses of inactivated hepatitis A vaccine (HAVRIX, 720 enzyme-linked immunosorbent assay units per dose; Glaxo SmithKline Biologicals, Rixensart, Belgium) on three different schedules: at ages 6 and 12 months (group 1), 12 and 18 months (group 2), and 15 and 21 months (group 3). Within each group, subjects were stratified to achieve a relatively equal number of children born to anti-HAV-positive and anti-HAV-negative mothers. The study was approved by the institutional review boards of the Alaska Area Indian Health Service and the CDC, by two Alaska Native Health Boards (Alaska Native Tribal Health Consortium and Southcentral Foundation), as well as by the US Food and Drug Administration under an Investigational New Drug Application phase 4. Participants also received other routine recommended vaccinations during the study period.

SAMPLING TIME POINTS AND MEASUREMENT OF ANTI-HAV

Serum samples were collected from study participants beginning at 1 month and 6 months after the second hepatitis A vaccine dose and postvaccination follow-up at ages 3 years, 5 years, 7 years, 10 years, 12–14 years, and 15–16 years (a total of eight sampling time points). Serum samples obtained through age 10 years were tested for anti-HAV in 2010 by the Assay Development and Diagnostic Reference Laboratory of the Division of Viral Hepatitis, CDC, and for the most recent study follow-up (i.e., among participants aged 12–14 and 15–16 years), at the CDC Arctic Investigations Program Laboratory in Anchorage, Alaska. Both labs used the ETI-AB-HAVK-PLUS enzyme immunoassay diagnostic kit in accordance with the manufacturer's instructions (DiaSorin Inc., Stillwater, MN). The ETI-AB-HAVK-PLUS High Positive Control, containing 1200–2000 mIU/mL anti-HAV-WHO 2nd International Standard (1998), was serially diluted; and dilutions were used as calibrators in the assay to quantify total anti-HAV in the measuring range between 5 mIU/mL and 80 mIU/mL. Serum samples with total anti-HAV levels >80 mIU/mL were further diluted as necessary to determine the actual anti-HAV levels. Geometric mean concentrations (GMCs) of anti-HAV were calculated using levels obtained from all participants, not only those who were seropositive.

DATA ANALYSIS

The original study was designed with a sample size of at least 30 subjects per subgroup (60 subjects per group), which resulted in 80% power to detect at least a two-fold difference in anti-HAV GMCs between subgroups in each group ($\alpha = 0.05$, two-sided). For the long-term follow-up study, only children enrolled at the Alaska Native Medical Center were invited to participate. Participants were excluded from further study if they received additional doses of hepatitis A vaccine ($n = 11$) or moved away from Anchorage ($n = 60$).

Anti-HAV levels were log-transformed before the statistical analysis. Antibody levels below the lower limit of detection of the assay were assigned a value of 5 mIU/mL. Comparisons of log anti-HAV levels by vaccination schedules and by maternal anti-HAV status at each time point were made using linear regression analysis. We analyzed the data according to vaccination schedule and maternal anti-HAV status and, among group 1 infants, by source of maternal anti-HAV (natural infection versus vaccine-induced). GMCs were calculated by taking the log transformation of the estimated anti-HAV levels.

Subjects with anti-HAV levels ≥ 20 mIU/mL were considered seropositive. The proportion of study subjects who were seropositive was compared within and among groups at the various sampling time points using logistic regression. Correlation between log anti-HAV levels at each time point and peak log anti-HAV levels (i.e., 1 month after second dose) through 15–16 years of age were measured with the Pearson correlation. Analyses were performed in SAS, version 9.2.

We also developed a random effects model of $\ln(\text{anti-HAV})$ levels over time. Fractional polynomials were used to determine the functional form of the time since vaccination curve; we included all data points after the initial 1-month follow-up, which enabled the initial postvaccination anti-HAV level to be used as a predictor in the model and which fit the data well for the range of observed data.

Results

STUDY POPULATION AND FOLLOW-UP

Of 311 infants and young children randomized in the original study, 183 participants were included in the long-term follow-up study (which began at age 3 years); 99 (50%) were males, and 189 (96%) were Alaska Native/American Indian. Sixty-two (31%) participants had results available at all eight time points, 161 (81%) had results at five or more time points, and 181 (92%) had results at four or more time points. The proportion of children with follow-up did not differ significantly by vaccine group or maternal anti-HAV status.

PERSISTENCE OF ANTI-HAV AFTER HEPATITIS A VACCINATION: SEROPOSITIVITY AND GMCS

The persistence of seropositivity after two doses of hepatitis A vaccine (percentage of vaccine recipients with anti-HAV >20 mIU/mL) and anti-HAV GMCs by study group and maternal anti-HAV status are shown in Table 1. The proportion of children in group 1 who remained seropositive was consistently lower than that of children in groups 2 and 3 who remained comparably seropositive to each other during follow-up. For example, the proportion of children who remained seropositive at age 15–16 years was 75% and 61% among group 1 children of anti-HAV-negative and anti-HAV-positive mothers, respectively, compared with 100% and 67% among children in groups 2 and 3. Regardless of group, the proportion who remained seropositive was lower consistently among maternal anti-HAV-positive than maternal anti-HAV-negative children. Compared with children in group 1, a significantly higher proportion of children in groups 2 and 3 remained seropositive at ages 7 years, 10 years, 12–14 years, and 15–16 years ($P=0.006$, $P=0.001$, $P=0.007$, $P=0.009$, respectively) among children of anti-HAV-negative mothers and ages 10 years and 12–14 years ($P=0.015$ and $P=0.040$, respectively) among children of anti-HAV-positive mothers. Within each group, there were no significant differences in the persistence of seropositivity between participants born to anti-HAV-negative versus anti-HAV-positive mothers until 12–14 years of age, but significant differences appeared at 15–16 years of age for group 2 and group 3 children (100% for maternal anti-HAV-negative versus 67% for maternal anti-HAV-positive, $P=0.032$ and $P=0.016$, respectively).

There was a significant decrease in anti-HAV levels over time within each group and maternal status category until participants reached age 12–14 years. Among group 1 children, GMCs were not statistically different between ages 12–14 years and 15–16 years, irrespective of maternal antibody status (37 mIU/mL and 49 mIU/mL among children of anti-HAV-negative mothers and 20 mIU/mL and 27 mIU/mL among those of anti-HAV-positive mothers). Group 1 children had consistently lower levels of anti-HAV than children in groups 2 and 3. Among participants in groups 2 and 3 combined, GMCs were statistically lower with the passage of time except between 1 month after dose 2 and age 3 years among maternal anti-HAV-negative and anti-HAV-positive children and among those with anti-HAV-positive mothers between age 10 years and age 12–14 years. Regardless of study group, children with a mother who was anti-HAV-positive had consistently lower anti-HAV levels than children whose mothers were negative, but this difference was not significant at any time point after age 7 years.

Anti-HAV levels were consistently higher among females than males. This difference was statistically significant at every time point among group 2 and 3 children with no maternal anti-HAV and at the first two time points in group 1 children with mothers with no detectable anti-HAV. No gender differences were observed with regard to seropositivity through 10 years of follow-up. However, in the current follow-up, we found that the GMCs of maternal antibody-positive ($n = 11$) and antibody-negative ($n = 8$) group 1 males at age 12–14 years were <20 mIU/mL and that the GMC of maternal antibody-positive males in groups 2 and 3 ($n = 9$) at age 15–16 years was merely 25 mIU/mL.

When included in a linear regression model of $\ln(\text{anti-HAV})$ at each time point, group, maternal status, and gender all remained statistically significant at every time point. The two-way interactions of each of these variables were not statistically significant at any time point. Native ethnicity was not significantly associated with anti-HAV levels at any time point.

Anti-HAV levels remained highly correlated with peak anti-HAV levels (1 month after second dose) through 15–16 years of age: Spearman rank correlations with peak anti-HAV level during the most recent time points were age 12–14 years ($R = 0.51$, $P < 0.001$) and age 15–16 years ($R = 0.51$, $P < 0.001$).

EFFECT OF NATURAL VERSUS VACCINE-DERIVED MATERNAL ANTI-HAV

To determine whether there was a difference in the persistence of anti-HAV among children in group 1 whose mothers were anti-HAV-positive as a result of natural infection versus vaccination, the GMC levels at every time point after the second vaccine dose were compared for children in the following categories: (1) children of anti-HAV-negative mothers, (2) children whose mothers were anti-HAV-positive due to previous HAV infection (i.e., natural immunity), and (3) children born to mothers who were anti-HAV positive as a result of vaccination received prior to pregnancy (Table 2). There were statistically significant differences ($P < 0.05$) between the GMCs of the three group 1 categories for the first three time periods and 12–14 years of age but not for the other time points. These differences, when present, were between group 1 children whose mothers had natural

immunity to HAV (who had lower GMCs) compared with the GMCs of maternal antibody-negative children and children of vaccinated mothers.

PROJECTED DURATION OF ANTI-HAV SEROPOSITIVITY AFTER VACCINATION

Results from a random effects model of $\ln(\text{anti-HAV})$ levels over time, which included all data points after the initial 1-month follow-up, are displayed in Fig. 1. Of the total number of anti-HAV levels that would have been obtained if all study participants had been sampled at all time points, 77% were actually obtained and included in the model. Among participants sampled at age 15–16 years, 80% were seropositive; of these, the model predicted that 84% would still be seropositive at 30 years after the second vaccine dose. Overall the model predicted that 64% of participants would be seropositive at 30 years.

Discussion

This study is the first to report the effects of maternal anti-HAV status on the persistence of anti-HAV seropositivity (i.e., 20 mIU/mL) through age 15–16 years after administration of two doses of inactivated hepatitis A vaccine among three groups of infants and toddlers beginning at age 6–21 months. In contrast to the 10-year follow-up of this cohort, in which there was a high frequency of seropositivity among all three study groups through age 10 years (100% among groups 2 and 3 and >90% among group 1 children, irrespective of maternal antibody status),⁽⁸⁾ our findings through age 15–16 years indicate a notable decline after age 10 years in the frequency of anti-HAV seropositivity, particularly among all group 1 children, who were vaccinated beginning at age 6 months (seropositivity 50%–75%), and among maternal anti-HAV-positive children in groups 2 and 3 (67%–87%). Among group 2 and 3 participants, who received their first of two doses of vaccine at ages 12 and 15 months, respectively, anti-HAV seropositivity remained >90% through age 15–16 years among all maternal anti-HAV-negative participants. However, among group 2 and 3 maternal anti-HAV-positive children, only 67% of participants were seropositive at age 15–16 years, even though group 3 maternal anti-HAV-positive children had higher anti-HAV GMCs 1 month after dose 2 than any children in groups 1 and 2. It appeared, then, that maternal antibody-positive status even affected the duration of seropositivity among some participants who initiated vaccination at age 15 months, despite the likelihood that levels of maternal anti-HAV among the majority of vaccinees by that age should have been undetectable,^(5,6,9,10) and that anti-HAV GMCs 1 month after dose 2 were similar between group 3 maternal anti-HAV-negative versus anti-HAV-positive children (i.e., 1613 mIU/mL versus 1577 mIU/mL, respectively). This phenomenon bears watching during subsequent observations of this cohort, given the potential detrimental effect of maternal anti-HAV on long-term maintenance of anti-HAV levels among persons vaccinated early in life. In this study, there were no participants vaccinated at ages 12 and 15 months (groups 2 and 3) whose maternal antibody positivity was the result of vaccination, so we are unable to tell whether there would be any interference among such infants in low HAV endemic countries, where recommendations suggest hepatitis A vaccination beginning at age 12 months.^(1,11) Other investigators have examined the effect of maternal anti-HAV on infant response to hepatitis A vaccination as well as the potential modification of the severity of neonatal diseases afforded by the transfer of maternal antibody in utero. A review of a number of studies

involving hepatitis A vaccination of infants as young as age 6 weeks highlighted the difference in vaccine response according to maternal antibody status. Although all the studies reviewed showed similar levels of seroconversion after vaccination among infants, with GMCs well above “the minimal protective level” irrespective of maternal anti-HAV status, maternal antibody-negative infants had higher postvaccination GMCs than their anti-HAV-positive counterparts.⁽¹²⁾ Another review and separate commentary examined the influence of maternal immunization on infant immune responses, in particular the potential salutary effects of maternal vaccination on the prevention of illness during pregnancy and subsequent modification of some infant infectious diseases after delivery, when neonatal response to vaccination is limited.^(13,14) With regard to the present subject, it is conceivable that maternal hepatitis A vaccination (if the mother is susceptible) could result in sufficient transfer of anti-HAV to protect against infant HAV infection before initiation of the vaccine series.

In countries with growing economies and improving living conditions, where an epidemiologic shift from high to intermediate HAV incidence may evolve rapidly, hepatitis A control programs may need to consider the age of hepatitis A vaccine initiation based on maternal anti-HAV prevalence and the likelihood of HAV exposure during early childhood.^(15,16) We found that children in group 1 who received vaccination starting at age 6 months consistently had lower anti-HAV GMCs than group 2 and 3 children during follow-up. Although GMCs for all three groups (Table 1), regardless of maternal antibody status, remained at or above the level of seropositivity through age 15–16 years, some children in maternal antibody-positive group 1 (50% [12/24] at age 12–14 years and 39% [7/18] at 15–16 years) and groups 2 and 3 (33% [7/21] at age 15–16 years) had anti-HAV levels <20 mIU/mL. Administration of hepatitis A vaccine to children aged <12 months might be useful (1) in countries where HAV infection occurs early in life and (2) for preexposure and postexposure prophylaxis for children aged 6–12 months if immunoglobulin is not available,⁽⁵⁾ which might include children traveling with their parents to endemic regions for prolonged periods of time. One month after the first vaccine dose in the original phase 4 immunogenicity study of this cohort, 54% (anti-HAV GMC 49 mIU/mL) and 94% (anti-HAV GMC 173 mIU/mL) of maternal antibody-negative and antibody-positive infants who initiated hepatitis A vaccination at age 6 months were seropositive, respectively. Future studies could examine the practical uses of the hepatitis A vaccine for children aged <12 months under the aforementioned conditions.

To determine whether the source of maternal anti-body might affect the persistence of anti-HAV among vaccinated infants, we examined the effect of vaccine-induced versus naturally induced maternal anti-HAV on GMCs among group 1 children. Group 1 children whose mothers had natural immunity to HAV had lower GMCs at all follow-up time points (except for age 15–16 years) than children whose mothers had vaccine-induced immunity or children of anti-HAV-negative mothers, although these differences were significant only for the first three time points and at age 12–14 years. There were no significant differences in anti-HAV GMCs between children of anti-HAV-negative and hepatitis A-vaccinated mothers. Notably, as illustrated in Table 2, a substantial proportion (58% [15/26]) of children from mothers who were anti-HAV-positive due to natural infection were no longer seropositive from ages 10 through 15–16 years, whereas those of vaccinated mothers

remained seropositive during follow-up except for a smaller proportion (36% [9/ 25]) of children at ages 12–14 and 15–16 years who became seronegative. Thus, it appeared that maternal antibody from natural infection had a more pronounced effect on the long-term persistence of anti-HAV than did maternal antibody from vaccination. As hepatitis A viral infection results in higher anti-HAV levels than those produced by vaccination,^(6,7) it is likely that higher transplacental anti-HAV levels among children of mothers with a history of HAV infection resulted in more pronounced suppression of the immunologic response to hepatitis A vaccine.⁽¹³⁾ Although experimental studies in mice have suggested that vaccines sharing similar epitopes as those recognized by maternal antibodies might result in reduced infant vaccine response,⁽¹⁷⁾ such a phenomenon was not evident in our study. It seems, however, with the passage of time after vaccination, that seropositivity wanes among infant vaccinees of anti-HAV-positive mothers, irrespective of the source of maternal antibody.

In this respect, it is worth noting that despite low overall hepatitis A incidence in the United States, HAV infection still occurs among susceptible persons, particularly among unvaccinated adults who were not exposed to HAV during childhood. Although hepatitis A incidence has plummeted since introduction of the vaccine, in 2013 a total of 1781 cases of hepatitis A were reported from 50 states to the CDC, a 14% increase from 2012. This increase reflects cases identified during a large hepatitis A outbreak from imported pomegranate arils consumed by unvaccinated persons in several southwestern states and Hawaii.^(2,18) Another hepatitis A outbreak in the United States occurred in 2013 among unvaccinated adults with developmental disabilities in group homes in Michigan.⁽¹⁹⁾ More recently, an outbreak of hepatitis was identified among unvaccinated travelers returning to the United States from the Caribbean coast of Mexico (CDC, unpublished data). Coinciding with recent trends in HAV seroprevalence in the United States, in which anti-HAV prevalence among adults has decreased (and susceptibility to infection increased),^(20,21) the majority of hepatitis A cases in these outbreaks, and among incident hepatitis A cases nationwide,⁽²⁾ occurred among adults. Whether such susceptibility might apply to vaccinated persons who have lost anti-HAV with the passage of time, such as vaccinated infants of anti-HAV-positive mothers, remains to be seen. As is the case with persons who have lost antibody to hepatitis B virus (HBV) surface antigen years after primary immunization, there is evidence to suggest persistence of cell-mediated immune memory despite a decrease in anti-HAV among persons vaccinated for hepatitis A.^(22–25) If such persons are exposed to HAV, the relatively long incubation period from exposure to onset of illness (4–8 weeks) might result in time enough for cellular immunity to mount a response sufficient to prevent symptomatic hepatitis. Indeed, such a dynamic is operative in “breakthrough” HBV infection, in which persons who have low or undetectable residual antibody to HBV surface antigen many years after vaccination may develop serologic evidence of infection (i.e., antibody to HBV core antigen) but do not have symptomatic illness or develop chronic infection after HBV exposure. However, in contrast to the relatively low transmission risk from breakthrough HBV infection among hepatitis B-vaccinated persons, it is unknown whether breakthrough HAV infection could occur among vaccinated persons and whether such persons, even those with asymptomatic break-through infection, could infect susceptible persons.

We found anti-HAV levels to be consistently higher among female children. Another study found that male sex was significantly associated with lower GMCs 10 years after receipt of three doses of inactivated hepatitis A vaccine among an unselected sample of adolescents and adults.⁽²⁶⁾ In that study, as well as ours, no gender differences were observed with regard to seropositivity through 10 years of follow-up. However, in the current follow-up, we found that the GMC of group 1 males at age 12–14 years was <20 mIU/mL and that the GMCs among maternal antibody-positive males in groups 2 and 3 at age 15–16 years were nearly at the threshold of seronegativity. The clinical significance of this finding is unclear, although follow-up of this cohort should continue to examine the frequency of seropositivity according to sex to determine whether such differences persist.

Nonetheless, among our cohort of children vaccinated during infancy and early childhood who were available for follow-up sampling, most (80%) maintained seropositivity through age 15–16 years; of those who remained seropositive at age 15–16 years, the model predicted that 84% would still be seropositive 30 years after the second vaccine dose. Thus, these data overall support current universal childhood US hepatitis A vaccine recommendations (i.e., among children aged 12 months–18 years, two doses of inactivated HAVRIX [0, 6–12 months] or VAQTA [0, 6–18 months]) and do not suggest a need for vaccine booster doses. Other modeling studies of adults vaccinated for hepatitis A have predicted similar durations of sustained seropositivity.^(27,28) In a recent study, investigators applied mathematical modeling to predict that at least 95% of persons vaccinated as adults would remain seropositive after 30 years and at least 90% would remain positive after 40 years.⁽²⁹⁾

This study is subject to several limitations. As shown in Table 1, the number of participants who were sampled through age 15–16 years from each of the categories and subcategories was approximately one-half of those initially enrolled in the follow-up study, and not all participants who remained had been sampled at all earlier time points. Therefore, the reduction in sample size could have affected our ability to detect statistically significant differences between subgroups; however, the number of time points sampled did not differ significantly by group or maternal antibody status. Second, maternal quantitative anti-HAV levels were not obtained in the original immunogenicity study but may have provided a more nuanced understanding of infant vaccine response, particularly with the assessment of the effect of maternal antibody derived from vaccination versus natural infection on infant response to hepatitis A vaccine. Third, the lowest anti-HAV level needed to confer protection has not been determined.^(24,25) Other studies have used a lower limit of detection of anti-HAV that ranged, depending on the assay used, from 10 mIU/mL to 33 mIU/mL. As we used a level of 20 mIU/mL, our determinations of seropositivity prevalence could have been comparatively too high or low. Other investigators have highlighted the variability among anti-HAV assays at relatively lower levels of antibody, which may affect assessment of seropositivity based on specific cutoff values⁽³⁰⁾; however, it is likely that such an effect was mitigated by our using the same assay for all study samples. Fourth, as our study cohort was comprised of Alaska Native children, the results we obtained may not be representative of other populations with different racial and ethnic compositions. However, previous vaccination studies have shown no difference in response to vaccination between Alaska Native persons and persons of other races/ethnicities.⁽²⁴⁾

In conclusion, this study demonstrated that seropositivity to hepatitis A persisted until at least age 15–16 years for most persons who initiated vaccination at age 6–21 months, and modeling suggested that seropositivity should persist for most persons for at least 30 years. Overall, these data support current US hepatitis A vaccine recommendations and do not suggest a need for vaccine booster doses. However, the prevalence of seropositivity among vaccinated infants and children whose mothers were anti-HAV-positive decreased after age 10 years; at ages 12–14 and 15-years, one of three such children no longer had levels of anti-HAV above 20 mIU/mL. Continued follow-up of this cohort will be valuable to determine whether the prevalence of seropositivity continues to decrease, regardless of maternal antibody status. To determine whether breakthrough infection among persons vaccinated for hepatitis A occurs, it is critical for hepatitis surveillance programs to determine the vaccination status of all reported cases of acute hepatitis A.

Acknowledgments

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Abbreviations:

anti-HAV	antibody to HAV
CDC	Centers for Disease Control and Prevention
GMC	geometric mean concentration
HAV	hepatitis A virus
HBV	hepatitis B virus

REFERENCES

- 1). Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006;55:1–23.
- 2). Centers for Disease Control and Prevention. Surveillance for viral hepatitis—United States, 2013 <http://www.cdc.gov/hepatitis/Statistics/2013Surveillance/index.htm>. Accessed May 23, 2015.
- 3). Racznik GA, Bulkow LR, Bruce MG, Zanis CL, Baum RL, Snowball MM, et al. Long-term immunogenicity of hepatitis A virus vaccine in Alaska 17 years after initial childhood series. J Infect Dis 2013;207:493–496. [PubMed: 23204169]
- 4). Piazza M, Safary A, Vegnente A, Soncini R, Pensati P, Sardo M, et al. Safety and immunogenicity of hepatitis A vaccine in infants: a candidate for inclusion in the childhood vaccination programme. Vaccine 1999;17:585–588. [PubMed: 10075165]
- 5). Dagan R, Amir J, Mijalovsky A, Kalmanovitch I, Bar-Yochai A, Thoelen S, et al. Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody. Pediatr Infect Dis J 2000;19:1045–1052. [PubMed: 11099084]
- 6). Letson GW, Shapiro CN, Kuehn D, Gardea C, Welty TK, Krause DS, et al. Effect of maternal antibody on immunogenicity of hepatitis A vaccine in infants. J Pediatr 2004;144:327–332. [PubMed: 15001936]
- 7). Bell BP, Negus S, Fiore AF, Plotnik J, Dhotre KB, Williams J, et al. Immunogenicity of an inactivated hepatitis A vaccine in infants and young children. Pediatr Infect Dis J 2007;26:116–122. [PubMed: 17259872]

- 8). Sharapov UM, Bulkow LR, Negus SE, Spradling PR, Homan C, Drobeniuc J, et al. Persistence of hepatitis A vaccine induced seropositivity in infants and young children by maternal antibody status: 10-year follow-up. *HEPATOLOGY* 2012;56:516–522. [PubMed: 22371069]
- 9). Burke DS, Nimmannitya S. Passively acquired antibody to hepatitis A virus in Thai infants. *Southeast Asian J Trop Med Public Health* 1980;11:415–416. [PubMed: 7444583]
- 10). Vargas V, Pedreira JD, Esteban R, Hernandez JM, Guardia J, Bacardi R. Materno-fetal transmission of hepatitis A antibody. *Acta Paediatr Scand* 1980;69:533. [PubMed: 7446103]
- 11). World Health Organization. WHO position paper on hepatitis A vaccines. *Wkly Epidemiol Rec* 2000;75:38–44. [PubMed: 10693358]
- 12). Vidar E. Vaccination of newborns against hepatitis A in the presence of maternally derived antibodies. *J Comp Pathol* 2007; 137:S42–S45. [PubMed: 17555761]
- 13). Englund JA. The influence of maternal immunization on infant immune responses. *J Comp Pathol* 2007;137:S16–S19. [PubMed: 17553516]
- 14). Englund JA. Maternal immunization—promises and concerns. *Vaccine* 2015;33:6372–6373. [PubMed: 26263199]
- 15). Verma R, Khanna P. Hepatitis A vaccine should receive priority in National Immunization Schedule in India. *Hum Vaccin Immunother* 2012;8:1132–1134. [PubMed: 22854671]
- 16). Chen Y, Zhang XJ, Zhao YL, Zhang YH, Wang SM, Hao ZY, et al. Waning of anti-HAV immunity in Shijiazhuang Prefecture, Hebei Province, China: a comparison of seroprevalence between 1992 and 2011. *Vaccine* 2014;32:6227–6232. [PubMed: 25258099]
- 17). Siegrist CA, Cordova M, Brandt C, Barrios C, Berney M, Tougne C, et al. Determinants of infant responses to vaccines in the presence of maternal antibodies. *Vaccine* 1998;16:1409–1414. [PubMed: 9711780]
- 18). Collier MG, Khudyakov Y, Selvage D, Adams-Cameron M, Epton E, Cronquist A, et al. Outbreak of hepatitis A in the USA associated with frozen pomegranate arils imported from Turkey: an epidemiological case study. *Lancet Infect Dis* 2014; 14:976–981. [PubMed: 25195178]
- 19). Bohm SR, Berger KW, Hackert PB, Renas R, Brunette S, Parker N, et al.; Centers for Disease Control and Prevention. Hepatitis A outbreak among adults with developmental disabilities in group homes—Michigan, 2013. *MMWR Morb Mortal Wkly Rep* 2015; 64:148–152. [PubMed: 25695320]
- 20). Ly KN, Klevens RM. Trends in disease and complications of hepatitis A virus infection in the United States, 1999–2011: a new concern for adults. *J Infect Dis* 2015;212:176–182. [PubMed: 25637352]
- 21). Ly KN, Klevens RM, Jiles RB. Letter to the editor in response to the editorial by Dr. Kenrad Nelson entitled, “The changing epidemiology of hepatitis A virus infections in the United States.” *J Infect Dis* 2015;212:1009–1010. [PubMed: 25784730]
- 22). Van Herck K, Van Damme P, Lievens M, Stoffel M. Hepatitis A vaccine: indirect evidence of immune memory 12 years after the primary course. *J Med Virol* 2004;72:194–196. [PubMed: 14695659]
- 23). Bian GL, Ma R, Dong HJ, Ni HX, Hu FJ, Chen Y, et al. Long-term clinical observation of the immunogenicity of inactivated hepatitis A vaccine in children. *Vaccine* 2010;28:47984801.
- 24). Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines. A systematic review. *Vaccine* 2012;31:3–11. [PubMed: 22609026]
- 25). Van Damme P, Banatvala J, Iwarson S, McMahon B, Van Herck K, Shouval D, et al. Hepatitis A booster vaccination: is there a need? *Lancet* 2003;362:1065–1071. [PubMed: 14522539]
- 26). Rendi-Wagner P, Korinek M, Mikolasek A, Vecsei A, Kollaritsch H. Epidemiology of travel-associated and autochthonous hepatitis A in Austrian children, 1998 to 2005. *J Travel Med* 2007;14:248–253. [PubMed: 17617847]
- 27). Van Herck K, Van Damme P. Inactivated hepatitis A vaccine-induced antibodies: follow-up and estimates of long-term persistence. *J Med Virol* 2001;63:1–7. [PubMed: 11130881]
- 28). Hens N, Habteab Ghebretinsae A, Hardt K, Van Damme P, Van Herck K. Model based estimates of long-term persistence of inactivated hepatitis A vaccine-induced antibodies in adults. *Vaccine* 2014;32:1507–1513. [PubMed: 24508042]

- 29). Theeten H, Van Herck K, Van Der Meeren O, Crasta P, Van Damme P, Hens N. Long-term antibody persistence after vaccination with a 2-dose Havrix (inactivated hepatitis A vaccine): 20 years of observed data, and long-term model-based predictions. *Vaccine* 2015;33:5723–5727. [PubMed: 26190091]
- 30). Agence française de sécurité sanitaire des produits de santé. Rapport du Contrôle de marche des dispositifs médicaux de diagnostic in vitro pour la détection et le dosage des anticorps totaux anti-VHA. Published September 2007 http://ansm.sante.fr/var/ansm_site/storage/original/application/f2cb9185991b8d6db2f86093a97a341a.pdf. Accessed November 22, 2015.

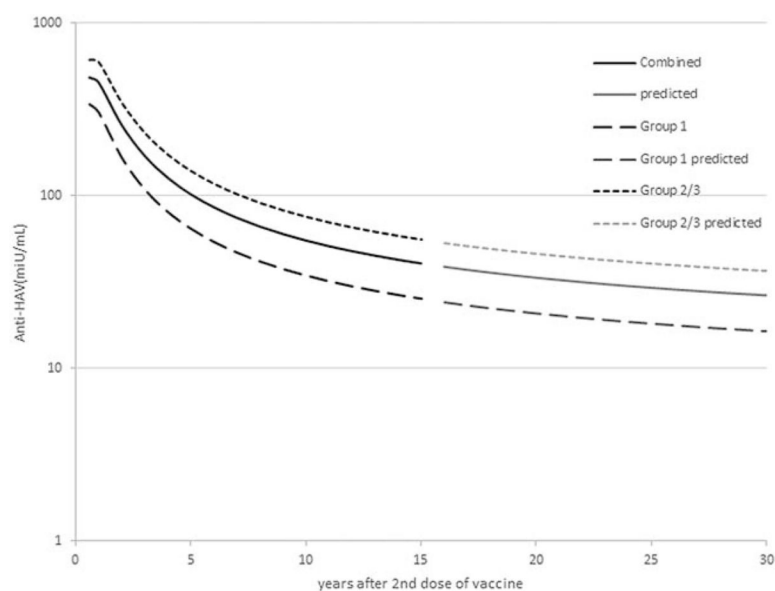


FIG. 1.

Random effects model of $\ln(\text{anti-HAV})$ levels over time with predicted values to 30 years after vaccination. Fractional polynomials were used to determine the functional form of the time since vaccination curve—terms included $(\text{time since second dose})^{-1}$ and $(\text{time since second dose})^{-1/2}$. The model included all data points after the initial 1-month follow-up after receipt of the second hepatitis A vaccine dose.

TABLE 1.
Anti-HAV Levels After Two Doses of Hepatitis A Vaccine by Group (Initial Vaccination Schedule), Maternal Anti-HAV Status, and Follow-up Period

Group*		1 Month After Dose 2			3 Years of Age			7 Years of Age			10 Years of Age			12–14 Years of Age			15–16 Years of Age		
		Maternal Anti-HAV Status	<i>n</i>	% Positive	GMC, mIU/mL (95% CI)	<i>n</i>	% Positive	GMC, mIU/mL (95% CI)	<i>n</i>	% Positive	GMC, mIU/mL (95% CI)	<i>n</i>	% Positive	GMC, mIU/mL (95% CI)	<i>n</i>	% Positive	GMC, mIU/mL (95% CI)	<i>n</i>	% Positive
1		Neg	40	100%	1196 (855–1673)	36	100%	219 (139–346)	33	97%	65 (44–97)	31	94%	45 (31–65)	22	59%	37 (22–62)	20	75%
		Pos	33	100%	668 (373–1199)	35	100%	120 (78–185)	31	100%	50 (35–72)	22	91%	33 (21–52)	24	50%	20 (14–30)	18	61%
2		Neg	37	100%	1513 (1095–2091)	35	100%	597 (433–824)	30	100%	154 (104–227)	21	100%	97 (61–155)	21	95%	75 (49–116)	17	100%
		Pos	17	100%	988 (528–1849)	16	100%	449 (231–870)	14	100%	71 (37–135)	9	100%	82 (32–207)	10	80%	57 (25–129)	9	67%
3		Neg	36	100%	1613 (1219–2135)	35	100%	506 (353–725)	34	100%	136 (94–195)	27	100%	100 (66–151)	22	91%	60 (39–93)	19	100%
		Pos	20	100%	1577 (1008–2465)	20	100%	359 (202–640)	19	100%	94 (64–137)	12	100%	58 (39–88)	15	87%	65 (38–113)	12	67%

Abbreviation: CI, confidence interval.

TABLE 2.
Anti-HAV Levels After Two Doses of Hepatitis A Vaccine Among Group 1 Infants, by Maternal Anti-HAV Status and Follow-up Period

Group*	Maternal Anti-HAV Status	1 Month After Dose 2		3 Years of Age		7 Years of Age		10 Years of Age		12–14 Years of Age		15–16 Years of Age	
		<i>n</i>	GMC, mIU/mL (95% CI)	<i>n</i>	GMC, mIU/mL (95% CI)	<i>n</i>	GMC, mIU/mL (95% CI)	<i>n</i>	GMC, mIU/mL (95% CI)	<i>n</i>	GMC, mIU/mL (95% CI)	<i>n</i>	GMC, mIU/mL (95% CI)
1	Neg	40	1196 (855–1673)	36	219 (139–346)	33	65 (44–97)	31	45 (31–65)	22	37 (22–62)	20	49 (31–77)
	Pos: Natural	17	299 (125–717)	18	76 (41–139)	15	44 (23–83)	9	31 (12–79)	11	13.7 (7–26)	6	36 (8–167)
	Pos: Vaccine	16	1636 (971–2756)	17	194 (111–342)	16	57 (40–83)	13	34 (21–56)	13	28 (18–44)	12	23 (14–36)

Abbreviation: CI, confidence interval.