Control of Hepatitis A Through Routine Vaccination of Children

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Hepatitis A continues to be one of the most frequently reported vaccine-preventable diseases in the United States. Hepatitis A incidence displays a cyclic pattern, and most disease occurs in the context of community-wide outbreaks during which a large proportion of patients do not have a recognized risk factor. Available data suggest that young children, frequently asymptomatic when infected, play an important role in hepatitis A virus (HAV) transmission. Until recently, immunoglobulin and improved hygiene were the only measures available to prevent and control hepatitis A. Although immunoglobulin has been shown to be effective in preventing hepatitis A among persons with a recognized exposure, it has limited effectiveness in controlling the spread of HAV infection in the community because many people are unaware of their exposure.

Hepatitis A vaccines, available in the United States since 1995, are highly effective in preventing disease among immunized persons. Routine vaccination of children living in small communities that had experienced recurrent hepatitis A epidemics and in which most adults are immune has been shown to be effective in helping to interrupt disease transmission. However, the impact of routine childhood vaccination on disease incidence in large communities that experience recurrent epidemics, where most of the population is thought to be susceptible to the disease, has not been determined.

Context The impact of routine hepatitis A vaccination of children living in large communities with elevated disease rates has not been evaluated.

Objective To determine the effect of routine vaccination of children on disease incidence in a community with recurrent hepatitis A epidemics.

Design, Setting, and Participants Community-based demonstration project conducted from January 12, 1995, through December 31, 2000, in Butte County, California, among children aged 2 to 17 years.

Intervention In 1995, vaccination was offered to children aged 2 to 12 years during vaccination clinics conducted on 2 occasions 6 to 12 months apart at most schools in the county. In 1996-2000, vaccine was distributed to community health care clinicians, who vaccinated eligible children without charge. Vaccine was also available at health department clinics, selected child care centers, and other sites.

Main Outcome Measures Hepatitis A vaccination coverage, hepatitis A incidence, and vaccine effectiveness.

Results During the study period, 29789 (66.2%) of an estimated 44982 eligible children received at least 1 vaccine dose; 17681 (39.3%) received a second dose. The number of hepatitis A cases among the entire county population declined 93.5% during the study period, from 57 cases in 1995 to 4 in 2000, the lowest number of cases reported in the county since hepatitis A surveillance began in 1966. The 2000 incidence rate of 1.9 per 100000 population was the lowest of any county in the state. Of the 249 cases reported during the 6-year period, 40 (16.3%) occurred among children 17 years of age or younger, of which 16 (40%) occurred in 1995 and only 1 in 2000. One of the 27 case patients eligible for vaccination had been vaccinated, having received the first dose 3 days before symptom onset. The estimated protective vaccine efficacy was 98% (95% confidence interval, 86%-100%).

Conclusions In this population, hepatitis A vaccine was highly effective in preventing disease among recipients. Childhood vaccination appears to have decreased hepatitis A incidence among children and adults and controlled the disease in a community with recurrent epidemics.

JAMA. 2001;286:2968-2973

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tine hepatitis A vaccination of children in one such community.

**METHODS**

Butte County, with an estimated year 2000 population of 207,158, is located in the San Joaquin Valley of California. During an outbreak of hepatitis A from 1985 to 1988, 495 cases (average annual incidence, 112.7 per 100,000 population) were reported, and between 1988 and 1992, the incidence fluctuated between 20 and 45 per 100,000 population. The number of reported cases increased to 128 (65.2 per 100,000 population) in 1993 and then to 230 (117.3 per 100,000 population) in 1994. The 1994 rate was highest among children younger than 15 years (193.0 per 100,000 population).

From January 12, 1995, through December 31, 2000, hepatitis A vaccine was offered free of charge to children residing in the county by means of a demonstration project conducted in 2 phases. In 1995, the project focused primarily on controlling the ongoing outbreak by vaccination of children under an investigational new drug (IND) protocol before the vaccine was licensed by the US Food and Drug Administration (FDA). From 1996 through 2000, following FDA licensure of the vaccine, the project evaluated the effectiveness of routine vaccination of children. The study was approved by the institutional review board of the Centers for Disease Control and Prevention (CDC) and the Butte County Board of Supervisors.

**Target Population**

During the first phase, in 1995, vaccination was recommended and made available to children aged 2 to 12 years. The vaccine was offered to eligible children during vaccination clinics conducted on 2 occasions 6 to 12 months apart at most schools in the county. School-aged children up to 12 years (or in the seventh grade) were encouraged to receive the vaccine during the school vaccination clinics. Preschool-aged children also could be vaccinated at the school clinics. In addition, vaccine was offered to all eligible children aged 2 to 12 years at routine vaccination clinics conducted at Butte County Health Department (BCHD) sites.

Each child was given a vaccine adverse event report card, thermometer, and instructions for parents on how to record temperature and adverse events. Parents were asked to return the cards to the school or health department and to report serious adverse events to the health department immediately by telephone.

The second phase of the study, 1996-2000, focused on establishment of sustained childhood hepatitis A vaccination in the county through community health care practitioners. Vaccine was distributed to clinicians who agreed to vaccinate eligible children in their practice without charge and provide information on each vaccinated child to a registry maintained by the BCHD. Vaccine was also made available at health department clinics, selected child care centers, and other sites, such as the Department of Agriculture’s Special Supplemental Program for Women, Infants, and Children (WIC) clinics. The target population increased annually to include those additional birth cohorts of children who had reached their second birthday and children who were older than 12 years. By the end of the study, children aged 2 to 17 years were eligible to receive vaccine and were included in the analysis.

The vaccination registry maintained by the BCHD recorded date and place of vaccination, demographic data, and adverse events. First- and second-dose vaccination coverage was calculated using registry data and population estimates. Population estimates, including race and ethnicity, were obtained from the State of California, Department of Finance, Demographic Research Unit. The estimated number of unvaccinated children was determined by subtracting the number of children vaccinated (from the registry) from the estimated population. These estimates were also used for calculating vaccine effectiveness.

**Hepatitis A Vaccine**

Inactivated hepatitis A vaccine (VAQTA, Merck & Co Inc, West Point, Pa) was administered as the pediatric formulation (25 U, approximately 25 ng of purified viral protein in 0.5-mL volume) on a 2-dose (0- and 6- to 12-month) schedule. Because the first phase of the study was conducted under an IND protocol, the written consent reflected that the vaccine had not been licensed by the FDA. When the vaccine was licensed in 1996, a standard, simplified consent form, similar to the vaccine information statement recommended by the CDC, was used. The vaccine is licensed for persons aged 2 years or older.

**Hepatitis A Surveillance**

Although hepatitis A reporting is required by California law, enhanced surveillance was established in the county in 1995, coincident with implementation of the vaccination program. Reporting was stimulated in sites most likely to encounter cases and included weekly contact with emergency department and walk-in clinic staff to ascertain the number of suspected cases or serologic test results indicative of hepatitis A. In addition, laboratories that conducted diagnostic testing for hepatitis A were contacted and asked to report all positive test results that originated from Butte County. Surveillance was further stimulated by mailing letters to primary care practitioners (including pediatricians, family physicians, and general practitioners) that encouraged reporting of suspected cases. In addition, information about the study was presented at regularly scheduled continuing education meetings for physicians and nurses.

A case patient was defined as a patient with a positive serologic test result for IgM antibody to HAV (anti-HAV) or the clinical diagnosis of hepatitis A without serologic confirmation. All suspected case patients were interviewed by a study nurse (I.H.). A detailed standard case investigation form, the Viral Hepatitis Surveillance Program form, was used to collect additional demographic and risk factor information on reported cases. Case patients were asked about re-
ceipt of hepatitis A vaccine, and the vacci-
nation registry was also searched for ver-
ification of receipt of vaccine.

To assess the impact of the vaccina-
tion program, age-specific hepatitis A in-
cidence in the county during the 6-year
vaccination program was compared with
the incidence during 1990-1994, be-
fore the program. The mean of the 5 or
6 annual rates, using the estimated popu-
lation denominator for the relevant year
for each rate, was calculated. In addi-
tion, statewide, age-specific hepatitis A
incidence was compared with that in
Butte County for 1990-1994 and 1995-
2000, using surveillance data reported to
the National Notifiable Diseases Surveil-
lance System (NNDSS) of the CDC.

The NNDSS data for 2000 are provisional.

Estimates of Vaccine Effectiveness
Vaccine effectiveness was estimated by
comparing the incidence of reported
hepatitis A among children who had re-
ceived at least 1 dose of vaccine to the
incidence among unvaccinated chil-
dren of the same age. Vaccine effec-
tiveness was calculated using the follow-
ing formula: 1 - (observed attack rate in
vaccine recipients/observed attack rate
in unvaccinated children). The hepa-
titis A attack rate in vaccine recipients was
calculated as follows: number of re-
ported cases among vaccinated chil-
dren (ie, receiving ≥1 dose of hepatitis
A vaccine)/number of vaccinated chil-
dren in the vaccine registry. The attack
rate for unvaccinated children was cal-
culated as follows: number of re-
ported cases among unvaccinated chil-
dren (ie, receiving 0 doses of hepatitis
A vaccine)/estimated number of unvaccinated
children in the target age group. Vaccine ef-
effectiveness estimates were based on
number of children eligible at the end
of the study period (ie, aged 2-17 years).

Statistical Analysis
Data were analyzed using Epi Info soft-
ware, version 6.04b (CDC) and SAS sta-
tistical software, version 8e (SAS Insti-
tute Inc, Cary, NC). The Taylor series
95% confidence interval (CI) for the es-
imate of vaccine effectiveness was cal-
culated.

RESULTS
Vaccination Coverage
From January 12, 1995, through De-
cember 31, 2000, of an estimated 44982
children in the age groups eligible for
hepatitis A vaccination, 29789 (66.2%)
received at least 1 dose of vaccine and
17681 (39.3%) received 2 doses. First-
dose vaccination coverage increased an-
nually from 35.2% to 66.2%, and sec-
ond dose coverage increased from
14.5% to 39.3% (FIGURE 1). Cumul-
tive first dose vaccination coverage was
similar among children aged 5 to 10
years (69.0%, 11 352/16460) and 11 to
17 years (67.8%, 14 047/20 730) and
lower among children aged 2 to 4 years
(56.3%, 4390/7792).

The number and ages of children vac-
cinated varied during the 2 phases of
the project. In 1995, when school-based vac-
nination was the primary strategy used,
10754 (35.2%) of the 30 575 children
aged 2 to 12 years received at least 1 dose
of hepatitis A vaccine. Of these, 9805
(91.2%) were school-aged (>5 years),
and 10205 (94.8%) received their first
dose of vaccine during school-based vac-
nination clinics. In 1996-2000 (the sec-
ond phase of the program), an addi-
tional 19 035 children received 1 or more
vaccine doses; of these, 10 668 (56.0%)
were aged 5 years or older and 8367
(44.0%) were 2 to 4 years. After 1995,
most children (14 484 [76%]) were vac-
cinated in clinical settings.

Disease Incidence
The average annual hepatitis A inci-
dence in Butte County during the 5 years
before the demonstration project (1990-
1994) was 47.9 per 100 000 population
(range, 122.5-11.8 per 100 000 population)
and declined by 56.8% to 20.7 per
100 000 population (range, 48.7-0.97 per
100 000 population) during 1995-2000
(FIGURE 2). The age-specific incidence
decreased among all age groups during
1995-2000 compared with that in
1990-1994, but the effect was most pro-

![Figure 1](volatile-url)

**Figure 1.** Hepatitis A Vaccination Coverage Among Children by Year in Butte County, California, 1995-2000

*Vaccination Coverage:
- First Dose
- Second Dose

Age groups varied by year: 1995 includes 2- to 12-year-olds; 1996 includes 2- to 13-year-olds; 1997 includes 2- to 14-year-olds; 1998 includes 2- to 15-year-olds; 1999 includes 2- to 16-year-olds; and 2000 includes 2- to 17-year-olds.

![Figure 2](volatile-url)

**Figure 2.** Reported Hepatitis A Cases in Butte County, California, 1980-2000 (n=1558)
nounced among the younger age groups (Figure 3). Incidence decreased 78.9% among children aged 17 years or younger (67.3 to 13.5 per 100000 population) compared with 44.3% among persons older than 17 years (41.3 to 23.0 per 100000 population).

Of the 245 cases reported to the BCHD between 1995 and 2000, 243 (99.2%) were serologically confirmed. Thirteen patients required hospitalization and 4 died (aged 39, 41, 56, and 79 years). During this period, the reported number of cases declined 93.5%, from 57 in 1995 to 4 in 2000 (Figure 2). Of the 40 (16.3%) cases that occurred among children 17 years or younger during 1995-2000, 16 (40%) occurred in 1995 and only 1 occurred in 2000.

During 1995-2000, 60.8% (n=149; cumulative incidence, 147.3 per 100000 population) of cases occurred among males. Non-Hispanic whites accounted for 87.3% (n=214; cumulative incidence, 123.2 per 100000 population) of the cases, whereas Native Americans (n=15; cumulative incidence, 449.1 per 100000 population), Hispanics (n=10; cumulative incidence, 53.9 per 100000 population), Asian and Pacific Islanders (n=5; cumulative incidence, 60.8 per 100000 population), and blacks (n=1; cumulative incidence, 36.2 per 100000 population) accounted for the remainder.

Recognized potential sources of infection reported by case patients included contact with a hepatitis A case (n=89, 36.3%) and illegal drug use (n=25, 10.2%). Antecedent international travel to a country with endemic hepatitis A (n=9), association with child care (n=7), homosexual activity (n=5), and association with a common source outbreak of hepatitis A (n=2) were each reported by less than 3% of case patients. For 108 case patients (44.1%), no risk factor could be identified. All 25 case patients who identified drug use as a risk factor were reported during 1996-1997.

During 1990-1997, annual hepatitis A incidence in Butte County was at least equal to, and up to 5.7 times higher, than the overall California rate (Figure 4). In 1998, the Butte County hepatitis A rate fell below the overall California rate and stayed lower through 2000. In 2000, the Butte County rate (1.9 per 100000 population) was the lowest reported in any county in the state (data not shown). Compared with the previous 5 years, age-specific incidence during the study period declined 80% among children aged 17 years or younger in the county, compared with 21% in the state (Figure 5).

Vaccine Effectiveness
During the study period, 27 hepatitis A cases occurred among children eligible for the vaccination program, including 26 among the 15193 unvaccinated children and 1 in a 12-year-old boy who had received his first dose of vaccine 3 days before onset of illness. The estimated protective efficacy of 1 or more doses of vaccine was 98% (95% CI, 86%-100%).

Adverse Reactions
No serious adverse events were reported among the 29789 children who received 1 or more doses during the study period. Among the 5471 vaccine doses for which report cards were

![Figure 3. Average Annual Age-Specific Hepatitis A Incidence in Butte County, California, 1990-1994 and 1995-2000](image1)

![Figure 4. Hepatitis A Annual Incidence in Butte County, California, and All of California, 1990-2000](image2)
Fig. 5. Average Annual Hepatitis A Incidence by Age Group for Butte County, California, and All of California, 1990-1994 and 1995-2000

available (accounting for 30.6% of prelicensure vaccine doses administered), adverse reactions were reported on 1983 (36.2%), were generally described as mild, and included injection site reactions, fever, or rash.

COMMENT

This 6-year project demonstrated the feasibility and effectiveness of routine childhood hepatitis A vaccination and its impact on community-wide rates of disease. Hepatitis A incidence declined to historic lows following the introduction of hepatitis A vaccination, and since 1998, the number of reported cases has been lower than in any year since hepatitis A surveillance began in 1966. The decline appears to be sustained; only 2 cases were reported to the CDC during the first half of 2001 (CDC, unpublished data, 2001). Furthermore, the 2000 Butte County disease rate was the lowest of any county in California, suggesting that community-wide childhood vaccination was responsible for a sustained reduction in hepatitis A incidence in Butte County. Finally, no serious adverse events were reported among the nearly 30,000 vaccine recipients, supporting the safety of hepatitis A vaccination.

Although the overall purpose of the demonstration project was to evaluate whether childhood hepatitis A vaccination could be sustained, the purpose of the first phase was to evaluate whether rapid vaccination of multiple age cohorts could control the ongoing outbreak.25 However, the impact of the first phase is uncertain. As has been the experience in other large communities, the vaccination program in Butte County was not begun until well into the second year of the outbreak, when hepatitis A incidence may have already been waning.25 Other California counties with similar historical patterns of hepatitis A incidence and without vaccination programs also reported declines in incidence during this time. However, vaccination may have shortened the epidemic, which lasted 2 years compared with the previous 3-year epidemic. In addition, sustained community-wide vaccination may prevent future outbreaks, as has been observed in smaller communities.25

Before the demonstration project, children had the highest disease incidence in Butte County, and incidence declined to levels below that of adults following the implementation of the vaccination program. Of the cases that were reported during the vaccination program, including during the peak year of 1997, a substantial proportion occurred among adult users of illegal drugs; this appears to have mitigated the impact of childhood vaccination on overall disease incidence. Other studies have suggested that HAV transmission can be sustained among adult users of illegal drugs with little transmission to or from children.26 However, the long-term impact of vaccination of children and adolescents on transmission among adult drug users is unknown.

This study has some potential limitations. Because the incidence of hepatitis A varies from year to year, it is not possible to know what the incidence would have been without the vaccination program and we did not have the benefit of a “control” community. However, we compared hepatitis A incidence in Butte County to that in the rest of California and also before and after implementation of the vaccination program, with Butte County serving as its own control. Both analyses suggested the effectiveness of the vaccination program.

Alternative explanations for the observed decline in hepatitis A incidence could be postulated. “Surveillance fatigue” could have occurred if cases continued to occur but were not reported to the surveillance system. However, hepatitis A reporting did not begin with the advent of the vaccination program but has been ongoing in Butte County and the rest of the state for more than 20 years. Although it is possible that the initial enthusiasm for the enhanced surveillance implemented during the program waned, it is extremely unlikely that passive routine surveillance would be affected. Furthermore, physicians were not the only source of reports; positive reports were also received from laboratories. Depletion of the pool of susceptible persons in the population would also lead to a decline in incidence. However, although the age-specific prevalence of immunity in Butte County is unknown, serologic surveys indicate that most of the US population remains susceptible to HAV infection.3 Although reasons for the spontaneous waning of community-wide outbreaks are not well understood, taking into consideration the relatively low baseline prevalence of immunity and the number of cases typically reported during outbreaks, a considerable proportion of the population remains susceptible to HAV infection even after outbreaks.

We calculated vaccine effectiveness in preventing symptomatic, clinically recognizable hepatitis A, not asymptomatic HAV infection. This allows for comparison between our results and those of published efficacy studies.18,19 We did not verify the vaccination status of children not listed in the vaccination registry. However, because of the widespread availability of the study vaccine, we believe that very few, if any, children in Butte County received hepatitis A vaccine outside the study.

Childhood hepatitis A vaccination in Butte County posed some unique challenges, including the lack of a routinely scheduled immunization visit for children aged 2 years or older and the need to initially administer vaccine under an IND protocol, which necessitated more involved consent procedures. School-based vaccination clinics...
were used at the outset as the primary vaccination sites and achieved only modest vaccination coverage rates in schoolchildren and low rates in preschool children. When clinician-based vaccination was introduced as the primary vaccination strategy for all children following vaccine licensure, vaccination coverage increased, indicating that it is possible to achieve fairly high levels of hepatitis A vaccination coverage among children.

To our knowledge, no other community of this size in the United States has delivered hepatitis A vaccine to such a large proportion of its children and sustained a vaccination program for 6 years. The Butte County experience suggests that, over time, routine vaccination of children can reduce overall disease rates in the community. This previews the potential impact of routine childhood hepatitis A vaccination, as recently recommended by the Advisory Committee on Immunization Practices for areas of the United States with consistently high hepatitis A infection rates.5

Author Contributions: Dr Bell had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. The data were not provided to Merck & Co Inc.

Study concept and design: Averhoff, Shapiro, Bell, Hyams, Nalin, Ward, Smith, Margolis.

Acquisition of data: Averhoff, Bell, Hyams, Nalin, Ward, Ward, Hyams, Deladisma, Smard, Nalin, Smith, Margolis.

Analysis and interpretation of data: Averhoff, Bell, Deladisma, Simard, Nalin, Smith, Margolis.

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