Screening travelers for hepatitis A antibodies

An observational cost-comparison study of vaccine use

ABSTRACT ● **Objectives** To measure the seroprevalence of antibodies to hepatitis A virus (anti-HAV) in a health plan population of travelers and to determine whether prevaccination screening for anti-HAV can reduce unnecessary vaccination and thus promote the most effective, economic use of hepatitis A vaccine. ● **Design** Observational, cost-comparison study. ● **Setting** Central injection clinic of a health maintenance organization medical center. ● **Subjects** Five hundred twenty-seven adults who denied having previous hepatitis A or vaccination. ● **Main outcome measures** Subgroups with the greatest prevalence of anti-HAV seen between June 1995 and April 1996 for immunizations before traveling to nonindustrialized countries. Relative costs of their screening and immunization. ● **Results** The presence of anti-HAV precluded the need for vaccination in 148 subjects (28.1%). The highest prevalence of anti-HAV (82.7%) was found in subjects born in nonindustrialized countries (62/75), in subjects who had previously traveled to areas of endemic hepatitis A (32.1% [135/420]), and in subjects born before 1945 (29.2% [92/315]). Costs of screening and vaccinating travelers were cheapest if prevaccination antibody sera testing was limited to subjects born in nonindustrialized countries and those born before 1945. ● **Conclusions** Prevaccination screening of travelers for hepatitis A can be done selectively on the basis of age and country of origin. This strategy could lead to a more economic use of the vaccine and clinic resources.

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INTRODUCTION

Travelers to nonindustrialized countries or to areas endemic for hepatitis A virus (HAV) are at risk for contracting hepatitis A, primarily through contact with contaminated food or water. For frequent or long-term travelers, the new hepatitis A vaccine provides longer-lasting protection than immune serum globulin (ISG),[1] which was previously the only prophylactic medication available to travelers to areas of endemic hepatitis A. The vaccine provides much higher antibody titers and much longer-lasting protection than that provided by ISG.

The symptoms of HAV infection are often mild or unnoticed. Therefore, the true prevalence of HAV infection is difficult to determine.[2] Previous research has identified specific groups of people who are more likely to have antibodies to HAV (anti-HAV). In nonindustrialized countries, HAV infection occurs frequently in children and is typically mild or asymptomatic.[2] Almost all children in areas of highly endemic HAV have anti-HAV before age 10 years.[3,4] Thus, people born in nonindustrialized countries have a higher prevalence of anti-HAV than the general US population.[4,5] Moreover, because sanitation in the United States and in other industrialized nations has improved during the past half century, the prevalence of anti-HAV is higher in older people and lower in those born in the past 30 to 40 years.[6] In industrialized nations, persons aged 51 years or older have historically had the highest seroprevalence rates of anti-HAV: 50% to 60% of the population aged 51 years or older test positive for anti-HAV in serum specimens.[4] In a 3-month pilot study conducted at Kaiser Permanente Medical Center in Denver, Colorado, during 1996, travelers were screened for anti-HAV.[7] Of the 49 seropositive patients found, 22 (45%) were born outside the United States, and 26 (96%) of the 27 remaining seropositive patients were aged 55 years or older.[7] Travelers to areas of endemic hepatitis A, particularly those who deviate from normal tourist routes, can also be presumed to have a higher incidence of anti-HAV.[1]

We undertook this study to ascertain the seroprevalence of anti-HAV in our health maintenance organization (HMO) population by examining factors other than age alone. After groups with the highest incidence of anti-HAV are identified, methods to implement selective prevaccination screening could be developed to reduce unnecessary vaccination.

METHODS

Kaiser Permanente Medical Center in Sacramento, California, is a staff-model HMO facility that provides care to more than 500,000 Kaiser Foundation Health Plan members who live in the surrounding area. All members of this health plan who travel outside the country receive information and immunizations at an adult injection clinic supervised by 2 registered nurses in consultation with a physician specializing in infectious disease. With the use of a prospective questionnaire administered in the injection clinic from June 1995 through April 1996, travel medicine needs were evaluated for 527 members from ages 18 through 82 years who were traveling to nonindustrialized

countries. This pilot work was used to devise a strategy for the most economic use of hepatitis A vaccine.

On the basis of questionnaire responses, travelers were categorized by age, country of origin, vaccination history, and previous travel experience. Only travelers who denied having previous vaccination with hepatitis A vaccine, known infection with HAV, or injection with ISG within the previous 6 months were included in the study. Before vaccination, travelers were screened for IgG anti-HAV levels using an enzyme immunoassay. Hepatitis A vaccine was administered to those who were not immune. Pediatric patients, travelers who elected not to use our travel clinic, and those who chose not to participate in the study were excluded from our analysis. Travelers to industrialized countries were excluded from this study, and 6 travelers were excluded because they were leaving the country before test results could be received. All of these excluded travelers could conceivably have a different anti-HAV profile than our study participants.

We compared the cost of prevaccination screening in subjects who lacked immunity. This cost analysis included 2 options: screening all travelers without categorizing them into subgroups and vaccinating all travelers without conducting prevaccination screening. The cost of the antibody test was estimated to be $7.00, and the mean wholesale price of 2 doses of HAV vaccine was estimated to be $118.90[8]: Estimated clinic personnel costs were based on a time requirement of 10 minutes per test (patient education, preparing laboratory slips, drawing blood specimens, and notifying patients of results reported in 2-3 days) at our organization's fully benefited contract rate of $35.00 per hour for registered nurses. The benefits include coverage for health and dental insurance, vacation pay, sick pay, and holiday pay in addition to hourly compensation.

Table 1 *Prevalence of antibodies to hepatitis A virus (anti-HAV) in 527 travelers screened at a central injection clinic of a health maintenance organization*

Group characteristics	No. of subjects tested	No. (%) of subjects positive for anti-HAV
Age, yr		
Overall*	527	146 (27.7)
18-50 (ie, born after 1945)	212	54 (25.5)
≥51 (ie, born in 1945 or earlier)	315	92 (29.2)
Born in nonindustrialized country†	75	62 (82.7)
Previously traveled to areas of endemic hepatitis A	420	135 (32.1)
Born in industrialized country		
Overall	428	71 (16.6)
Age 18-50 yr (ie, born after 1945)‡	158	10 (6.3)
≥51 yr (ie, born in 1945 or earlier)	270	61 (22.6)

*Includes patients who did not fit measures of other groups because of indefinite birth history.
†Includes 1 subject each from Spain, Venezuela, Iran, Tanzania, Rwanda, Zambia, Mexico, and Thailand; 2 from Peru; 3 each from Yugoslavia and unspecified African countries; 6 from Philippines; 12 each from China and Vietnam or Cambodia; and 29 from India.
‡Includes 1 subject each from Netherlands and Sweden; 2 each from Australia, Canada, Scotland, and Germany; 3 each from England, Japan, and Ireland; and 139 from United States.

RESULTS

Specific subgroups had a higher rate of HAV immunity than other groups (table 1). Of 527 travelers whose questionnaire responses noted travel to nonindustrialized countries, 75 were born in nonindustrialized countries; of these 75 travelers, 62 (82.7%) had HAV immunity—the highest overall rate of any group, regardless of age. In comparison, only 71 (16.6%) of 428 travelers born in industrialized countries showed immunity to HAV. However, when this group of travelers was categorized by age, the percentage of HAV immunity was even lower than the 17% rate for travelers aged 50 years or younger who were born in industrialized countries. Of the 158 travelers in this category, 10 (6.3%) had anti-HAV. For travelers aged 51 years or older who were born in industrialized countries, the percentage was higher than the 17% rate for all travelers born in nonindustrialized countries. Of the 270 travelers in this category, 61 (22.6%) had anti-HAV. A large percentage (80.0%) of the 527 travelers responding to the questionnaire had previously traveled to areas of endemic hepatitis A, and 135 (32.1%) of these 420 subjects showed HAV immunity. Screening by age alone was not as good a predictor of HAV immunity as other indicators. HAV immunity was found in 54 (25.5%) subjects aged 18 through 50 years and in 92 (29.2%) subjects aged 51 years or older.

Combining travelers aged 51 years or older and those born after 1945 in a nonindustrialized country yielded a group that had the highest prevalence of anti-HAV (table 2).[8] The calculated cost for screening and immunizing the seronegative subjects in this group was $52,481, or $99.58 per traveler seen. The next cheapest strategy (prevaccination screening of all travelers with subsequent immunization as needed) was calculated to cost $54,276, or $102.99 per traveler. The third cheapest strategy (screen and immunize those who had traveled to areas where hepatitis A was endemic) was calculated to cost $54,284, or $103.01 per traveler seen. Screening travelers aged 18 through 50 years who were born in industrialized countries was calculated to cost $66,512, or $126.21 per traveler seen. Vaccination of all patients without any prevaccination screening was calculated to cost $65,732, or $124.73 per traveler seen. The cost difference between the cheapest screening strategy and the most expensive screening strategy was $14,031, or $26.63 per traveler seen; and the difference in cost between the cheapest strategy and the strategy of vaccinating all travelers without any prevaccination screening was $13,251, or $25.15 per traveler seen. The difference in cost between the cheapest strategy and

Table 2 *Cost comparison (in 1996 $US) of prevaccination strategies for screening 527 members of a health maintenance organization for anti-HAV*

Subgroup screened (No. subjects)	Laboratory cost of screening, $*	Personnel cost of screening, $†	Cost of vaccine‡ (No. subjects vaccinated), $§	Personnel cost of vaccine administration, $‖	Total cost, $	Cost of strategy per traveler seen, $	Cost ranking of screening strategy¶
None; vaccination only (527)	NA	NA	62,660 (527)	3,072	65,732	124.73	9
All (527)	3,680	3,074	45,301 (381)	2,221	54,276	102.99	2
Age 18-50 yr (212)	1,484	1,237	56,240 (473)	2,758	61,719	117.11	7
Born after 1945 in industrialized country (158)	1,106	921	61,471 (517)	3,014	66,512	126.21	10
Born after 1945 in a nonindustrialized country (52)	364	303	57,429 (483)	2,816	60,912	115.58	5
Age ≥51 yr (315)	2,205	1,838	51,721 (435)	2,536	58,300	110.63	4
Born in 1945 or earlier in industrialized country (270)	1,890	1,575	55,407 (466)	2,717	61,589	116.87	6
Born in 1945 or earlier in nonindustrialized country (23)	161	134	60,520 (509)	2,967	63,782	121.03	8
Age ≥51 yr or born after 1945 in nonindustrialized country (367)	2,569	2,140	45,539 (383)	2,233	52,481	99.58	1
Previously traveled to area of endemic hepatitis A (420)	2,940	2,450	46,609 (392)	2,285	54,284	103.01	3

NA = not applicable.
*Based on Kaiser Permanente Regional Laboratory, Berkeley, California, cost of $7.00 per test and 5 minutes of personnel time to draw the specimen at fully benefited cost.
†Additional personnel cost based on 10 minutes per test (explain to patient, prepare laboratory slips, review results, notify patient of results) at fully benefited cost of $35.00 per hour.
‡Based on mean wholesale cost of $59.45 per injection (Havrix vaccine; SmithKline Beecham Biologicals, Rixensart, Belgium)[8]; 2-shot series administered in 6 to 12 months.
§Subgroup members who tested negative for anti-HAV plus others who were vaccinated presumptively and were not tested.
‖Based on time estimate of 5 minutes per injection (including registration time) at $35.00 per hour.
¶1 = least costly, and 10 = most costly.

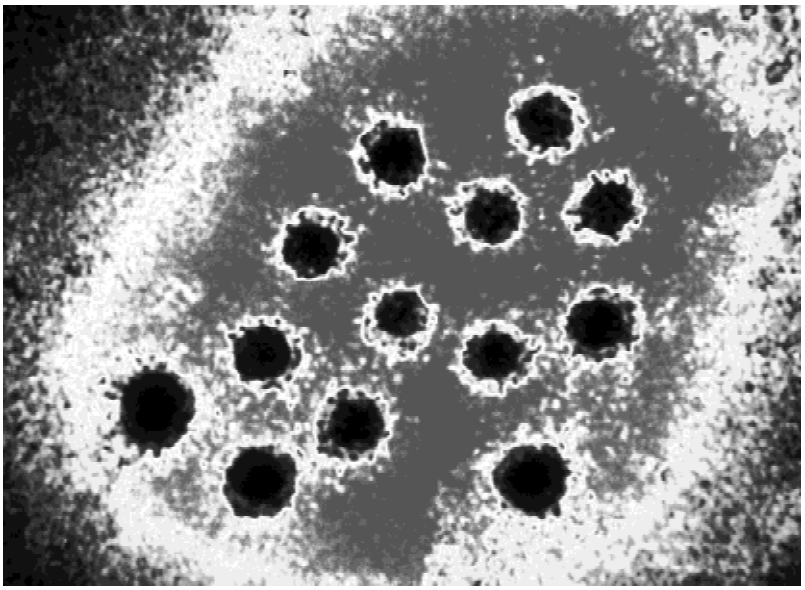
the strategy of screening all travelers was $1,795, or $3.41 per traveler seen.

DISCUSSION

The HAV vaccine is safe and effective: response rates as high as 99% to 100% after 2 doses have been reported,[9,10] and the vaccine has shown an exceptional safety profile.[11] Hepatitis A vaccine may provide protection for at least 20 years[5] and is the preferred method of prophylaxis for frequent or long-term travelers. Because medicine has become increasingly cost-conscious, most medical organizations would seek a vaccine that effectively prevents morbidity while minimizing costs and unnecessary vaccination.

The prevalence of anti-HAV varies widely among socioeconomic groups, even within the same geographic area.[2,12] Travelers to nonindustrialized countries risk exposure to hepatitis A, which can cause clinically significant morbidity.[13,14] Our study shows that prevaccination screening for anti-HAV may be useful for certain subgroups of travelers to nonindustrialized countries and that age alone is an insufficient variable for achieving the most cost-effective screening. Screening for anti-HAV in all travelers was less expensive than vaccinating all travelers without screening.

The cheapest strategy for providing vaccine to the study group was to selectively screen subgroups who had the highest rates of HAV immunity. In contrast, screening the group least likely to have anti-HAV was the most expensive way to carry out vaccination. After our screening program identified the subgroups of travelers who have the highest prevalence of anti-HAV, the cheapest strategy was to screen all travelers born before 1945 and those born in nonindustrialized countries after 1945. All other travelers were offered vaccination without screening because the incidence of anti-HAV in those travelers was low. No clinically significant adverse effects have been reported elsewhere in persons receiving the vaccine who have existing immunity to HAV.[5]



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The hepatitis A virus particles are prominent in this transmission electron micrograph

Only a small difference in cost per traveler was seen between the cheapest screening strategy and that of screening all travelers ($3.41). In a clinic such as ours with a high volume of travelers, selective screening can save money over time.

Given the difference in cost between administering vaccine without screening and administering vaccine with screening, one of the most expensive strategies in this analysis was to vaccinate all travelers without prevaccination screening. In addition, although traveler satisfaction was not directly measured in this study, the nurses operating the travel clinic reported an overwhelmingly positive response to the strategy of prevaccination screening. This positive response was especially true for travelers in the subgroups with a high prevalence of anti-HAV, in whom having a single blood test was preferable to receiving a series of 2 vaccinations. Avoiding unnecessary vaccinations and future trips to the clinic was highly desired by our travelers in general. Overall, travelers expressed high satisfaction when they were assured that they were already protected from HAV infection and that they, therefore, did not need the series of 2 vaccinations.

Our study assumes 100% compliance with the 2-injection vaccination series. However, even if the compliance rate for the second vaccination drops to as low as 50%, our cost ranking of screening strategies remains unchanged. A related observation is that, given 0% compliance with the second vaccination (ie, a single-injection vaccine series), the cost ranking of screening strategies changes so that the strategy of screening all travelers becomes slightly less expensive than screening all travelers born before 1945 and those born in nonindustrialized countries after 1945.

Another issue to consider is how the cost and effectiveness of using ISG for hepatitis A prevention compares with that of using the vaccine. The cost of ISG is about $28.72 per 2 mL.[8] The ISG vaccine provides protection for 3 to 6 months and is administered by the deep intramuscular route. The cost of both the ISG and the clinic visit needed to administer it would exceed the cost of 2 doses of HAV vaccine and their administration costs if a traveler went to nonindustrialized areas more than 4 times. The use of HAV vaccine for frequent travelers (travel abroad >4 times during a lifetime) would be more economical and would reduce the number of office visits needed by the traveler.

The cost of the vaccine is not expected to decrease greatly in the near future. However, how a change in vaccine cost would alter our cost ranking of screening strategies is a question that could be asked. On the basis of our cost assumptions, our recommended screening strategy would remain the most economic strategy, even with a 50% decrease in vaccine cost, and the most expensive strategy would remain so.

Another factor that could possibly affect our results is the effect of a less specific or less sensitive test for detecting anti-HAV. A more specific or a more sensitive test or 1 more specific and sensitive would not change our cost comparison. If the screening test is 10% less sensitive (ie, gives more false-negative results), the cost ranking of screening strategy remains unchanged for rankings 1 through 3. If the screening test is 10% less specific (ie, gives more false-positive results), then the strategy of screening travelers with previous travel to hepatitis A endemic areas becomes the least costly strategy, followed by the strategy of screening travelers 51 years or older or those born after 1945 in a nonindustrialized country.

Our findings and screening strategy may not be applicable to patient populations in other areas of the United States or in other industrialized nations because seroprevalence rates for anti-HAV may differ and because costs of vaccine and vaccine administration may also vary.

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