Recommendations for Prevention of Hepatitis A Based on a Cost-Effectiveness Analysis

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Background. Hepatitis A viral infection poses a substantial risk for travelers from low-endemic countries visiting high-endemic destinations. In this study, the general indications for the optimal prevention of hepatitis A are derived using a cost-effectiveness analysis based on the risk exposure determined by frequency and duration of travel as well as natural immunity.

Methods. Three possible hepatitis A prevention strategies are compared to no prophylaxis: active immunization; an initial screening for HAV followed by active immunization of susceptible travelers; and passive immunization with immune globulins. Using a number of baseline assumptions, a scenario for travel from low- to high-endemic countries and an average travel duration and frequency rate, threshold values were obtained comparing active versus passive immunization.

Results. The study shows that, for travelers not expected to journey more than twice in a 10-year period, passive immunization is the most cost-effective prophylaxis for travel from both very-low or low-to-high endemic areas. For more frequent travel, vaccination is more cost effective, as well as for journeys of 6-months' duration or longer. As well, pretravel screening before vaccination was shown to be worthwhile, except when the probability of natural immunity is low.

Conclusions. As the results indicate, the cost effectiveness of a strategy is related to several considerations: the prices of vaccine and screening tests, travel destinations and endemic conditions, frequency and duration of travel, and natural immunity. A decision-tree–based simulation model is helpful in determining the strategy to employ. (*J Travel Med* 1:127–135, 1994)

It is known that the risk of infection with the hepatitis A virus (HAV) is substantial for travelers from low-endemic countries to high-endemic destinations.[1] Although the incidence of hepatitis A is quite high, the disease-related morbidity and case fatality rate is low when compared to hepatitis B. Possible preventive strategies, when considered alongside advice on hygiene and dietary precautions, include passive and active immunization. Prophylaxis with immune globulin provides relatively cheap, but short-term, protection, whereas the recently developed active vaccine gives long-term protection, but at greater cost, since the full vaccination schedule requires three injections. However, it is possible to perform a screening test to assess the possibility of natural immunity. In its recently published protocol for vaccination requirements for hepatitis A the World Health Organization (WHO) recommends screening (before possible vaccination) of all people born and raised in developing countries and for people born before 1945 in industrialized countries. This strategy prevents wasting of vaccines.[2] Correspondence to the editor published in other journals[3–8] has revealed that individual practitioners in travel clinics have difficulty in making balanced decisions about vaccination protocols because of the complexities involved. Decisions are probably no less difficult for the individual traveler.[9] Clearly, a rational prevention policy requires consideration of the relative costs and benefits of the various possible strategies.

The present authors have developed a decision tree-based model to calculate the cost effectiveness (CE) of the various alternative strategies for HAV prevention in Belgian travelers to high-endemicity areas.[10] It was shown that the most cost-effective choice depends on a large number of epidemiologic, behavioural, and economic parameters. Since, in general, it was found that prevention was not cost saving, two conclusions were formulated in advance:

1. If the objective is cost minimization, no hepatitis A prevention should be undertaken because infections can only be prevented with additional cost.
2. If there is no budgetary restriction, the optimal strategy is clearly the most effective, i.e., vaccination.

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Using this decision tree-based model, the authors tried to answer the more difficult question of which strategy was the most cost effective when a limited budget for hepatitis A prevention is a given. In this article, some general indications for the optimal allocation of any given hepatitis A budget are derived based on two main factors: the risk exposure as determined by frequency of travel and duration of stay; and the natural immunity. The latter is determined by endemicity in the country of origin and age-specific prevalence in the population.

Methods

Three possible strategies for prevention of HAV infection in travelers will be compared to doing nothing: active immunization with an inactivated hepatitis A vaccine (SmithKline Beecham Biologicals, Rixensart, Belgium),[11,12] first screening for the presence of HAV antibodies in the blood and then vaccinating only susceptible travelers; and passive immunization with immune globulin.[13] The costs and effects associated with each of these three alternatives will be calculated for three levels of endemicity in the country of origin (moderate, low, and very low), for short and long durations of stay and for high and low travel frequency. The basic decision tree for the simulation model is represented in Figure 1.

The model is used to calculate the expected incremental net medical care costs per infection prevented (i.e., additional costs of prevention minus cost savings). Obviously the results are highly dependent on the estimates of the various probabilities of immunity and infection. These estimates are based on the best evidence available in the literature. The Belgian data,[10,14,15] which were collected based on travel behavior and costs, were assumed to be valid for the calculation based on other Western European countries and the United States. Sensitivity analysis was used extensively to assess the sensitivity of results to assumptions made about key model parameters. Threshold analysis was performed to provide an indication of which strategy is optimal over which range of a certain parameter (e.g., the higher the prevalence of immunity, the more likely screening will be cost-effective.

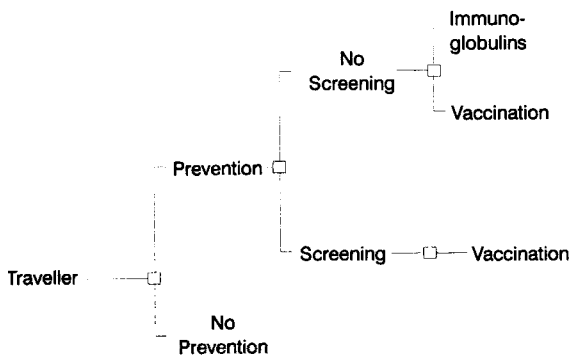

Figure 1 Basic decision tree

Because in the baseline analysis, only direct medical care costs are considered, the implicit (narrow) viewpoint taken for analysis is that of the payer for medical care, which may be the patient or some public or private insurer. In the sensitivity analysis, this viewpoint will be somewhat broadened to a more societal perspective when indirect costs attributable to (for example) productivity or work losses are included.

Disease and Epidemiology

Hepatitis A is an acute inflammatory disease of the liver caused by HAV. The HAV virus is spread by the feco-oral route, usually by person-to-person contact.[16,17] This means that transmission is facilitated by poor hygiene and sanitation. HAV has a worldwide distribution closely related to levels of economic development. Transmission often occurs in epidemic clusters.[18] The continuous decline in incidence of HAV in many developed and developing countries can be attributed to better conditions of sanitation and improvement in standards of living. As the endemicity of HAV decreases, the average age of exposure and subsequent infection has shifted to an older age group wherein clinical illness is more frequent.

HAV disease is usually self-limiting, and it shows a variety of clinical features.[19] The severity of illness is age dependent. Among children and newborns, HAV infection is usually asymptomatic and mostly anicteric. Among adults, symptomatic infection occurs in 80 to 90%.[20,21]

HAV infection only rarely has a fulminant evolution. The case–fatality rate is low. It ranges from .02% to 1.5%,[22] depending on the age of onset of hepatitis A infection. Chronic disease has not been documented, but in 6 to 10% of clinical cases, a relapse in liver inflammation may occur.[23,24]

Baseline Estimates

Infection Patterns: Because the benefits of HAV prevention in travelers originating from high-endemic countries are negligible, only populations from lower-endemic countries will be considered. With reference to data from the Centers for Disease Control,[18] the following three regions with typical HAV infection patterns can be defined:

1. Very-low-endemic regions are characterized by an average annual HAV attack rate of .003% (3/100,000) and an average prevalence of HAV antibodies of 20%. This pattern is seen in the Scandinavian countries.
2. The annual attack rate for hepatitis A infection in low-endemic regions is estimated at an average of .01%, and the prevalence of HAV immunity is 25%. Examples include North America, Switzerland, and Germany.
3. The average annaul attack rate for hepatitis A infection in moderately-endemic regions is .05%, with an average HAV immunity prevalence of 45%. Southern, Central, and Eastern European countries represent this third pattern.

The distinction between various regions of origin is important for two reasons. Firstly, the potential benefits of HAV screening increase with a rising prevalence of immunity in the screened population. Secondly, the higher the risk (i.e., the endemicity of HAV) in the home country, the greater the benefits are for protection against HAV infection. This is obviously an advantage of vaccination, which provides long-term protection (i.e., travelers remain protected after their return) as against the immune globulin, which can only offer short-term protection. The HAV prevalences given here are average data. Since the prevalence of HAV immunity rises with the age of the population in each of these three regions, the recommendations made for each region are dependent on the age of the target group. For the baseline calculations an average age of 35 years has been assumed.

Travel Characteristics: Belgian data indicate that the average duration of travel to high endemic countries is 25 days.[15] Additionally, since the expected frequency of travel is so crucial to the economic results, the frequency of travel in the first scenario calculations has already been varied. Frequency ranged from one 25-day period in the first year of a 10-year period to one 25-day visit per year every year over 10 years. In order to illustrate the importance of ranging this frequency, recent travel behavior data[15] is referred to, and this shows that 65% of the traveler population studied (n = 1423) intended to repeat a journey in the future: 39% of this number intended to repeat their journey once every year; 47% once every 2 or 3 years; and 14% every 5 years.

As a baseline assumption for the annual attack rate of HAV in susceptible travelers to endemic countries a figure of 3.6% is used as reported by Steffen.[1] This figure is adapted to the duration of a traveler's stay abroad. This attack rate varies in the sensitivity analysis according to the travel destination and conditions.

Clinical Course of HAV Infection: It is assumed that 10% of all HAV infections among travelers are asymptomatic.[19–21] This assumption was based on surveys. These surveys indicate that about 50% of symptomatic infections will be mild and treatable by a general practitioner. About 30% will develop a moderate HAV infection, which will require specialist treatment. The percentages of severe (i.e., the % requiring hospitalization) and fulminant cases are estimated at 19.9% and 0.1%, respectively. As has been suggested, relapse rates vary inversely with the severity of the clinical infection.[23,24] Relapse rates are estimated at 9, 7, and 2% after mild, moderate, and severe hepatitis A, respectively. The average costs of treating mild, moderate, severe, fulminant, and relapsing hepatitis were estimated at $342, $434, $2216, $22,152, $434 (U.S.) respectively (this estimation is based on the 1991 cost of Belgian health care).[14] In the baseline scenario, no indirect costs of HAV infections attributable to productivity losses were included. All costs in later years were discounted at a rate of 5%.

HAV Prevention Strategies: The vaccination strategy is aimed at the active immunization of the entire target group with the HAV vaccine. However, because the vaccine is administered in two doses plus a booster (at 0, 1, and 12 months), compliance—and therefore protection—is assumed to be less than complete. The authors' assumption is that 100% will receive the first dose, 60% will receive the second dose, and only 50% will receive the booster after 1 year (Table 1). The rate and duration of protection with only one dose, with two doses, and with the full schedule are estimated based on the currently available evidence on seroconversion rates.[12,25,26] The costs of vaccination are assumed to be $30 for one dose plus $10 for the costs of administering the vaccine.

To avoid the waste of expensive vaccine on immunizing the already immune, initial screening for HAV antibodies should be considered. The HAV antibody screening test has a high sensitivity (99%) and specificity (99%).[27] The total cost of screening one traveler is estimated at $30. Compliance with the vaccination schedule of those found to be susceptible after screening is assumed to be identical to the compliance of those vaccinated without prior screening.

Until recently, the recommended prevention strategy for travelers to high-endemic regions was passive immunization with the administration of immune globulins. The protection rate is estimated at 85%, and protection at the recommended dose of 0.02 ml per kg lasts for 3 months.[13,28] Compliance may also be incomplete for passive immunization in the sense that individuals may not always be willing or able to receive immune globulins before each trip. Estimated compliance is at 100% for the first trip and at 50%

for subsequent trips. Unit costs of passive immunization, i.e., the purchase and administration of one dose, are estimated at $24 (U.S.), which is a weighted average of the cost of cheap (aspecific) and more expensive (specific) immune globulins, according to the relative proportion of each used in different Belgian travel clinics .

For a summary table of all baseline assumptions of the model see Table 1.

Results and Discussion

For each of the three preventive strategies and for each type of region of origin, the expected number of infections and the expected direct medical costs incurred were calculated using the baseline assumptions. Comparison to the doing nothing strategy—which proves for all scenarios to be the cheapest, but the least effective—allows the computation of each strategy's cost effectiveness, i.e., the net medical cost per HAV infection prevented.

Baseline Cost-Effectiveness

In Figure 2, the cost effectiveness (CE) ratios for the three intervention strategies compared to doing nothing are presented for travelers from a low-endemic country (e.g., North America, Switzerland, or Germany)[18] to high-endemic regions (e.g., developing countries). On the horizontal axis, the expected travel frequency in the subsequent 10 years is varied from once times 25 days to 10 times 25 days. For those not expected to undertake such a journey more often than once or twice, passive immunization with immune globulin is the most cost-effective preventive action. For a traveler traveling once in a 10-year period, the expected net medical cost under a passive immunization strategy amounts to $22.8 (U.S.), whereas the probability of an infection in the next 10 years is reduced from 0.25% (i.e., the weighted average of the incidence at home and abroad) to 0.087%. Combining these two in a cost-effectiveness ratio results in an expected cost of $14,454 (U.S.) per HAV infection prevented. Although vaccinating this traveler would further reduce the probability of infection to 0.035%, the investment needed to obtain this reduction amounts to $82.5 (U.S.), which results in a net medical cost per infection prevented of $39,316 (U.S.). As soon as the same traveler is expected to travel three or more times in 10 years, it becomes more cost effective to vaccinate before the first trip. The subsequent increased risk of HAV infection would require repeated passive immunization. This practice would considerably increase the cost per infection prevented.

It can be shown that the same conclusions hold for travelers leaving from very-low-endemic regions (e.g., Sweden), that is to say as soon as travelers are expected to go to high-endemic regions for 25 days more than twice in a 10-year period, vaccination becomes the most cost-effective alternative. Because travelers leaving from moderately-endemic regions (e.g., Greece) also remain protected in their living environment after their return, active immunization is more cost effective than immune globulin if these travelers are expected to go abroad more than once in a 10-year period.

The first step is to decide between vaccination or administration of immune globulins. The decision about whether to screen or not to screen before vaccination will be dealt with later. The effect of the age of the traveler on the model and the contribution of screening will also be discussed below.

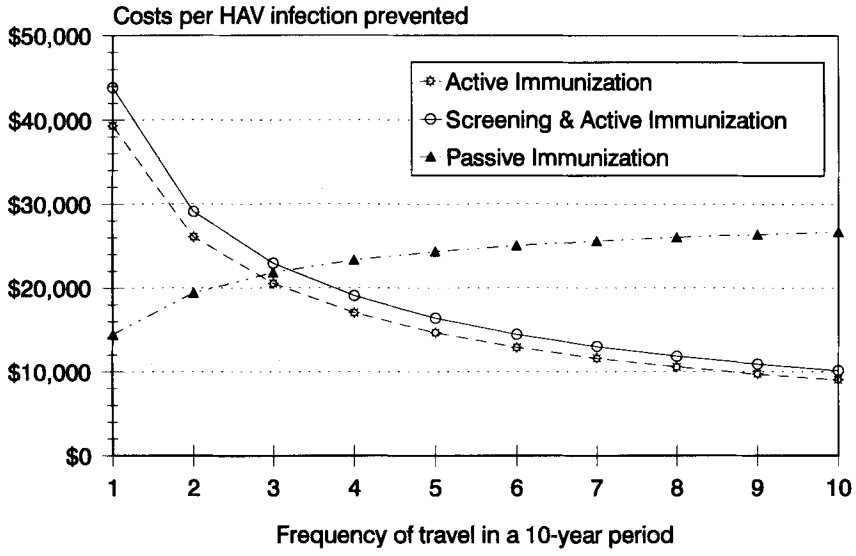

Figure 2 Costs per infection prevented in U.S. dollars. (On the vertical axis the costs per infection prevented are displayed for the three prevention strategies compared to doing nothing for travelers leaving from low-endemic regions. The horizontal axis reflects the travel behavior, which varies from once in a 10-year period to 10 times in a 10-year period).

Table 1 Overview of Baseline Assumptions

Epidemiologic Data	*Very-Low-Endemic Region (%)*	*Low-Endemic Region (%)*	*Moderate-Endemic Region (%)*
Country of Origin			
HAV-Prevalence	20	25	45
HAV-Annual incidence	0.003	0.01	0.05
Developing countries			
HAV-Annual incidence		3.6	
Clinical Data: HAV			%
Clinical Manifestation			
Symptomatic hepatitis			90
Mild hepatitis			50
Moderate hepatitis			30
Severe hepatitis			19.9
Fulminant hepatitis			0.1
Relapse after mild hepatitis			9
Relapse after moderate hepatitis			7
Relapse after severe hepatitis			2
Vaccine Data: HAV	*Dose 1*	*Dose 2*	*Dose 3*
Compliance	100%	60%	50%
Duration of protection	1 year	2 years	10 years
Protection rate	90%	98%	99%
Screening Data			*(%)*
Parameters			
Sensitivity of the screening test			99
Specificity of the screening test			99
Passive Immunization Data			
Protection rate		85%	
Duration of protection of 1 dose		90 days	
Compliance: first dose		100%	
Compliance: second dose		50%	
Economic Data			*$ (U.S.)*
Unit cost for treating:			
Mild hepatitis			342
Moderate hepatitis			434
Severe hepatitis			2,216
Fulminant hepatitis			22,152
Relapsing hepatitis			434
Unit cost for:			
Vaccination			40
Screening			30
Passive immunization			24
Discount rate			5 %

Table 2 Optimal Strategy by Region of Origin, Travel Frequency, and Duration of Stay

Region of Origin	*Expected Travel Frequency in 10 Years*				
	Once		*Twice*		*Three Times or More*
Very-low-endemic or Low-endemic region	Ig's:	less than 180 days	Ig's:	less than 90 days	Vaccination
	Vaccination:	more than 180 days	Vaccination:	more than 90 days	
Moderate-endemic region	Ig's:	less than 180 days	Vaccination		Vaccination
	Vaccination:	more than 180 days			

Active or Passive Immunization?

In Table 2 some general guidelines for the choice between the vaccine and immune globulin in HAV prevention are formulated based on the economic analysis. These recommendations are valid under the baseline assumptions listed in Table 1.

In general, for the three considered regions of endemicity, it can be stated that for an expected travel frequency to a high-endemic region of three times or more in the next 10 years, vaccination is more cost effective, whereas passive immunization is more cost effective for travel frequencies of once in 10 years. The duration of travel can also be varied whereas the frequency is kept constant. Passive immunization remains the most cost-effective strategy for a single journey provided that the duration is less than the threshold value of 180 days. For journeys longer than 6 months, vaccination becomes more cost effective, even for a single journey.

For people with an expected travel frequency of twice in a period of 10 years, recommendations are dependent on the region of origin. Passive immunization is never the most cost effective alternative for travelers from a moderately endemic region, and for travelers from a low- or a very-low-endemic region, it is only so if the duration of the stay abroad is less than 90 days. In all other cases, active immunization is the preferred strategy from a cost-effectiveness point of view.

Vaccination or Screening and Vaccination?

Once the choice has been made for longer term protection, the next step is to consider whether or not to screen for hepatitis A antibodies.

The availability of a sensitive and specific screening test offers the opportunity of screening travelers first for the presence of HAV antibodies (IgG antibodies) and then vaccinating only susceptible persons. The objective is to avoid wasting vaccine on individuals with already acquired natural immunity.

Four parameters may affect the screening decision as follows: (1) the expected prevalence of natural immunity in the target group (which is mostly dependent on age and degree of endemicity); (2) the cost of the vaccine; (3) the cost of the test; and (4) the sensitivity and specificity of the test. Although other means of testing for HAV antibodies, such as questionnaires and saliva tests, have been reported to be useful in that these avoid the need for a needle puncture,[29] blood tests are preferred because of their superior accuracy. Since the sensitivity and specificity of blood tests are close to 100%, this parameter can be kept constant in the decision making process.

Figure 3 shows the results of varying the three other key parameters simultaneously. The cost of the test and the prevalence of HAV immunity are varied on the horizontal and the vertical axis respectively. For the baseline ($40 U.S.) and two other costs of the vaccine, the prevalence of HAV antibodies at which the costs per infection prevented under vaccination and those under screening and vaccination are equal has been calculated. By connecting these break-even points we obtained three lines for respective vaccine costs, which each divide the diagram into two areas: for all combinations below each line, vaccination is the most cost-effective strategy; above each line prior screening is optimal.

An example follows to clarify the usefulness of the data presented in Figure 3. For German travelers[30] the following HAV-prevalence rates by age group have been reported: <20 years: 5%; 21–30 years: 5%; 31–40 years: 13%; 41–50 years: 28%; 51–60 years: 50%. It can be verified from Figure 3 that at a cost of the screening, $30 (U.S.), and for a vaccination cost of $40 (U.S.), immediate vaccination is the most cost-effective option for HAV-prevalence rates below 35%. This means that the threshold level for cost-effective screening for German travelers lies between the ages of 40 and 60 years. Therefore, above 50 years of age, screening before vaccination could be systematically proposed. The optimal choice will obviously vary with the endemicity of the region of origin and the age of the individual.

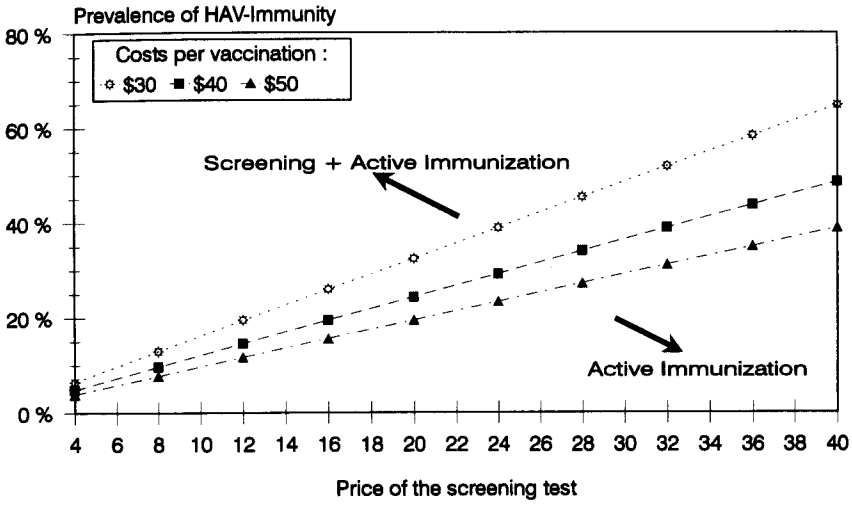

Figure 3 For three different vaccination costs, the dotted threshold lines show the total of all combinations of the cost of the screening test and the prevalence rates of HAV-immunity at which both strategies are equally cost effective. For combinations above the lines screening plus vaccination is more cost effective than immediate vaccination and vice versa.

Sensitivity Analysis

When travel destination and circumstances are considered, to test the sensitivity of the results to changes in various key parameters, extensive sensitivity analysis was performed. It is clear that destination and the circumstances of a proposed journey have a major impact on the risk of exposure to an HAV infection. The results of varying travel destinations and circumstances, and their associated estimated attack rates, are presented in Figure 4. The situation considered in Figure 4 is one of travelers from low-endemic countries (e.g., North America) who expect to travel to Mediterranean countries compared to traveling to developing countries for 25 days, three times, in 10 years. It can be seen that, in each case, the most cost-effective prevention strategy is vaccination. However, although the expected net medical costs for preventing one HAV infection are estimated at no less than $239,000 (U.S.)–$180,606 (U.S.) for a traveler leaving for a Mediterranean area (annual attack rates 0.018–0.13%),[1] this decreases to $20,528 (U.S.) per infection prevented for travelers to developing countries. For hikers, the annual attack rate has been reported to be 20% during their stay abroad.[1] So if hygiene conditions during the journey are expected to be quite low (e.g., hikers in developing countries), direct medical costs per infection prevented are calculated at $2,000–$3,000 (U.S.).

In order to identify the most sensitive key parameters, all parameters were increased by 10%. Figure 5 shows the changes in the cost-effectiveness ratio expressed as the percentage change from the baseline results. It can be seen that the cost-effectiveness (CE) ratios of some strategies are somewhat sensitive to assumptions regarding the attack rate abroad, i.e., the cost of the vaccine, the cost of the immune globulin, and to a lesser extent, to the traveler's compliance with the vaccination schedule. A 10% increase in the attack rate abroad causes an almost 8% decrease in the CE ratio. On the other hand, the results turn out to be somewhat insensitive to the costs of treating the HAV infections and the discount rate used.

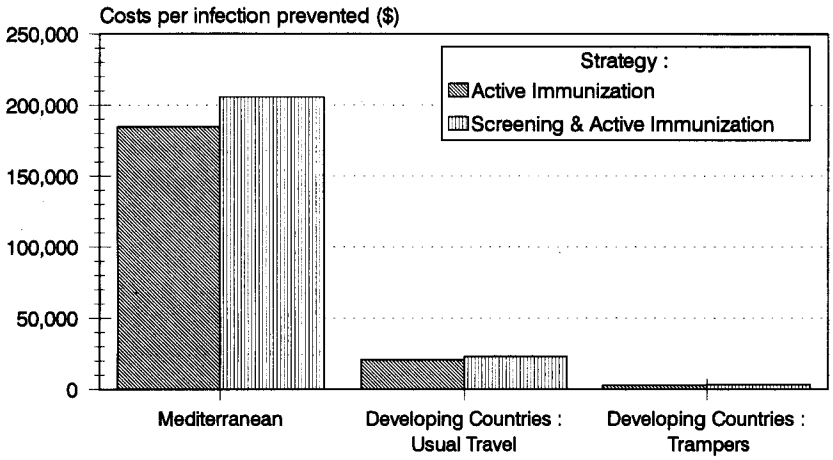

Figure 4 Effect of travel destination and circumstance.

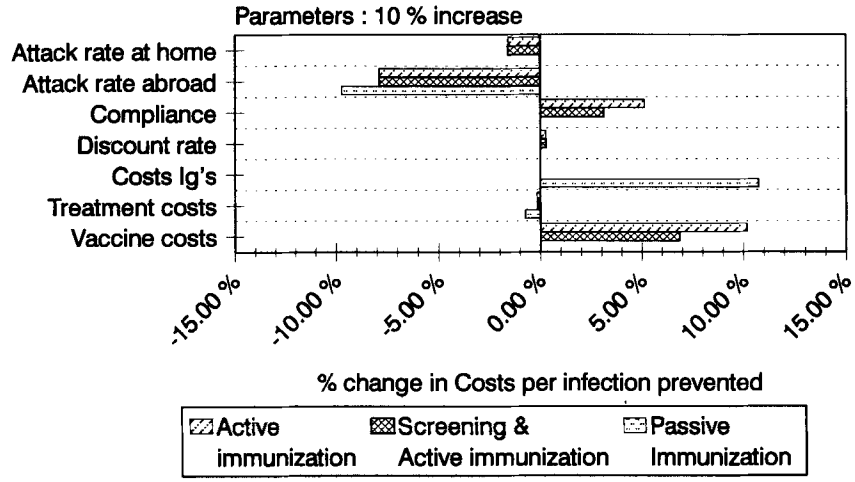

Figure 5 Sensitivity analysis: key parameters. (Percentage changes in costs per infection prevented as a result of a 10 % increase in seven key parameters).

Up to this point, the analysis has only included direct medical costs. Obviously the inactivity of HAV infected individuals also entails indirect costs of productivity losses. To the extent that HAV prevention results in reduced infection rates, it also serves to reduce these indirect costs. The monetary valuation of these indirect costs may vary by country, but the CE ratios are linearly related to the estimated cost per day of inactivity due to an HAV infection. The average number (weighted) of inactivity days due to any HAV infection (mild, moderate, severe, or fulminant) is estimated at 28.5 days. Consequently the net total costs (direct plus indirect) per infection prevented need to be adjusted for the number of infections prevented by 28.5 times the cost per day. Assuming the cost per day of inactivity to be $150 (U.S.), the baseline CE results of HAV prevention in travelers from low- to high-endemic countries for 25 days, three times in 10 years, then becomes $16,252 (U.S.) for active immunization, $18,664 (US) for screening prior to active immunization and $17,565 (U.S.) for passive immunization. It is clear that the CE ratios are more favourable the higher the estimated cost per day lost due to HAV.

Conclusions

The main objective of this article is to provide a rational basis for the choices faced by physicians, travel clinics, and individuals when considering HAV prevention. With the help of the decision tree-based simulation model, some general indications were obtained for the selection of optimal preventive strategies based on the costs and effects of the various alternatives. Using a number of assumptions in the baseline scenario, some threshold values were obtained for the duration and frequency of travel from low- to high-endemic countries for making the choice between passive and active immunization. It was shown that passive immunization remains the most cost-effective strategy for those expected to travel to high-endemic areas no more than twice over the next 10 years. For all other scenarios, it is worth considering a screening test before vaccination unless the probability of natural immunity is low.

What is shown is that cost-effectiveness results are very sensitive to some parameters (e.g., price of vaccine and screening test, travel destinations, and conditions), but not to others (cost of treatment of an HAV infection). Generally, inclusion of indirect costs attributable to HAV-related inactivity improves the cost effectiveness of HAV prevention.

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A resident of the Dominican Republic demonstrates some characteristic features of leprosy. Note loss of eyebrows (starting at the lateral margins), facial feature coarsening, and macular hypopigmentation. Ulcerations, muscle atrophy, contractures, and clawhand deformity follow peripheral nerve involvement. Chemoprophylaxis, outpatient medication, and vaccine trials offer hope to afflicted populations; however, success in prevention is chiefly dependent on nutrition and alleviation of crowded conditions.