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Hepatitis A vaccine immunogenicity 25 years after vaccination in Alaska

Maya Ramaswamy[1], **Dana Bruden**[1], **Leisha D. Nolen**[1], **Emily Mosites**[1], **Mary Snowball**[2], **Noele P. Nelson**[3], **Michael Bruce**[1], **Brian J. McMahon**[2]

[1]Arctic Investigations Program, Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, Alaska

[2]Liver Disease and Hepatitis Program, Alaska Native Tribal Health Consortium, Anchorage, Alaska

[3]Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Anchorage, Alaska

Abstract

The hepatitis A vaccine is recommended for all children greater than or equal to 1 year of age, however, the duration of vaccine protection is unknown and protection through adulthood is crucial to prevent symptomatic hepatitis later in life. We report on 25 years of follow-up of a cohort of Alaska Native individuals who were vaccinated in early childhood. We assessed the duration of vaccine protection by calculating the geometric mean concentration and proportion of participants with protective levels of IgG antibody to hepatitis A virus (anti-HAV) (≥20 mIU/mL) every 2 to 3 years. We estimated the amount of time until the anti-HAV dropped below protective levels using survival analyses. At 25 years, 43 of the original 144 participants were available, mean anti-HAV levels were 91.5 mIU/mL, and 35 (81.4%) had protective levels of anti-HAV. Using data from all persons and all time points, a survival analysis estimated 78.7% of participants had protective levels of anti-HAV at 25 years. The high level of protective antibodies in this cohort indicate that supplemental doses of hepatitis A vaccine are not needed 25 years after completion of the vaccine series.

Keywords

hepatitis A virus; immunization; vaccines

Correspondence Maya Ramaswamy, Arctic Investigations Program, Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 4055 Tudor Centre Dr, Anchorage, AK 99508. ohj0@cdc.gov.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

1 | INTRODUCTION

Hepatitis A virus (HAV) infection continues to contribute to morbidity in adults globally.[1,2] Before the mid 1990s, rates of acute HAV were high in the United States (29 per 100 000 population in 1971).[3] In Alaska, recurrent and cyclical hepatitis A outbreaks were first reported in the 1960s.[4-6] The disease particularly affected Alaska Native people in rural communities, where water and sewer services were often limited.

An HAV outbreak began in 1987 and ended in 1991 in rural southwest Alaska affecting 1892 people.[7] During this outbreak, a collaborative team at the Alaska Native Medical Center (ANMC) and Centers for Disease Control and Prevention (CDC) Arctic Investigations Program conducted a pre-licensure phase III clinical randomized trial study in 1990 to assess the immunogenicity of a hepatitis A vaccine in children and adults. The cohort comprised of children was followed for the next 25 years to examine the long-term duration of immunogenicity in Alaska Native children.[8,9] Infection in very young children is usually asymptomatic and children shed HAV in their stool for prolonged periods of time, which can cause symptomatic acute hepatitis in older children and adults. As infected children are often the source of HAV transmission to adults, CDC and the Advisory Committee on Immunization Practices (ACIP) recommended hepatitis A vaccination of children in Western states with cases above the national average starting in 1996 and universal routine vaccination of children at age 12 to 23 months in 2006, with permissive catch-up vaccination.[10] This strategy resulted in a dramatic decrease in the incidence of acute HAV in the United States (from 9.1 per 100 000 population before the vaccination recommendation in 1992 to 2.6 per 100 000 population in 2003 after the vaccination recommendation).[3] However, to maintain long-term immunity, protection must persist throughout adulthood; otherwise, booster doses may be needed. This paper reports on the duration of hepatitis A immunity 25 years after childhood vaccination.

2 | MATERIALS AND METHODS

In 1991, a cohort of Alaska Native children aged 3 to 6 years was recruited to assess the initial immune response to a three-dose hepatitis A vaccine series and the duration of protection. This schedule is shown to be comparable to the current two-dose schedule.[8,11] Participants were recruited during well-child clinic visits at the ANMC in Anchorage, Alaska. Parents or guardians of each child provided consent to participate in the study, and children also provided assent. Approvals for the study were initially obtained from the Alaska Area Native Health Service Research and Publications Committee and the Anchorage Native Health Board and subsequently obtained from the Alaska Area Institutional Review Board (AAIRB) (ethics review #IRB00000636; protocol #2015-03-017-11), the CDC IRB, and two Tribal Health Organizations, the Alaska Native Tribal Health Consortium, and Southcentral Foundation. Participants were selected from the greater Anchorage area to ensure participants had access to the clinic and to increase retention over time.

Participants were randomized to three different vaccine dosage schedules: (a) 0, 1, and 2 months; (b) 0, 1, and 6 months; and (c) 0, 1, and 12 months. Information on the

administered vaccine has been described elsewhere[12] but, briefly, children received three doses of the inactivated hepatitis A vaccine HAVRIX (360 Elisa Units; GlaxoSmithKline Biologicals, Rixenart, Belgium). Each participant had serum samples taken between 1 and 3 months after vaccination. Serum samples were then collected from each available participant annually for the first 5 years, and then every 2 to 3 years thereafter until the 25th year. Laboratory methods for assessing anti-HAV concentrations have been described elsewhere.[12] We assessed IgG anti-HAV concentrations at each time point by calculating the geometric mean concentration (GMC) and calculated the proportion of participants with protective levels of anti-HAV (≥20 mIU/mL) at each time point.

Using data from all participants initially enrolled in the study, a Kaplan-Meier survival curve and the log-rank statistic were used to compare the time until anti-HAV concentrations dropped to less than 20 mIU/mL for schedule A and for combined schedules B and C. Schedules B and C were combined for the survival analysis because GMCs were not statistically different. Participants who inadvertently received additional vaccine doses beyond their third dose were censored from the analysis. For participants whose anti-HAV concentrations dropped to less than 20 mIU/mL, the time of censor was estimated as the mid-point between their last follow-up visit with a value of greater than or equal to 20 mIU/mL and the first follow-up visit with a concentration of less than 20 mIU/mL. For participants whose anti-HAV concentrations never dropped to less than 20 mIU/mL, the time of censor was their final follow-up visit.

3 | RESULTS

Of the 144 original participants, 43 (29.9%) were available at the 25-year follow-up time point, including 14 (32.5%) in schedule A (0, 1, and 2 months), 15 (35%) in schedule B (0, 1, and 6 months), and 14 (32.5%) in schedule C (0, 1, and 12 months). The mean age of these participants at the time of initial vaccination was 4.5 years. There were no statistically significant differences in sex, mean age at initial vaccination, or distribution among vaccine schedules between those who participated at the 25-year follow-up time point and those who did not participate (data not shown). Between the 22- and 25-year follow-up time points, no participants had received an interval hepatitis A vaccine and thus none were censored.

Mean anti-HAV levels were 91.5 mIU/mL at 25 years for all participants. Between schedules, there was a statistically significantly lower GMC among participants who received vaccines on schedule A (42.9mIU/mL) compared with schedules B (100.6mIU/mL) and C (176.5mIU/mL) ($P = .004$). Overall, 81.4% (35 out of 43) of the remaining participants maintained protective levels of anti-HAV (64.3% [9 out of 14] from schedule A, 86.7% [13 out of 15] from schedule B and 92.9% [13 out of 14] from schedule C) at 25 years (Figure 1), a 5.6% decrease from the previous measurement 22 years after vaccination.

Using a Kaplan-Meier curve and data from all time points and all participants, participants on schedule A had 37.1% probability of dropping below the protective level of anti-HAV, while participants on the combined schedules B and C had 12.3% probability of dropping below the protective level (Figure 2). Overall, 78.7% of participants were estimated to have protective levels of anti-HAV at the 25-year follow-up time point.

4 | DISCUSSION

In the United States, the hepatitis A vaccine is recommended as a childhood immunization by ACIP and CDC but the duration of long-term protection from HAV into adulthood is unknown.[10] We found that at the 25-year follow-up time point, the majority of the remaining participants exhibited protective levels of anti-HAV. The mean GMC was 91.5 mIU/mL for all participants, well above the 20 mIU/mL protective cut-off. Using a survival analysis, 78.7% of participants had protective levels of anti-HAV at the 25-year follow-up time point. More importantly, for those participants who received vaccine on schedules B and C, the probability of remaining above the protective level and the GMC was significantly higher at 25 years than those who received vaccine on schedule A. It should be noted that the protective level of anti-HAV (≥20 mIU/mL for HAVRIX) was determined based on animal studies and the absolute lower limit of protective levels of anti-HAV have not yet been determined.[10]

The hepatitis A vaccine was initially licensed as a three-dose series of 360 Elisa Units at 1, 2, and 6 months. The vaccine formulation changed a few years after licensure to 720 Elisa Units, given at 1 and 6 months. This amounted to 25% more antigen per series. It is likely that the current vaccine, both due to the higher concentration of vaccine and greater time between doses, should provide a longer duration of protection. A study we conducted in Alaska comparing immunogenicity between the administration of two- and three-dose hepatitis A vaccine supports the similarity between the immune response, observing no significant differences in GMC anti-HAV in those receiving the previous and current vaccine formulation.[11] Though no published long-term immunogenicity studies are available for the other form of hepatitis A vaccine commonly used in the United States (VAQTA), we believe that our findings on long-term protection very likely apply to this vaccine as the response after the initial series is equivocal in both vaccines.[13,14]

Other studies have examined hepatitis A vaccine immunogenicity in children globally; however, long-term immunogenicity studies in children have been limited to 11 years.[15,16] In adults, data indicate that long-term protection lasts up to 12 years.[17] Our study is the longest-enduring cohort of participants vaccinated with hepatitis A vaccine in childhood in the world, covering a 25-year follow-up period, and our findings support previous models that predicted the persistence of a protective level of anti-HAV 25 years after vaccination.[17-19]

Participation was limited to 43 individuals at the 25-year follow-up time point, likely due to the long duration of the study. However, the study participants at the 25-year follow-up time point were representative of the entire cohort in terms of sex, age, vaccine schedule assignment, and initial and 4-year anti-HAV GMCs. Previously, 30 participants were censored as a result of receiving additional vaccination after their third dose; the last-censored participant received an additional dose in 2008. We were able to compensate for the low numbers using data from the entire cohort in our survival analysis. Additionally, missing data imputation methodology at the 22-year follow-up time point of this cohort resulted in similar coefficients and conclusions as the complete case analysis.[11]

We determined that childhood hepatitis A vaccination results in immunity that lasts over 25 years. Our data indicate that a supplemental vaccine dose is not necessary up to 25 years after hepatitis A vaccine is administered in childhood. This study provides evidence that the US strategy of universal hepatitis A vaccination of children will provide protection from infection well into adulthood.

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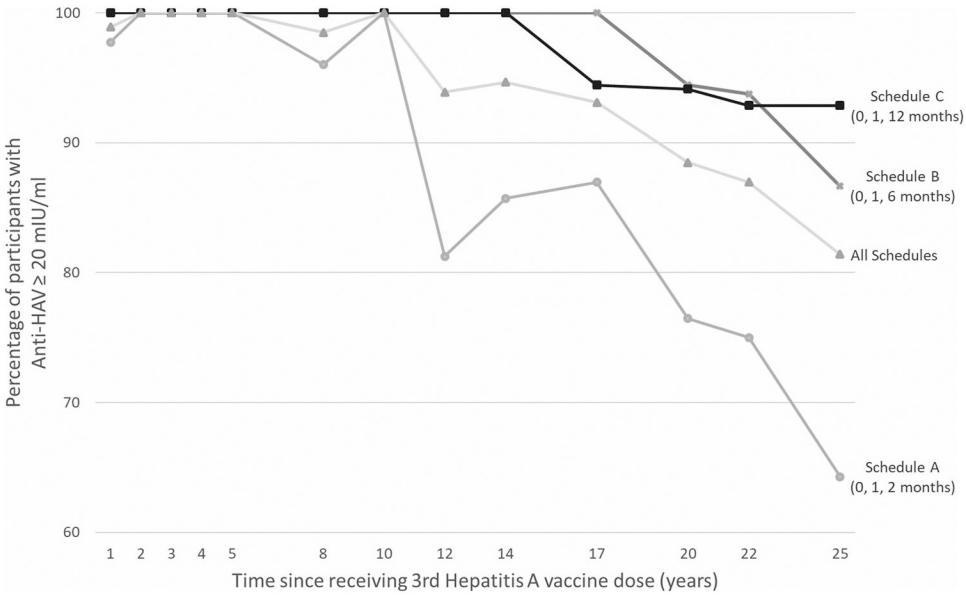

FIGURE 1.

The percentage of participants in the Alaska hepatitis A childhood vaccine study (1991-2017) with anti-HAV greater than or equal to 20 mIU/mL by primary vaccine series and time since receiving the third dose of vaccine (n = 144). HAV, hepatitis A virus

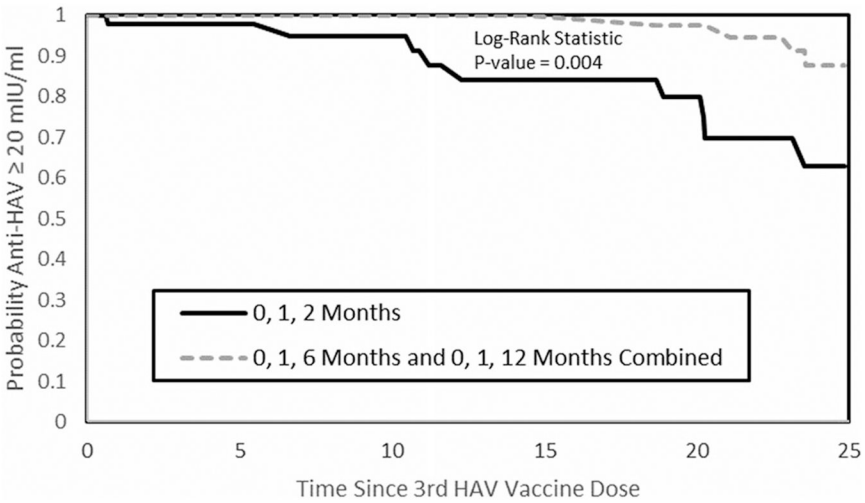

FIGURE 2.

Survival probabilities of protective antibody levels in the Alaska hepatitis A childhood vaccine study (1991-2017) for time until anti-HAV greater than or equal to 20 mIU/mL according to primary vaccine series. HAV, hepatitis A virus