Seroprevalence of Hepatitis A Virus Antibodies in the U.S.: Results from the National Health and Nutrition Examination Survey

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ABSTRACT

Objectives. We described seroprevalence of antibody to hepatitis A virus (anti-HAV) in the United States during 1999–2006 and compared it with seroprevalence before the availability of vaccine.

Methods. We analyzed data from the 1988–1994 and 1999–2006 National Health and Nutrition Examination Survey (NHANES) to obtain estimates of anti-HAV seroprevalence for the U.S. household population. We grouped region of residence based on the 1999 Advisory Committee on Immunization Practices recommendations into 17 states with any recommendation (vaccinating) and 33 states without any recommendation (non-vaccinating).

Results. During 1999–2006, the overall seroprevalence of anti-HAV was 34.9% (95% confidence interval [CI] 33.1, 36.7). During 1999–2006, U.S.-born children living in vaccinating states (33.8%, 95% CI 26.2, 42.2) had a higher seroprevalence than children in non-vaccinating states (11.0%, 95% CI 9.4, 12.8; $p<0.001$). Seroprevalence among children increased from 8.0% (95% CI 6.3, 10.1) during 1988–1994 to 20.2% (95% CI 16.0, 24.8) during 1999–2006 ($p<0.001$). For U.S.-born children aged 6–19 years, the strongest factor associated with seroprevalence was residence in vaccinating states. Among U.S.-born adults aged >19 years, the overall age-adjusted seroprevalence of anti-HAV was 29.9% (95% CI 28.3, 31.5) during 1999–2006, which was not significantly different from the seroprevalence during 1988–1994 (32.2%, 95% CI 30.1, 34.4).

Conclusions. Increases in seroprevalence among children in vaccinating states suggest a positive effect of the 1999 vaccination recommendations.

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Hepatitis A vaccines were licensed in the United States in 1995. Shortly thereafter, the Advisory Committee on Immunization Practices (ACIP) made recommendations for routine vaccination of children aged 2–18 years living in communities with the highest rates of infection and disease.[1] By 1999, epidemiologic evidence suggested that the strategy had a limited impact on national disease incidence;[2] thus, in 1999, ACIP recommended routine vaccination for children living in 11 mostly western states, with mean incidence rates that were at least twice the 1987–1997 national mean (i.e., ≥20 cases per 100,000 population). In an additional six states, where mean incidence rates were higher than the national average, but less than twice that value (i.e., 10–19 cases per 100,000 population), ACIP recommended consideration of routine vaccination of children.[2] The impact of this expansion was dramatic: by 2003, acute hepatitis A disease had declined overall by 76%, from a rate of 10.7 per 100,000 population during 1990–1997 to 2.6 per 100,000 population in 2003.[3] In 2007, the rate was the lowest ever reported (1.0 per 100,000 population).[4] In 2006, ACIP recommended integration of hepatitis A virus (HAV) vaccine into the routine childhood vaccination schedule, with HAV vaccine administered for all children at age 12 months.[5]

Population-based seroprevalence surveys play a critical role in supplementing data systems for disease incidence, vaccination coverage, and vaccine adverse events in the development of vaccination policy.[6] Before the availability of vaccine, seroprevalence of antibody to HAV (anti-HAV) in the population solely reflected prior infection.[7] Currently, seroprevalence can reflect immunity due to either previous infection or to vaccination. Our objectives were to describe patterns in the seroprevalence of anti-HAV in the U.S., evaluate sociodemographic factors associated with seroprevalence during 1999–2006, and compare these findings with seroprevalence patterns before the availability of vaccine.

METHODS

The National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics, obtains nationally representative data on the health and nutritional status of the U.S. civilian noninstitutionalized population. We analyzed data from the continuous NHANES, available for 1999–2006, and NHANES III, which was conducted from 1988 to 1994. The continuous NHANES data files are released in two-year cycles. NHANES uses a complex, stratified, multistage probability sampling design and collects information using standardized household interviews, physical examinations, and testing of biologic samples. For NHANES 1999–2006, non-Hispanic black people, Mexican Americans, adolescents, and low-income people were sampled at higher frequencies than other people to provide more precise estimates for these groups. More detailed information on survey design for NHANESs, including approval from the Institutional Review Board for data collection and analysis, is available from the survey documentation.[8,9]

Laboratory testing

Blood specimens from people aged 6 years and older were processed, stored, and shipped to CDC's Division of Viral Hepatitis Laboratory. A qualitative determination of total anti-HAV in serum or plasma was measured using a solid-phase competitive enzyme immunoassay (HAVAB-EIA, Abbott Laboratories, Abbott Park, Illinois).

Definitions

A person testing positive for anti-HAV was considered immune to HAV through either vaccination or natural infection. Race/ethnicity was categorized, based on a subjects' self-reported information, as non-Hispanic white, non-Hispanic black, or Mexican American. Subjects who were not classified into one of these categories were classified as "other." Age was grouped as 6–11, 12–19, 20–29, 30–39, 40–49, 50–59, and ≥60 years of age. Country of birth was categorized as U.S.-born or non-U.S.-born. Poverty index was calculated by dividing total family income by the poverty threshold index adjusted for family size at year of the interview and categorized as either below the federal poverty level (FPL) (<FPL) or at or above the FPL (≥FPL) as determined by the U.S. Census Bureau.[10]

Education level was measured as last year of school completed using head of household education for children aged 6–19 years and individual education for adults aged >19 years. Education was grouped into three levels: less than high school graduate, high school completed, and more than high school graduate. Household crowding was calculated by dividing the number of household residents by the total number of household rooms (excluding bathrooms) reported as people per room (PPR) and grouped into three levels (<0.5 PPR, 0.5–0.99 PPR, and ≥1.0 PPR). Health insurance status was categorized as any insurance or none.

People were grouped by state of residence, according to the 1999 ACIP hepatitis A vaccination recommendations, into two groups: (*1*) the 17 vaccinating

states, where hepatitis A vaccination was recommended (Alaska, Arizona, California, Idaho, New Mexico, Nevada, Oklahoma, Oregon, South Dakota, Utah, and Washington) or considered (Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming) and (*2*) the remaining 33 non-vaccinating states, where no routine childhood vaccination was recommended in 1999 (Alabama, Connecticut, Delaware, Florida, Georgia, Hawaii, Kansas, Kentucky, Iowa, Illinois, Indiana, Louisiana, Massachusetts, Maryland, Maine, Michigan, Minnesota, Mississippi, North Carolina, North Dakota, Nebraska, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, South Carolina, Tennessee, Virginia, Vermont, Wisconsin, and West Virginia). This stratification required the use of residence data not available in the NHANES public-use data files, and is consistent with previous studies.[3]

Analyses were conducted overall and separately for children (6–19 years of age) and adults (>19 years of age) because vaccination recommendations differed for these groups. Most analyses were restricted to U.S.-born people to best reflect U.S.-acquired immunity. In addition, both univariate and multivariate analyses were stratified by the regions described previously.

Statistical analysis

Seroprevalence estimates were weighted to represent the total U.S. civilian, noninstitutionalized household population and to account for oversampling and nonresponse to the household interview and physical examination.[11] Because we used a variable based on U.S. geography, we were unable to use the publicly released masked stratum and primary sampling units (PSUs) to designate the complex sample design in our analyses. The true stratum and PSU designations were used instead. We estimated 95% confidence intervals (CIs) using the exact binary method.[11] We age-adjusted prevalence estimates by the direct method to the projected 2000 U.S. Census population[12] (using the same age groupings listed previously) to allow comparisons across population subgroups and between NHANES 1988–1994 and NHANES 1999–2006 data.

We evaluated statistical comparisons between subgroups using a t-statistic obtained from a linear contrast procedure in SUDAAN® version 10.0.[13] We considered $p<0.05$ to be significant. An estimate was designated as unstable when the relative standard error (RSE) of the estimate was >30% (RSE = standard error of the percent negative/percent negative expressed as a percent) or when the number of negative individuals was <10. Estimates of variance were considered unstable when the degree of freedom in a subgroup was <10.

We used a backward stepwise logistic model in SUDAAN to examine which variables were independently associated with anti-HAV seroprevalence. Variables with a Satterthwaite-adjusted F-statistic $p<0.05$ were considered to be significant predictors. We compared full and final reduced models.

RESULTS

Of the 30,930 participants at least 6 years of age sampled in NHANES 1988–1994, 25,733 (83%) were interviewed and 23,527 (91% of those interviewed) were examined. Serum samples were available for anti-HAV testing for 21,260 (90%) of the examined individuals. Consent to conduct anti-HAV testing was less frequent in the youngest (84% for those aged 6–11 years) or oldest (82% for those aged ≥70 years) age groups (range for all those other age groups = 91%–95%). Consent to testing was also lower among non-Hispanic black (88%) compared with non-Hispanic white (90%) or Mexican American (93%) people; among those with less than a high school education (89%) compared with those with at least a high school education (91%–92%); and among those who had health insurance (90%) compared with those who had no health insurance (92%) (all $p<0.01$).

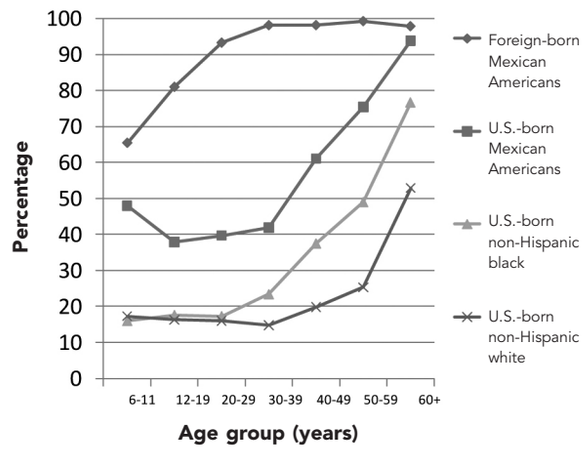
There were 43,029 people at least 6 years of age sampled in NHANES 1999–2006; of these, 34,338 (80%) were interviewed and 32,534 (95% of those interviewed) were examined. Serum samples were available for anti-HAV testing for 29,858 (92%) of the examined individuals. Consent to conduct anti-HAV testing was lower in the youngest age group (84% for those aged 6–11 years vs. 91%–95% of those in all other age groups); among non-Hispanic black people (89% vs. 93% for both non-Hispanic white and Mexican American people); and among those living in more crowded households (91% and 92% for households with 0.5–0.99 PPR and ≥1.0 PPR, respectively, compared with 93% for those with <0.5 PPR) (all $p<0.01$).

NHANES 1999–2006

During 1999–2006, the overall seroprevalence of anti-HAV (U.S.- and non-U.S.-born individuals) was 34.9% (95% CI 33.1, 36.7). Seroprevalence increased with age as follows: 22.9% among children aged 6–11 years, 22.8% among people aged 12–19 years, 28.3% among people aged 20–29 years, 30.1% among people aged 30–39 years, 32.1% among people aged 40–49 years, 36.5% among people aged 50–59 years, and 59.7% among people aged ≥60 years (data not shown).

The age-specific seroprevalence varied by race/ethnicity and country of birth (Figure 1). Seroprevalence

Figure 1. Age-specific seroprevalence of antibodies to hepatitis A virus by country of birth and race/ethnicity: NHANES, 1999–2006



NHANES = National Health and Nutrition Examination Survey

was highest among Mexican Americans not born in the U.S. (all comparisons $p<0.05$) regardless of age. Seroprevalence also was higher among U.S.-born Mexican Americans compared with U.S.-born non-Hispanic white and non-Hispanic black people for all age groups ($p<0.001$). Seroprevalence was similar among non-Hispanic white and black people aged 6–29 years; however, among those aged ≥30 years, seroprevalence was higher among non-Hispanic black people than among non-Hispanic white people.

Among U.S.-born people, during 1999–2006, the overall seroprevalence of anti-HAV was 28.1% (95% CI 26.4, 29.9), and age-specific seroprevalence varied by residence. In vaccinating states, seroprevalence was higher among younger people (6–11 years, 39%) and older adults (≥60 years, 59%) and lowest among adults aged 30–39 years (21%) (Figure 2). In non-vaccinating states, seroprevalence among children aged 6–11 years was low (10%) and increased steadily to 55% among adults aged ≥60 years. For all age categories younger than 40 years, seroprevalence was higher in vaccinating states than in non-vaccinating states (all comparisons $p<0.05$).

NHANES 1999–2006 vs. 1988–1994

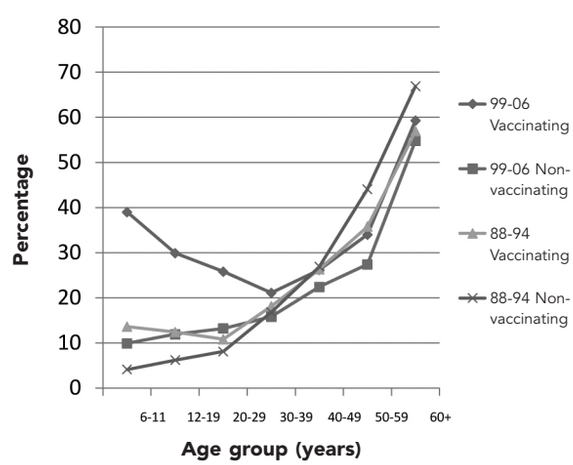
In the total population, the overall age-adjusted seroprevalence of anti-HAV during 1999–2006 (34.7%, 95% CI 32.8, 36.6) was not significantly different from the seroprevalence during 1988–1994 (32.4%, 95% CI 30.4, 34.4). However, among U.S.-born people, very different patterns emerged by age and residence in vaccinating or non-vaccinating states (Figure 2). Among U.S.-born children and young adults (aged 6–29 years), there were significant increases between survey periods in seroprevalence in both non-vaccinating states (relative increases ranging from 63% [$p<0.01$] to 141% [$p<0.001$]) and vaccinating states (relative increases ranging from 139% to 187%, $p<0.001$ for all comparisons). Among people aged ≥50 years in non-vaccinating states, the anti-HAV seroprevalence declined between survey periods from 44.1% (95% CI 39.3, 49.0) among those aged 50–59 years during 1988–1994 to 27.4% (95% CI 23.6, 31.3) during 1999–2006; and from 66.9% (95% CI 62.8, 70.9) for those aged ≥60 years during 1988–1994 to 54.8% (95% CI 50.3, 59.3) for the same age group in 1999–2006 ($p<0.001$ for both). In vaccinating states, age-specific anti-HAV seroprevalence did not change between surveys among people aged ≥30 years.

U.S.-born children: 1999–2006

The overall age-adjusted seroprevalence of anti-HAV among U.S.-born children aged 6–19 years was 20.2% (Table 1). During 1999–2006, U.S.-born children living in vaccinating states (33.8%) had a higher seroprevalence of anti-HAV than children in non-vaccinating states (11.0%). This pattern held true across all demographic subgroups ($p<0.001$ in all subgroups).

Age-adjusted seroprevalence of anti-HAV among U.S.-born children aged 6–19 years during 1999–2006

Figure 2. Age-specific seroprevalence of antibodies to hepatitis A virus among U.S.-born people by residence in vaccinating and non-vaccinating states based on 1999 recommendations: NHANES 1988–1994 and 1999–2006



NHANES = National Health and Nutrition Examination Survey

Table 1. Age-adjusted seroprevalence of anti-HAV among U.S.-born people aged 6–19 years, by regional HAV vaccination recommendation: NHANES 1988–1994 and 1999–2006

	NHANES 1988–1994			*NHANES 1999–2006*		
Characteristics	*All U.S. states Percent (95% CI)*	*Vaccinating states[a] Percent (95% CI)*	*Non-vaccinating states[b] Percent (95% CI)*	*All U.S. states Percent (95% CI)*	*Vaccinating states[a] Percent (95% CI)*	*Non-vaccinating states[b] Percent (95% CI)*
Overall	8.0 (6.3, 10.1)	12.9 (9.5, 17.1)	5.3 (3.6, 7.6)[c]	20.2 (16.0, 24.8)[d]	33.8 (26.2, 42.2)[d]	11.0 (9.4, 12.8)[c,d]
Gender						
Male	7.6 (5.3, 10.6)	12.6 (7.3, 19.7)	4.7 (2.8, 7.4)[c]	18.9 (14.9, 23.5)[d,e]	32.7 (25.2, 41.0)[d]	10.1 (8.5, 11.8)[c,d]
Female	8.5 (6.7, 10.6)	13.3 (10.6, 16.3)	5.9 (3.9, 8.6)[c]	21.5 (17.0, 26.5)[d]	34.9 (26.6, 44.0)[d]	12.1 (9.8, 14.7)[c,d]
Race/ethnicity						
Non-Hispanic white (ref.)	6.6 (4.5, 9.3)	9.6 (5.3, 15.7)	5.1 (3.1, 7.9)	16.8 (11.6, 23.0)[d]	28.8 (18.2, 41.4)[d]	9.8 (8.0, 11.7)[c,d]
Non-Hispanic black	6.1 (4.2, 8.4)	9.3 (3.8, 18.5)[f]	5.4 (3.6, 7.8)	16.9 (13.5, 20.7)[d]	41.1 (31.3, 51.4)[d]	12.7 (9.3, 16.8)[c,d]
Mexican American	24.2 (20.8, 27.8)[g]	25.5 (22.1, 29.3)[g]	14.5 (5.5, 29.0)[f,h]	42.3 (38.4, 46.3)[d,g]	45.1 (40.9, 49.3)[d,i]	23.4 (17.6, 30.0)[c,g]
Poverty index						
<FPL	14.9 (11.3, 19.1)[g]	23.5 (15.9, 32.7)[i]	10.1 (6.2, 15.3)[c,i]	22.0 (17.8, 26.7)[d]	36.2 (29.0, 43.8)[d]	12.3 (9.1, 16.0)[c]
≥FPL	6.4 (4.6, 8.6)	10.6 (7.3, 14.8)	4.1 (2.3, 6.7)[c]	19.8 (15.3, 25.0)[d]	33.2 (24.6, 42.7)[d]	10.8 (9.1, 12.8)[c,d]
Crowding (people per room)						
≥1	12.9 (9.7, 16.7)[g]	18.6 (12.4, 26.2)[i]	8.6 (5.3, 13.0)[c,e]	26.1 (21.5, 31.2)[d,g]	39.1 (31.3, 47.4)[d,e]	13.0 (9.9, 16.7)[c]
<1	6.7 (5.1, 8.7)	11.0 (7.9, 14.7)	4.6 (2.9, 6.9)[c]	18.5 (14.4, 23.1)[d]	31.6 (23.7, 40.5)[d]	10.7 (9.0, 12.5)[c,d]
Education of head of household						
<High school	12.5 (9.4, 16.1)[i]	22.5 (16.8, 29.2)[i]	7.6 (4.0, 13.0)[c]	25.3 (21.2, 29.8)[d,i]	40.4 (32.4, 48.8)[d]	12.0 (9.1, 15.4)[c]
High school graduate	7.8 (5.2, 11.2)	10.9 (6.4, 17.0)	6.3 (3.5, 10.2)	18.2 (13.2, 24.1)[d]	31.5 (21.6, 42.7)[d]	10.1 (7.9, 12.6)[c]
>High school (ref.)	5.7 (3.5, 8.7)	9.9 (4.8, 17.4)[f]	3.1 (1.7, 5.2)[c]	19.3 (14.8, 24.5)[d]	32.0 (23.5, 41.6)[d]	11.3 (9.4, 13.4)[c,d]
Health insurance						
Any	7.2 (5.5, 9.3)	12.7 (8.8, 17.5)	4.2 (2.8, 6.0)[c]	19.6 (15.5, 24.3)[d]	33.6 (25.6, 42.3)[d]	10.9 (9.2, 12.7)[c,d]
None	10.6 (6.4, 16.1)	12.5 (8.8, 17.2)	9.7 (3.6, 19.9)[f]	23.7 (17.4, 31.0)[d]	34.9 (25.2, 45.8)[d]	11.8 (7.4, 17.6)[c]
Year of survey						
2003–2006				23.9 (16.7, 32.3)	44.9 (33.1, 57.1)[i]	10.4 (7.8, 13.5)
1999–2002				16.5 (12.8, 20.8)	23.4 (16.2, 31.9)	11.7 (9.8, 13.8)

[a]Includes states with HAV vaccination recommended (Alaska, Arizona, California, Idaho, New Mexico, Nevada, Oklahoma, Oregon, South Dakota, Utah, and Washington) or considered (Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming)

[b]Includes states with no HAV vaccination recommended: Alabama, Connecticut, Delaware, Florida, Georgia, Hawaii, Kansas, Kentucky, Iowa, Illinois, Indiana, Louisiana, Massachusetts, Maryland, Maine, Michigan, Minnesota, Mississippi, North Carolina, North Dakota, Nebraska, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, South Carolina, Tennessee, Virginia, Vermont, Wisconsin, and West Virginia

[c]$p<0.05$ for comparison of vaccinating states with non-vaccinating states within survey cycle by levels of each cofactor

[d]$p<0.05$ for comparison of NHANES 1988–1994 with NHANES 1999–2006 for the total sample and for vaccinating and non-vaccinating states by levels of each cofactor

[e]$p<0.05$ for comparison of each subgroup with the appropriate reference group within each survey and population

[f]Estimate may be unstable (relative standard error >30%).

[g]$p<0.001$ for comparison of each subgroup with the appropriate reference group within each survey and population

[h]Estimate of the variance is unstable based on <10 degrees of freedom.

[i]$p<0.01$ for comparison of each subgroup with the appropriate reference group within each survey and population

anti-HAV = antibody to hepatitis A virus

HAV = hepatitis A virus

NHANES = National Health and Nutrition Examination Survey

CI = confidence interval

Ref. = reference group

FPL = federal poverty level

also varied by race/ethnicity, level of household crowding, gender, and education (Table 1). Seroprevalence was higher among Mexican Americans than among non-Hispanic white children in the U.S. overall ($p<0.001$) and in non-vaccinating states ($p<0.001$). Similarly, seroprevalence was higher among Mexican Americans compared with non-Hispanic black children in the U.S. overall ($p<0.001$) and in non-vaccinating states ($p<0.01$). In vaccinating states, Mexican American children had a higher seroprevalence than non-Hispanic white children ($p<0.01$) but not significantly higher than non-Hispanic black children. Among U.S.-born children overall, higher anti-HAV seroprevalence was associated with higher levels of crowding ($p<0.001$), female gender ($p<0.05$), and head of household having less than a high school education ($p<0.01$).

In the full multivariable model for U.S.-born children aged 6–19 years (Table 2), the strongest factor associated with anti-HAV seroprevalence was residence in vaccinating states ($p<0.001$). Mexican American children were more likely to be anti-HAV positive compared with non-Hispanic white children ($p<0.05$). Children were more likely to be anti-HAV positive during 2003–2006 than during 1999–2002 ($p<0.05$). Gender, poverty status, crowding, education of head of household, and insurance status were not associated with seroprevalence in U.S.-born children overall. In vaccinating states, the only factors significantly associated with immunity were younger age ($p<0.01$) and later (2003–2006) survey cycle ($p<0.01$). In non-vaccinating states, only Mexican American race/ethnicity ($p<0.001$) was associated with anti-HAV positivity. Results from reduced models (data not shown) for the combined population and both vaccinating and non-vaccinating states were similar to those shown in Table 2.

Comparison with 1988–1994 among U.S.-born children

The overall age-adjusted seroprevalence among U.S.-born children increased from 8.0% in 1988–1994 to 20.2% in 1999–2006 ($p<0.001$) (Table 1). A statistically significant increase in seroprevalence from 1988–1994 to 1999–2006 was seen in all levels of the demographic and socioeconomic variables measured (all comparisons $p<0.01$). This pattern held when analyses were restricted to vaccinating states. In non-vaccinating states, the difference between surveys was no longer significant among U.S.-born Mexican American children and children in lower socioeconomic groups (i.e., those with no insurance, lower education, living <FPL, and living in crowded housing).

U.S.-born adults: 1999–2006

During 1999–2006, the overall age-adjusted seroprevalence of anti-HAV among U.S.-born adults aged >19 years was 29.9%; seroprevalence was higher among females compared with males ($p<0.05$); among Mexican Americans ($p<0.001$) compared with both non-Hispanic white and non-Hispanic black people; and among non-Hispanic black people ($p<0.001$) compared with non-Hispanic white people (Table 3). Seroprevalence was consistently higher among individuals from lower socioeconomic subgroups including those living <FPL compared with ≥FPL ($p<0.001$); living in households with higher crowding ($p<0.001$); having less than a high school education compared with having more than a high school education ($p<0.001$); and having no health insurance compared with having any health insurance ($p<0.01$).

During 1999–2006, among all U.S.-born adults, age-adjusted seroprevalence was significantly higher among those living in vaccinating states (33.9%) compared with those living in non-vaccinating states (27.6%, $p<0.01$) (Table 3). Seroprevalence was higher among those living in vaccinating states across most demographic subgroups, and reached statistical significance for males ($p<0.001$), non-Hispanic white people ($p<0.01$), and those in mostly higher socioeconomic subgroups, including adults living at ≥FPL ($p<0.001$), those living in less crowded households ($p<0.05$), those with health insurance ($p<0.001$), and those with more than a high school education.

In the overall multivariable model for U.S.-born adults aged >19 years (Table 4), older age and Mexican American race/ethnicity were the factors most strongly associated with immunity. Adults aged ≥40 years had significantly increased adjusted odds of being anti-HAV positive. U.S.-born Mexican Americans and non-Hispanic black people were also more likely to be anti-HAV positive compared with non-Hispanic white people. Adults living in vaccinating states, those living below the FPL, and those with less than a high school education were also more likely to be anti-HAV positive; gender, household crowding, and insurance status were not associated with anti-HAV positivity. Adults were less likely to be anti-HAV positive during 2003–2006 than during 1999–2002. These patterns were similar in vaccinating and non-vaccinating states. Results from the reduced models (data not shown) for the combined adult population and both vaccinating and non-vaccinating states were similar to those from the full models presented in Table 4.

Comparison with 1988–1994 U.S.-born adults

The overall age-adjusted seroprevalence of anti-HAV among U.S.-born adults aged >19 years (29.9%) was not statistically different from the seroprevalence in 1988–1994 (32.2%, $p>0.05$ (Table 3). Changes between 1988–1994 and 1999–2006 varied in direction and statistical significance by demographic subgroup and by region of residence.

Table 2. Predictors of anti-HAV seroprevalence from logistic regression models among U.S.-born people 6–19 years of age by region based on HAV vaccine recommendation: NHANES 1999–2006

Characteristics	*All* OR (95% CI)	*Vaccinating states*[a] OR (95% CI)	*Non-vaccinating states*[b] OR (95% CI)
Region			
Vaccinating states[a]	3.8 (2.4, 6.0)[c]	NA	NA
Non-vaccinating states[b]	Ref.		
Survey year			
2003–2006	1.7 (1.1, 2.6)[d]	2.8 (1.5, 5.4)[e]	0.8 (0.5, 1.2)
1999–2002	Ref.	Ref.	Ref.
Age group (in years)			
12–19	0.8 (0.7, 1.0)	0.6 (0.5, 0.9)[e]	1.3 (0.9, 1.7)
6–11	Ref.	Ref.	Ref.
Race/ethnicity			
Mexican American	1.9 (1.2, 3.2)[d]	1.8 (1.0, 3.1)	3.1 (1.8, 5.1)[c]
Non-Hispanic black	1.4 (1.0, 1.9)	1.5 (0.8, 2.7)	1.4 (0.9, 2.0)
Non-Hispanic white	Ref.	Ref.	Ref.
Gender			
Male	0.9 (0.8, 1.1)	1.0 (0.8, 1.2)	0.9 (0.7, 1.1)
Female	Ref.	Ref.	Ref.
Poverty index			
<FPL	0.9 (0.7, 1.1)	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)
≥FPL	Ref.	Ref.	Ref.
Crowding index (people per room)			
≥1.00	1.1 (0.8, 1.5)	1.1 (0.7, 1.7)	1.1 (0.7, 1.9)
0.50–0.99	1.0 (0.7, 1.2)	1.0 (0.8, 1.4)	0.8 (0.6, 1.2)
<0.50	Ref.	Ref.	Ref.
Education of head of household			
<High school	1.1 (0.8, 1.4)	1.3 (0.9, 2.1)	0.8 (0.6, 1.1)
High school graduate	0.9 (0.7, 1.1)	0.9 (0.7, 1.3)	0.8 (0.7, 1.1)
>High school	Ref.	Ref.	Ref.
Health insurance			
Any	1.0 (0.7, 1.3)	1.0 (0.7, 1.5)	0.9 (0.6, 1.5)
None	Ref.	Ref.	Ref.

[a]Includes states with HAV vaccination recommended (Alaska, Arizona, California, Idaho, New Mexico, Nevada, Oklahoma, Oregon, South Dakota, Utah, and Washington) or considered (Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming) in 1999

[b]Includes states with no HAV vaccination recommended in 1999: Alabama, Connecticut, Delaware, Florida, Georgia, Hawaii, Kansas, Kentucky, Iowa, Illinois, Indiana, Louisiana, Massachusetts, Maryland, Maine, Michigan, Minnesota, Mississippi, North Carolina, North Dakota, Nebraska, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, South Carolina, Tennessee, Virginia, Vermont, Wisconsin, and West Virginia

[c]$p<0.001$ for comparison of subgroup and reference group in model

[d]$p<0.05$ for comparison of subgroup and reference group in model

[e]$p<0.01$ for comparison of subgroup and reference group in model

anti-HAV = antibody to hepatitis A virus

HAV = hepatitis A virus

NHANES = National Health and Nutrition Examination Survey

OR = odds radio

CI = confidence interval

NA = not applicable

Ref. = reference group

FPL = federal poverty level

Table 3. Age-adjusted seroprevalence of anti-HAV among U.S.-born adults >19 years of age, by regional HAV vaccination recommendation: NHANES 1988–1994 and 1999–2006

	NHANES 1988–1994			*NHANES 1999–2006*		
Characteristics	*All U.S. states Percent (95% CI)*	*Vaccinating states[a] Percent (95% CI)*	*Non-vaccinating states[b] Percent (95% CI)*	*All U.S. states Percent (95% CI)*	*Vaccinating states[a] Percent (95% CI)*	*Non-vaccinating states[b] Percent (95% CI)*
Total	32.2 (30.1, 34.4)	30.3 (25.9, 34.9)	33.2 (31.0, 35.6)	29.9 (28.3, 31.5)	33.9 (31.0, 37.0)	27.6 (25.7, 29.5)[c,d]
Gender						
Male	30.7 (28.3, 33.3)[e]	27.8 (23.4, 32.6)[e]	32.2 (29.3, 35.3)	28.6 (26.9, 30.4)[f]	34.5 (31.2, 37.9)[c]	25.4 (23.6, 27.2)[c,d,g]
Female	33.5 (31.3, 35.8)	32.5 (27.9, 37.3)	34.2 (32.0, 36.5)	31.0 (29.1, 32.9)	33.4 (30.2, 36.7)	29.6 (27.1, 32.1)[c]
Race/ethnicity						
Non-Hispanic white (ref.)	29.0 (26.8, 31.3)	25.6 (22.2, 29.3)	30.7 (28.2, 33.3)[d]	26.6 (24.9, 28.3)	29.8 (26.9, 32.8)	24.8 (22.8, 27.0)[c,d]
Non-Hispanic black	50.6 (48.3, 52.9)[g]	51.0 (45.0, 56.9)[g]	50.5 (48.0, 52.9)[g]	41.7 (39.7, 43.7)[c,g]	43.1 (38.5, 47.8)[c,g]	41.4 (39.1, 43.6)[c,g]
Mexican American	66.9 (64.3, 69.4)[g]	67.8 (65.0, 70.5)[g]	55.4 (46.6, 64.0)[d,g]	62.9 (60.0, 65.6)[c,g]	63.6 (60.7, 66.4)[c,g]	53.5 (41.8, 64.9)[g]
Poverty index						
<FPL	49.3 (45.6, 53.0)[g]	51.0 (42.0, 59.9)[g]	48.6 (44.3, 52.9)[g]	41.9 (38.6, 45.3)[c,g]	45.6 (39.4, 51.9)[g]	39.5 (35.3, 43.7)[c,g]
≥FPL	30.1 (27.9, 32.3)	28.6 (24.4, 33.1)	31.0 (28.7, 33.4)	28.3 (26.8, 29.8)	32.4 (29.7, 35.1)	26.0 (24.2, 27.9)[c,d]
Crowding index (people per room)						
≥1.00	48.8 (45.5, 52.0)[g]	52.8 (46.7, 58.8)[g]	47.3 (43.3, 51.3)[b]	41.1 (37.6, 44.7)[c,g]	42.5 (37.1, 48.0)[c,g]	39.5 (34.7, 44.5)[c,g]
0.50–0.99	33.9 (31.3, 36.6)[g]	30.3 (24.9, 36.2)	35.7 (33.3, 38.2)[e]	32.5 (30.2, 34.8)[g]	37.2 (33.4, 41.0)[b,c]	29.6 (26.5, 32.7)[c,d,f]
<0.50 (ref.)	28.7 (26.5, 31.0)	27.1 (22.9, 31.7)	29.6 (26.8, 32.5)	28.0 (26.5, 29.6)	31.0 (27.5, 34.7)	26.6 (25.0, 28.3)[d]
Education of head of household						
<High school	50.0 (47.1, 52.9)[g]	47.9 (42.0, 53.9)[g]	51.1 (47.6, 54.5)[g]	41.7 (39.2, 44.2)[c,g]	46.2 (41.1, 51.3)[g]	39.1 (35.7, 42.5)[c,d,g]
High school	32.0 (29.6, 34.4)[g]	31.3 (26.9, 36.1)[e]	32.5 (29.7, 35.5)[g]	29.1 (27.1, 31.2)[e]	32.0 (29.1, 35.0)	27.5 (24.6, 30.5)[c,d,e]
>High school (ref.)	22.4 (20.3, 24.6)	22.7 (17.9, 28.1)	22.5 (20.3, 24.8)	26.1 (24.6, 27.7)[c]	30.7 (27.9, 33.6)[c]	23.6 (21.9, 25.3)[d]
Health insurance						
Any	30.9 (28.9, 33.0)[g]	28.6 (24.6, 32.8)[g]	32.2 (30.0, 34.5)[g]	29.3 (27.7, 31.0)[e]	33.6 (30.7, 36.6)[c]	27.0 (25.1, 29.0)[c,d,g]
None	45.1 (40.6, 49.7)	41.9 (33.0, 51.2)	46.5 (42.4, 50.7)	34.8 (31.4, 38.3)[c]	35.5 (29.2, 42.1)	34.5 (30.4, 38.8)[c]
Year of survey						
2003–2006				26.6 (24.8, 28.4)[c,g]	31.4 (28.6, 34.3)	23.8 (21.4, 26.3)[c,d,g]
1999–2002				33.4 (30.7, 36.2)	36.5 (31.3, 42.0)	31.6 (28.7, 34.6)

[a]Includes states with HAV vaccination recommended (Alaska, Arizona, California, Idaho, New Mexico, Nevada, Oklahoma, Oregon, South Dakota, Utah, and Washington) or considered (Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming) in 1999

[b]Includes states with no HAV vaccination recommended in 1999: Alabama, Connecticut, Delaware, Florida, Georgia, Hawaii, Kansas, Kentucky, Iowa, Illinois, Indiana, Louisiana, Massachusetts, Maryland, Maine, Michigan, Minnesota, Mississippi, North Carolina, North Dakota, Nebraska, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, South Carolina, Tennessee, Virginia, Vermont, Wisconsin, and West Virginia

[c]$p<0.05$ for comparison of NHANES 1988–1994 with NHANES 1999–2006 for the total sample and for vaccinating and non-vaccinating states by levels of each cofactor

[d]$p<0.05$ for comparison of vaccinating states with non-vaccinating states within survey cycle by levels of each cofactor

[e]$p<0.01$ for comparison of each subgroup with the appropriate reference group within each survey and population

[f]$p<0.05$ for comparison of each subgroup with the appropriate reference group within each survey and population

[g]$p<0.001$ for comparison of each subgroup with the appropriate reference group within each survey and population

anti-HAV = antibody to hepatitis A virus

HAV = hepatitis A virus

NHANES = National Health and Nutrition Examination Survey

CI = confidence interval

Ref. = reference group

FPL = federal poverty level

Age-adjusted seroprevalence of anti-HAV in 1999–2006 was significantly lower than that in 1988–1994 among adults in lower socioeconomic subgroups including those living below the FPL ($p<0.01$), living in more crowded households ($p<0.01$), having less than a high school education ($p<0.001$), and having no health insurance ($p<0.001$) (Table 3). Seroprevalence was also significantly lower during 1999–2006 than during 1988–1994 among non-Hispanic black ($p<0.001$) and Mexican American ($p<0.05$) people. In contrast, among those with more than a high school education, seroprevalence was significantly higher in 1999–2006 than in 1988–1994 ($p<0.01$). In vaccinating states, results were inconsistent (Table 3). While not always statistically significant, seroprevalence generally increased from 1988–1994 to 1999–2006 among adults in higher socioeconomic groups and decreased among those in lower socioeconomic groups. In non-vaccinating states, seroprevalence decreased significantly between 1988–1994 and 1999–2006 ($p<0.001$ for the overall population) for almost all subgroups ($p<0.05$).

DISCUSSION

We studied patterns of seroprevalence of anti-HAV during a pre-vaccine era and the vaccine eras to describe changes in population immunity over time. While overall seroprevalence changed little, it increased among U.S.-born children during 1999–2006 compared with 1988–1994 (the pre-vaccine era). This increase was almost entirely attributable to a large increase among children living in "vaccinating states," the population that was the primary target for routine hepatitis A vaccination in recommendations made in 1999.[2] Furthermore, seroprevalence was higher among younger children during 2003–2006 (i.e., the later survey cycles, when higher coverage might be expected). While we cannot prove that immunity increased in children because of vaccination, nor was it our intention to do so, our findings suggest that vaccination may have played a large role in increased immunity.

Results of hepatitis A vaccination coverage surveys provide evidence that vaccination indeed was occurring during the time the 1999–2006 survey was conducted. Vaccination with at least one dose of hepatitis A vaccine was 51% among children aged 24–35 months living in states with a recommendation to vaccinate by 2003, but only 1% among children living in states without a recommendation;[14] similar differences were documented through 2007.[15,16] At the same time, incidence of infection declined among children, especially in vaccinating states;[3] together, these findings strongly suggest that vaccination was largely the reason for the observed changes in seroprevalence of anti-HAV. Interestingly, and consistent with our findings, coverage surveys indicate higher vaccination coverage among children of less educated mothers as well as among Hispanic people, suggesting effective targeting of vaccination efforts to those at higher risk.[14]

In addition to the overall rise in the seroprevalence of anti-HAV, the pattern of immunity we observed among children surveyed during 1999–2006 was different from that found during 1988–1994, when anti-HAV positivity was attributable primarily to infection with HAV. Among children who were surveyed in 1988–1994, those living in poverty, living in areas with high hepatitis A incidence, and with Mexican American ethnicity were associated with anti-HAV seroprevalence.[7] In 1999–2006, poverty and other socioeconomic factors were not associated with anti-HAV seroprevalence in the final multivariable models. However, seroprevalence remained higher among Mexican American children, likely reflecting both increased travel-related exposures to the virus[17] as well as higher vaccination coverage.[14,18]

In contrast with the pattern of immunity among children, seroprevalence of anti-HAV was slightly, but not statistically significantly, lower among U.S.-born adults in the 1999–2006 survey compared with the 1988–1994 survey. This finding was most marked among adults aged 50–59 years and in non-vaccinating states, and was largely the result of an ongoing cohort effect described elsewhere.[7] Given the considerable rise in population immunity among children without a similar increase among adults, the decline in hepatitis A incidence among adults may be attributable to a herd immunity effect.[19] A large herd immunity effect of hepatitis A vaccination of children has been considered plausible because of the capacity of children with unrecognized or asymptomatic infections to transmit HAV to adults.[20]

We observed higher seroprevalence of anti-HAV among non-Hispanic black adults compared with non-Hispanic white adults in both NHANES 1988–1994 and 1999–2006. Adult seroprevalence likely reflects exposures during childhood decades ago. The lack of change in seroprevalence over time among adults in our study is consistent with the low vaccination levels in the first national survey of vaccination coverage among adults.[21] Results of that survey indicated that adults with higher socioeconomic status, those aged 18–29 years, and those with public insurance were more likely to have received hepatitis A vaccination. While travelers to countries with intermediate or high hepatitis A endemicity and other groups at increased risk of hepatitis A have been recommended for vaccination for many

Table 4. Predictors of anti-HAV seroprevalence from logistic regression models among U.S.-born adults >19 years of age by region based on HAV vaccine recommendation: NHANES 1999–2006

Characteristics	*All U.S. states Percent (95% CI)*	*Vaccinating states[a] Percent (95% CI)*	*Non-vaccinating states[b] Percent (95% CI)*
Region			
Vaccinating states[a]	1.3 (1.1, 1.6)[c]	NA	NA
Non-vaccinating states[b]	Ref.		
Survey year			
2003–2006	0.7 (0.6, 0.8)[d]	0.8 (0.6, 1.0)[e]	0.7 (0.5, 0.8)[d]
1999–2002	Ref.	Ref.	Ref.
Age group (in years)			
≥60	7.5 (5.8, 9.8)[d]	4.7 (3.1, 7.2)[d]	10.7 (7.3, 15.8)[d]
50–59	2.5 (1.9, 3.1)[d]	1.7 (1.2, 2.5)[c]	3.3 (2.3, 4.8)[d]
40–49	1.7 (1.4, 2.1)[d]	1.1 (0.8, 1.6)	2.4 (1.8, 3.1)[d]
30–39	1.1 (0.9, 1.3)	0.8 (0.6, 1.1)	1.4 (1.1, 2.0)[e]
20–29	Ref.	Ref.	Ref.
Race/ethnicity			
Mexican American	4.0 (3.3, 4.9)[d]	3.7 (3.1, 4.5)[d]	3.8 (2.1, 6.6)[d]
Non-Hispanic black	1.9 (1.6, 2.2)[d]	1.7 (1.3, 2.3)[d]	1.9 (1.6, 2.3)[d]
Non-Hispanic white	Ref.	Ref.	Ref.
Gender			
Male	0.9 (0.8, 1.0)	1.1 (1.0, 1.3)	0.8 (0.7, 0.9)[c]
Female	Ref.	Ref.	Ref.
Poverty index			
<FPL	1.4 (1.2, 1.7)[d]	1.4 (1.1, 1.9)[c]	1.4 (1.1, 1.7)[c]
≥FPL	Ref.	Ref.	Ref.
Crowding index (people per room)			
≥1.00	1.0 (0.8, 1.3)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)
0.50–0.99	1.1 (1.0, 1.2)	1.2 (0.9, 1.4)	1.1 (0.9, 1.2)
<0.50	Ref.	Ref.	Ref.
Education of head of household			
<High school	1.8 (1.6, 2.2)[d]	1.8 (1.5, 2.2)[d]	1.9 (1.5, 2.4)[d]
High school graduate	1.1 (1.0, 1.2)	1.0 (0.8, 1.2)	1.1 (1.0, 1.3)
>High school	Ref.	Ref.	Ref.
Health insurance			
Any	1.0 (0.8, 1.1)	1.1 (0.9, 1.4)	0.9 (0.7, 1.1)
None	Ref.	Ref.	Ref.

[a]Includes states with HAV vaccination recommended (Alaska, Arizona, California, Idaho, New Mexico, Nevada, Oklahoma, Oregon, South Dakota, Utah, and Washington) or considered (Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming) in 1999

[b]Includes states with no HAV vaccination recommended in 1999: Alabama, Connecticut, Delaware, Florida, Georgia, Hawaii, Kansas, Kentucky, Iowa, Illinois, Indiana, Louisiana, Massachusetts, Maryland, Maine, Michigan, Minnesota, Mississippi, North Carolina, North Dakota, Nebraska, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, South Carolina, Tennessee, Virginia, Vermont, Wisconsin, and West Virginia

[c]$p<0.01$ for comparison of subgroup and reference group in model

[d]$p<0.001$ for comparison of subgroup and reference group in model

[e]$p<0.05$ for comparison of subgroup and reference group in model

anti-HAV = antibody to hepatitis A virus

HAV = hepatitis A virus

NHANES = National Health and Nutrition Examination Survey

CI = confidence interval

NA = not applicable

Ref. = reference group

FPL = federal poverty level

years,[1] coverage remains low[22] and it is unlikely that the impact of this vaccination would be detectable in a population-based serologic survey such as the current NHANES study.

Limitations

This study was subject to several limitations, which should be considered when interpreting these data. First, NHANES data are generalizable to the U.S. noninstitutionalized civilian population and do not represent people residing in institutions (e.g., prisoners). While seroprevalence might be higher among some high-risk institutionalized people, an estimated 1.4% of the U.S. population was institutionalized in 2000; thus, it is unlikely that the overall seroprevalence would have been substantially underestimated.

Limitations specific to this study primarily related to the use of a qualitative enzyme immunoassay, which is unable to distinguish whether antibodies were a result of infection or vaccination. However, the seroprevalence patterns we identified were consistent with results of coverage surveys and trends in hepatitis A incidence.[3,14] Finally, the sensitivity of the assay used in this study was considerably less than that of the assays used to measure antibody response in vaccine immunogenicity studies. Given that the effect of the suboptimal sensitivity of the qualitative assay was equal across population groups, this limitation likely underestimated the overall level of population immunity, but did not affect comparisons across groups and surveys.

CONCLUSIONS

We found that overall seroprevalence of anti-HAV during the vaccine era of 1999–2006 remained unchanged with respect to the pre-vaccine era, indicating that approximately one-third of Americans had evidence of immunity to HAV infection; as in previous surveys, seroprevalence was highly age dependent. However, changes in the pattern of seroprevalence, including regional variation and increases in seroprevalence among U.S.-born children living in vaccinating states, were likely the effect of implementing the 1999 ACIP hepatitis A vaccination recommendations. In light of large overall declines in hepatitis A incidence, these findings suggest a considerable herd immunity effect of childhood vaccination. Seroprevalence data are a useful component of the data systems needed to guide vaccination policy; continued monitoring is important as the epidemiology of hepatitis A changes in the U.S.

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