Impact of a statewide childhood vaccine program in controlling hepatitis A virus infections in Alaska

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Abstract

Historically, Alaska experienced cyclic hepatitis A virus (HAV) epidemics, and the HAV rate among Alaska Native people was significantly higher than among other racial/ethnic groups. We evaluated the impact of a statewide childhood vaccination program initiated in 1996 on HAV epidemiology in Alaska by analyzing HAV cases reported to the State of Alaska. HAV incidence in all age groups declined 98.6% from 60.0/100,000 in 1972–1995 to 0.9/100,000 in 2002–2007. The largest decrease (99.9%) was in Alaska Native people, whose incidence (0.3) in 2002–2007 was lower than the overall U.S. 2007 rate (1.0). Among age groups, the decrease (99.8%) among children aged 0–14 years was the largest. Routine childhood vaccination has nearly eliminated HAV infection in Alaska.

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1. Introduction

Hepatitis A virus (HAV) is one of the most common causes of icteric hepatitis worldwide [1] and was one of the most frequently reported vaccine-preventable diseases in the United States [2,3]. Hepatitis A infection rates have differed historically by race; the highest HAV rates in the United States occurred among American Indian [4] and Alaska Native (AN) people [5]. In Alaska, from the 1950s to 1990s, HAV epidemics occurred every 10–15 years resulting in thousands of persons developing icteric hepatitis [3,4]. AN people in traditional rural villages were disproportionately affected by HAV epidemics. In a statewide epidemic occurring in the mid-1970s, AN persons accounted for >60% of reported cases, although they constituted only 16% of the state’s population [4]. In 1993, a retrospective serosurvey showed evidence of past HAV infection, indicated by the presence of total antibody to HAV, among 85% of AN persons born before 1945 [4].

Hepatitis A vaccines, Havrix® (GlaxoSmithKline, Rixensart, Belgium) and Vaqta® (Merck & Co., Whitehouse Station, NJ), were developed in the 1980s. Formulations evaluated in randomized control trials had protective efficacies of 99–100% [6,7]. One of the immunogenicity trials, which included both children and adults, was conducted in Alaska in the late 1980s and the early 1990s [7]. In 1992, while the trials were ongoing, a large outbreak of HAV started in rural Alaska and spread to the urban areas. In 1992–1993, the peak reported incidence of HAV in the affected regions exceeded 2000 cases per 100,000 persons per year [8]. In an attempt to control this epidemic in the period immediately prior to HAV vaccine licensure, the Alaska Area Native Health Service, regional Alaska Native health corporations, and the State of Alaska Section of Epidemiology (SOE) conducted a demonstration project in 1993 to 1994 to administer Havrix® as part of the Phase III trials [8]. One dose of Havrix® was given to more than 5000 susceptible persons in 25 Alaskan communities, halting the epidemic within 4–8 weeks of administration in communities with high vaccination coverage [9].

Hepatitis A vaccines were licensed in 1995 and recommended by the Advisory Committee on Immunization Practice (ACIP) for routine vaccination of U.S. children in populations with high rates of HAV such as those found in American Indian and Alaska Native (AI/AN) communities throughout the United States [5]. An immunization effort, initiated in 1996–1997, that included AI/AN children as well as children from states with high HAV incidence led to a 20-fold decrease in HAV incidence from 1997 to 2001 among all AI/AN to a level similar to the overall U.S. rate, one of the...
largest decreases in HAV reported [10]. During 2001–2007, HAV infection rates among AI/AN people were lower than rates among other racial/ethnic populations in the United States, reaching 0.5 per 100,000 population among AI/AN people, and hepatitis A vaccination coverage among 24- to 35-month-old AI/AN children was higher than that in U.S. children from other racial/ethnic populations [11].

The Alaska SOE implemented universal hepatitis A vaccination with state-supplied vaccine for all Alaska children ages 2–14 years in January 1996[12]; the vaccine recommendations were expanded to 2–18 years in 1997 [13]. Beginning in 2001, hepatitis A vaccine was required by the State of Alaska for daycare and school attendance; in 2006 the age recommendations were expanded which included 1–18 year olds [14] (Fig. 1).

In this paper we analyzed all Alaska HAV cases reported to the Alaska SOE from 1972 to 2007 to assess the impact of routine statewide childhood hepatitis A vaccination in decreasing HAV infections in all Alaskans and compared results in AN with other racial and ethnic groups living in Alaska.

2. Methods

2.1. Population statistics

Denominators for calculating incidence rates were derived using the 1970, 1980, 1990 and 2000 U.S. census data. We evaluated cases and population by race (AN vs. other), region, and age group. The average change in population for each group was calculated and the estimated population per group was interpolated for 1972 through 2007. Alaska Native people included Eskimo, Aleut, Athabascan, Tsimpsian, Haida, Tlingit, and non-Alaska American Indian groups; all others were considered non-Alaska Native. However, in 8.8% of cases, race was not stated. Persons were considered urban if they resided in the Municipality of Anchorage or the Matanuska-Susitna Borough. All others were considered rural. The denominators used for periods greater than one year were the sum of the estimated populations for each year.

2.2. Hepatitis A virus infection surveillance

Cases of acute hepatitis have been reportable to the Alaska SOE since statehood; specific hepatitis types, including HAV infections, have been reported to the Alaska SOE since 1974 [15]. A confirmed case is defined as an acute illness with discrete onset of symptoms and with the presence of jaundice or elevated aminotransferase levels, and either a serologically confirmed immunoglobulin M (IgM) antibody to HAV or an epidemiological link to a person who has laboratory-confirmed HAV [16]. During the time period of interest, 1972–2007, HAV cases were reported to the Alaska SOE by health care providers and by laboratories including the Alaska State Virology Laboratory, Alaska Native Medical Center, and out-of-state commercial laboratories. Demographic data collected included age group, location of exposure, race/ethnicity, and region of residence. The age group variable identified age in 5-year increments from 0 to 89 years of age. These were collapsed into age categories of 0–14, 15–24, 25–44, and 45 and older for analysis. The location of exposure was categorized as exposed within Alaska or exposed outside of Alaska (imported case); race/ethnicity was categorized as AN, other, and unknown; and region was categorized as Anchorage/Matanuska Susitna Valley, Gulf Coast, Interior, Northern, Southeast, and Southwest regions.

2.3. Vaccine coverage

Estimated vaccine coverage with hepatitis A vaccine among children 24–35 months of age was reported by the National Immunization Survey for the United States and individual states during 2003–2005. Data tables for the National Immunization Survey were downloaded [17]. In addition, estimated hepatitis A vaccine coverage was provided from the 2006 National Immunization Survey (Written communication, CDC).

2.4. Statistical methods

Yearly incidence rates of HAV were reported by age, AN race, and region for 1972–2007. We calculated mean incidence for five time periods: three pre-licensure periods (early, 1972–1982; middle, 1983–1993; and late, 1994–1995), early vaccine implementation period (1996–2001), and the routine vaccination period (2002–2007) following school requirements for HAV vaccination. Comparisons between AN and non-Native people were reported with a relative risk (RR), 95% confidence interval (95% CI) and P-value for significance testing.

2.5. Imported cases

Alaska SOE classified HAV cases as “imported” when investigation of the case revealed that exposure occurred outside of Alaska. No evaluation of the completeness of reporting of the exposure location has been performed; however, it is likely that the few cases occurring after routine vaccination were more carefully evaluated than cases occurring during peak HAV incidence years.

3. Results

3.1. Hepatitis A virus disease rates

Prior to routine hepatitis A vaccination in 1996, the average yearly incidence of HAV infection in Alaska was 60 per 100,000 persons, with a high of 386.9 during an epidemic year and a low of 3.4 during an inter-epidemic year. In the pre-vaccine period...
AN people experienced an average yearly incidence (243.8 per 100,000) over 10-fold higher than non-Native Alaskans (19.2 per 100,000; RR 12.7 [95% CI 12.0, 13.4]; \( P < 0.001 \)), with a yearly high incidence of 1809 per 100,000 and a low of 0 (Fig. 2).

With the exception of a pre-licensure immunogenicity trial involving 163 AN children and 144 AN and non-Native adults conducted in Anchorage in 1989–1992 [7], the first widespread use of HAV vaccine in Alaska occurred during 1993–1994, when the vaccine was administered in the rural Northern region during an approved pre-licensure demonstration project conducted at the time of the hepatitis A outbreak [8] (Fig. 1). In communities in which more than 80% of susceptible persons were vaccinated, the outbreak ceased in 4–8 weeks, whereas, in a large community with <50% of susceptibles vaccinated, the outbreak continued for 50 weeks [8]. The statewide yearly incidence decreased from 134.9 in 1993 to 8.5 per 100,000 in 1995, while the yearly incidence in AN people decreased from 748 per 100,000 in 1993 to 13.4 per 100,000 in 1995 with the conclusion of the Northern region outbreak (Fig. 2).

Vaccination of all Alaskan children 2–14 years of age was initiated in 1996 and gradually expanded around the state [12]. Vaccination was required for school entry in 2001; accordingly, 2002–2007 is referred to as the routine vaccination period [14] (Fig. 1). These interventions resulted in a 98.4% decrease in HAV in all-aged Alaskans from 60.0 in the pre-licensure period to 0.9 per 100,000 during the routine vaccination period, 2002–2007 (Table 1). Among AN people, there was a 99.9% decrease in HAV incidence during this period. The HAV incidence in 2002–2007 was the same or lower in AN than in non-Native Alaskans, 0.3 and 0.7 per 100,000, respectively (RR 0.54, 95% CI [0.36, 1.25]; \( P = 0.195 \)) (Table 1).

Prior to routine vaccination, case investigations revealed that most HAV cases were associated with outbreaks occurring within Alaska; however, since 2001, 71.4% of HAV cases have been imported cases, many of which were acquired during travel outside of the United States.

3.2. Cases prevented

From 2002–2007, 34 cases of HAV infection were reported to SOE. If rates from the pre-vaccine period had persisted during these 6 years, 2086 symptomatic cases of HAV infection would have been expected; therefore, we estimate that 2052 symptomatic HAV cases have been prevented.

3.3. Vaccine coverage

The estimated vaccine coverage with 1 or more doses of HAV vaccine in 24- to 35-month-old children evaluated in the National Immunization Survey was significantly higher in Alaskan children than U.S. children during 2003 (72.7, 95% confidence interval \( \pm 7.4 \) vs. 16.0 \( \pm 7.4 \)), 2004 (69.9 \( \pm 7.9 \) vs. 17.6 \( \pm 1.0 \)), 2005 (66.8 \( \pm 9.1 \) vs. 21.3 \( \pm 1.2 \)) [17], and 2006 (65.9; 95% CI 57.1, 73.7 vs. 26.2; 25.1, 27.4) (written communication, Natalie Darling, CDC, July 17, 2008).

Alaska Native tribal facilities documented evidence of HAV vaccination among their child user population 2–18 years of age in their electronic databases in June 2002. Among 52,821 AN children 2–18 years of age evaluated, 65% had evidence of 1 or more HAV vaccinations. In September 2008, the vaccine coverage for 2 doses of HAV vaccine among 11,242 adolescent AN children 11–17 years
Fig. 3. (a and b) Hepatitis A virus infection rate per 100,000 by year and age group, 1972–2007, among Alaska Native (a) and non-Native Alaska people (b). *Note that the scale for the Y-axis of (a) (0–4500 per 100,000) is 10-fold higher than the Y-axis scale for (b) (0–450 per 100,000).

of age with 2 or more visits to a tribal facility within 3 years was 94% (RJS).

4. Discussion

Historically, Alaska experienced cyclic epidemics of HAV. Similar to American Indians in the continental United States, the HAV rate among AN people was significantly higher than among other racial/ethnic groups [12]. The majority of AN people lived in small isolated villages not connected by the road system. At the time of the epidemics most villages did not have pumped in water and sewage, making hand washing and bathing difficult. While these epidemics started in rural Alaska, the epidemics spread to urban areas, affecting both AN and non-AN populations, as evidenced by the high incidence of HAV in non-Native children. It is possible that increasing rates of in-home running water contributed to somewhat lower HAV incidence in later pre-licensure period; however, after childhood vaccination of all Alaska children was initiated the incidence of HAV in Alaska declined dramatically and has remained at levels similar to those in other states who had low HAV rates prior to vaccine [18]. While there was a 96.3% decline in HAV incidence from pre- to post-licensure period in non-Native Alaskans, the most dramatic decline has been among AN people, who experienced a 99.9% reduction in HAV infection to an annual incidence (0.3 per 100,000 people) in 2002–2007 which is lower than the overall U.S. 2007 rate (1.0) [18].

This dramatic success was achieved with vaccination of children only, demonstrating the key role they play in community transmission of HAV. Similar declines have occurred in other states and in AI/AN populations with routine childhood vaccination [10], and in countries like Chile that have instituted routine childhood vaccination [19]. However, Alaska’s experience suggests that a sustained decrease in HAV in populations requires high vaccination coverage. In Alaska, voluntary childhood immunization starting in 1996 led to a 98% decrease in the annual HAV incidence in children 0–14 years to 2.2 per 100,000/year in 1996–2001. Mandatory HAV immunization, beginning in the fall of 2001 for children attending Alaska schools and licensed daycare facilities [14], assured high vaccination coverage and resulted in an additional sustained 90% decrease in childhood HAV infection to 0.2 per 100,000/year in 2002–2007, effectively eliminating HAV transmission. Although the largest decrease in HAV has been among children, HAV infections have also declined >90% in all adult age groups, suggesting that in a setting where many adults have natural immunity from prior infection, vaccination of children has a strong herd immunity effect and eliminates sustained transmission of HAV among all ages [20]. The rate of HAV infection in Alaskan adults is lower than reported in other states with routine childhood vaccination, possibly because most AN adults, and many non-Native Alaskan adults, were exposed to HAV in previous epidemics and have natural immunity [21].

In Israel, following implementation of a 2-dose universal hepatitis A immunization program with vaccine coverage rates of 90% for the first dose and 85% for the second dose, a 95% or greater reduction was seen in mean incidence compared to pre-immunization rates [22]. Similarly, following a preadolescent HAV vaccination program with a 95–98% compliance in Catalonia, Spain, a 90% reduction in incidence was reported for non-vaccinated older children and adults [23]. In Argentina, following implementation of a vaccination program of 12-month olds, an 88% decrease in HAV incidence was noted [24]. Although the vaccination coverage was reported at 95%, the lower decline of HAV in Argentina may be due to the fact that only 12-month olds were vaccinated. The experience in Alaska can help inform the future vaccine policies of countries such
Table 1
Number (rate per 100,000) of reported cases of hepatitis A virus infection, Alaska, 1972–2007.

<table>
<thead>
<tr>
<th>Pre-vaccine</th>
<th>Vaccine Implementation</th>
<th>Routine vaccination</th>
<th>% reduction, pre to post*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>3436 (83.8)</td>
<td>2877 (70.6)</td>
<td>259 (22.2)</td>
</tr>
</tbody>
</table>

Race/ethnicity
- **Alaska Native**:
  - 1972–1982: 2166 (326.7)
  - 1983–1993: 1942 (216.8)
  - 1994–1995: 159 (83.0)
  - Total: 4267 (243.8)
  - % reduction: 99.9%

- **Non-Native**:
  - 1972–1982: 1016 (29.5)
  - 1983–1993: 696 (14.5)
  - 1994–1995: 54 (5.5)
  - Total: 1766 (19.2)
  - % reduction: 96.3%

- **Unknown**:
  - 1972–1982: 254
  - 1983–1993: 239
  - Total: 339
  - % reduction: 9%

RR (P-value)
- 1972–1982: 11.1 (P < 0.001)
- 1983–1993: 14.9 (P < 0.001)
- 1994–1995: 15.0 (P < 0.001)
- Total: 12.7 (P < 0.001)

95% CI
- 1972–1982: (10.3, 11.9)
- 1983–1993: (13.7, 16.3)
- 1994–1995: (11.0, 20.9)
- Total: (12.0, 13.4)

Age (years)
- **0–14**: 1825 (154.3)
- **15–24**: 714 (85.8)
- **25–44**: 535 (37.9)
- **45+**: 114 (16.9)

Region
- **Anchorage**: 803 (42.2)
- **Gulf Coast**: 78 (18.2)
- **Interior**: 210 (30.3)
- **Northern**: 760 (182.2)
- **Southwest**: 1400 (460.6)

Population estimates for regions on July 1, 2008: Anchorage (367,509), Gulf Coast (75,876), Interior (104,421), Northern (23,612), Southeast (69,202), Southwest (39,100) and Total (679,720).

* P < 0.001 for % reduction for all groups.

Table 2
Number (rate per 100,000) of reported cases of hepatitis A virus infection, Alaska, 1972–2007, by age and ethnic group.

<table>
<thead>
<tr>
<th>Pre-vaccine</th>
<th>Vaccine Implementation</th>
<th>Routine vaccination</th>
<th>% reduction, pre to post**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–14</td>
<td>Alaska Native</td>
<td>1622 (664.9)</td>
<td>1188 (380.3)</td>
</tr>
<tr>
<td></td>
<td>Non-Native</td>
<td>144 (15.3)</td>
<td>184 (15.0)</td>
</tr>
<tr>
<td></td>
<td>RR (P-value)</td>
<td>43.3 (P &lt; 0.001)</td>
<td>25.3 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(36.5, 51.8)</td>
<td>(21.7, 29.7)</td>
</tr>
<tr>
<td>15–24</td>
<td>Alaska Native</td>
<td>230 (157.7)</td>
<td>348 (217.2)</td>
</tr>
<tr>
<td></td>
<td>Non-Native</td>
<td>431 (62.8)</td>
<td>107 (14.9)</td>
</tr>
<tr>
<td></td>
<td>RR (P-value)</td>
<td>2.5 (P &lt; 0.001)</td>
<td>14.6 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(2.1, 3.0)</td>
<td>(11.7, 18.3)</td>
</tr>
<tr>
<td>25–44</td>
<td>Alaska Native</td>
<td>168 (102.2)</td>
<td>312 (118.5)</td>
</tr>
<tr>
<td></td>
<td>Non-Native</td>
<td>311 (25.0)</td>
<td>324 (17.0)</td>
</tr>
<tr>
<td></td>
<td>RR (P-value)</td>
<td>4.1 (P &lt; 0.001)</td>
<td>7.0 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(3.4, 5.0)</td>
<td>(5.9, 8.2)</td>
</tr>
<tr>
<td>45+</td>
<td>Alaska Native</td>
<td>49 (44.7)</td>
<td>66 (41.4)</td>
</tr>
<tr>
<td></td>
<td>Non-Native</td>
<td>59 (10.4)</td>
<td>61 (6.5)</td>
</tr>
<tr>
<td></td>
<td>RR (P-value)</td>
<td>4.3 (P &lt; 0.001)</td>
<td>6.3 (P &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>(2.9, 6.4)</td>
<td>(4.4, 9.2)</td>
</tr>
</tbody>
</table>

* Cases with unknown race by age, 2002–2007: 0–14 years, 1 case; 15–24 years, 0 case; 25–44 years, 2 cases; 45+ years, 6 cases.

** P < 0.001 for % reduction for all groups.
as Brazil, where improved sanitation has increased the number of non-immune young people leading to periodic outbreaks [25]. The epidemiology of HAV in rural Alaska was characterized by periodic large community-wide outbreaks beginning in isolated AN villages with little transmission during the inter-epidemic period in these villages. While most adults had existing antibody to HAV, epidemics occurred when a large proportion of seronegative children aged <15 years developed during the inter-epidemic period [21]. Previous studies have reported that more than half of children who are positive for IgM antibody to HAV during outbreaks are anicteric but capable of spreading the disease [6]. The Alaskan HAV vaccine demonstration project just prior to licensure suggested that where 80% of persons are immune, outbreaks are halted. Efforts to control HAV have been aimed at school-aged children and toddlers; in 2005 the licensed age for HAV vaccine was reduced to 12 months [18]. By focusing vaccination efforts on children and mandating HAV immunization for school-aged children, transmission of HAV has been halted. Several studies have identified children as an important potential source of HAV transmission in communities [26,27] and justify the call for universal hepatitis A vaccination among children [28].

Past epidemics of HAV in Alaska have caused significant morbidity in affected individuals and had a profound impact on communities. During the 1992 HAV epidemic, two children and two adults died of fulminant hepatitis failure. HAV epidemics decreased school attendance, interfered with fishing and hunting activities necessary for AN families, and caused lost work time. In addition, during epidemics, village health providers, public health nurses and Alaska Native Health corporations devoted a large amount of money and time to caring for ill individuals and attempts to halt these epidemics by widespread use of immune globulin often proved futile [29]. Thus, the ability to eliminate HAV has community and economic benefit beyond the saved medical costs.

Since HAV transmission has been nearly eliminated in Alaska, universal vaccination has resulted in a shift in continued HAV infections from community-wide outbreaks to uncommon sporadic cases, primarily acquired outside of Alaska and the United States, and rare food-borne outbreaks [30]. The risk of such imported cases is growing in the United States because of increased travel of U.S. citizens to endemic areas, importation of food from other countries, and adoption of children from endemic countries [18].

One limitation of our study is that 8.8% of cases had unknown race. This could have resulted in an underestimate of the incidence in AN prior to vaccination and an overestimate of the reduction in incidence in AN after vaccination if AN were included in those persons where ethnicity was not known. However, the impact of this limitation is likely to be small because HAV cases whose ethnicity was not declared were included as AN if they were beneficiaries of AN tribal health care organizations. Another limitation is the potential that cases of acute HAV infection were not identified. We expect that surveillance for acute viral hepatitis in Alaska is nearly complete because of laboratory reporting of anti-HAV IgM tests to the Alaska SOE by the limited numbers of labs performing these tests in both Alaska and commercial labs outside of Alaska. Even if surveillance were incomplete, requirements for reporting have not changed over time, so we may be underestimating rates, but changes over time are unlikely to be a surveillance artifact.

5. Conclusion

High childhood vaccine coverage through routine childhood vaccination and mandatory school vaccination has nearly eliminated transmission of HAV infection in Alaska. The largest declines have been among AN people who historically had one of the highest HAV rates in the United States and now experience a lower HAV than other Alaskans and the US general population. The continued occurrence of HAV cases, which are now mostly imported, is a reason to remain vigilant with surveillance and to maintain a strong immunization program.

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References