Cost-effectiveness analysis of hepatitis A prevention in travellers

Guy Tormans*, Pierre Van Damme*‡ and Eddy Van Doorslaer†

The advent of new vaccines and the changing epidemiology of hepatitis A call for an update of the economic evaluation of costs and benefits associated with the various alternative preventative strategies. A decision-tree-based model has been developed which enables the calculation of expected costs and expected numbers of hepatitis A virus HAV infections based on different intervention strategies. The model is sufficiently generic to allow for the evaluation of both population-wide strategies and strategies targeted at particular risk groups. An economic analysis focusing on travellers from Europe to high-endemic countries compared a non-intervention strategy to the following three strategies: active immunization with HAV vaccine; screening for HAV antibodies and vaccinating only susceptibles; passive immunization by means of immunoglobulin. The net cost per HAV infection prevented proved very sensitive to a number of important input parameters of the model. These included epidemiological characteristics such as HAV attack rate and prevalence of immunity, behavioural characteristics such as compliance with the vaccination scheme and vaccine characteristics such as rate and duration of protection. Our estimated expected cost per HAV infection prevented among Belgian travellers to high-endemic countries for three weeks per year over ten years amounts to approximately US$4880 for active immunization, US$5621 for screening followed by vaccination of susceptibles and US$29932 for passive immunization. Although these estimates are clearly sensitive to a number of crucial assumptions pertaining to the input parameters of the model, it seems safe to conclude that vaccination is more cost-effective than the currently recommended passive immunization with immunoglobulin. Screening for antibodies before vaccinating may be more cost-effective for risk groups having a sufficiently high prevalence of immunity.

Keywords: Hepatitis A; vaccination; cost-effectiveness analysis

INTRODUCTION

Hepatitis A virus (HAV) infection is a more prevalent disease but with a less serious self-limited morbidity and a lower disease mortality than that caused by the hepatitis B virus. HAV is an enterically transmitted disease with a worldwide distribution, closely related to the level of economic development and often occurring in epidemic clusters. In many developed and developing countries, disease incidence and prevalence has decreased markedly, due to better general hygienic measures. The age of infection has shifted to older age groups, also related to improving socioeconomic and hygienic conditions and safer water supplies. As expression of clinical disease is highly age-related, the shift of infection to older age groups will increase the number of clinical infections.

From epidemiological studies, several groups at high risk for HAV have been recognized. Travellers to endemic regions, whether for tourism or business, run a significant risk of infection with HAV[1]. Until recently, the only options for prevention were precautionary measures and passive immunization with immunoglobulin. With the development of hepatitis A vaccines, the potential for longer term protection has increased substantially.

Three possible strategies for prevention of HAV infection in travellers are compared: active immunization with the new HAV vaccine; screening for HAV antibodies first and then vaccinating only susceptibles; passive immunization by means of hepatitis A immunoglobulin.

METHODS

The decision–analysis model used to compare each of these three strategies to non-intervention is very similar

*Department of Epidemiology and Community Medicine, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium. †Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands. ‡To whom correspondence should be addressed

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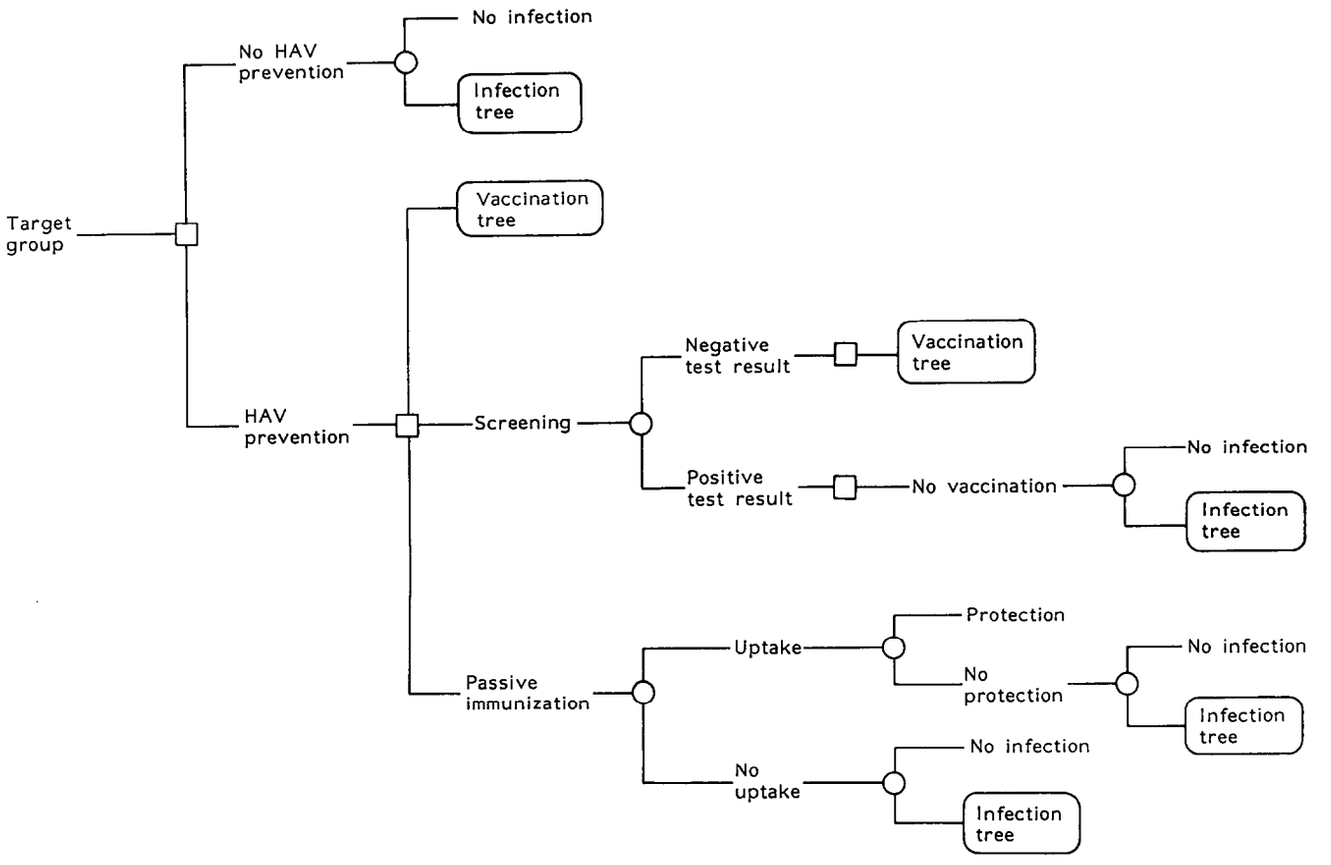

Figure 1 Basic decision tree. □, Decision node; ○, chance node

to the model that Mulley *et al.* used to evaluate hepatitis B prevention strategies[2]. The aim is to calculate the expected incremental net medical care costs per infection prevented. This means that for each strategy calculation is made as follows: from the additional costs of preventive intervention, the medical care costs saved as a result of prevention are subtracted, and then the total divided by the expected number of hepatitis A infections prevented.

The structure of the decision problem is depicted in *Figure 1*. It describes the possibilities of becoming infected depending on the strategies chosen and the associated probabilities of immunity and infection. In *Figure 2*, the events occurring after the decision to vaccinate are shown. The model is flexible enough to allow for evaluation of both population-wide strategies and strategies targeted at particular risk groups. This evaluation focuses only on travellers. The calculation of the expected costs and expected numbers of infections under each strategy are dependent on the input data. These are based on the best estimates available in the literature and on epidemiological surveys organized in Belgium.

INPUT DATA AND ASSUMPTIONS

Epidemiology

The target group at risk is assumed to consist of 1000 Belgian travellers to an endemic country. At a mean age of 40 years, the prevalence of HAV antibodies is estimated at 40%*, implying that 400 of these travellers were naturally immune due to an earlier infection[3-4]. Estimates of attack rates in travellers vary with the destination. The annual attack rate of HAV in susceptibles travelling to endemic countries is estimated to be 3.6% during their stay abroad. This figure is based on Steffen's estimated

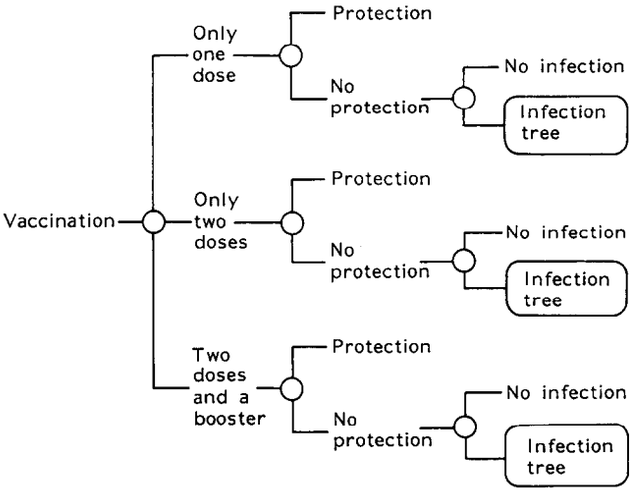

Figure 2 Vaccination tree

*Vranckx and Muylle[4] report a 68% prevalence of HAV antibodies in blood donors of this age group but other recent European figures suggest a lower figure of ≈ 40% among travellers[3,5]. In the sensitivity analysis, the impact of a changing prevalence rate will be assessed.

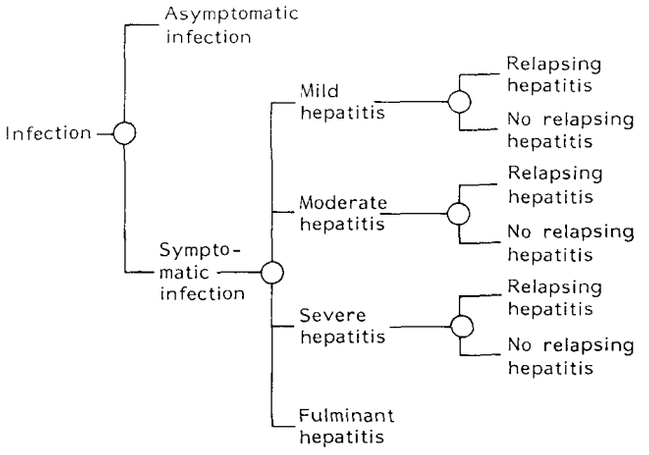

Figure 3 Infection tree

Table 1 Vaccination strategy: assumptions

Dose	Compliance (%)	Duration of protection (years)	Protection rate (%)
First	100	1	90
Second	60	2	98
Booster	50	10	99

average monthly attack rate for business people and tourists travelling under reasonably good hygienic conditions (R. Steffen, personal communication, 1992). The annual risk of HAV infection while at home is estimated to be only 0.3%, based on Frösner's estimate for Germany[6]. In reality, travel patterns are very diverse. For simplicity, we have assumed that all travellers in this target group annually spend a period of 19 consecutive days in an endemic country with a time span of 10 years of travel.

Clinical course of HAV infection

It is well known that the development of symptoms following HAV infection is strongly related to age. We have assumed that at the age of 40, 10% of all infections will be asymptomatic[7,8]. For symptomatic infections, we have distinguished between mild, moderate, severe and fulminant hepatitis (*Figure 3*). This distinction was based on the way in which these various manifestations are being treated. Interviews with an expert panel of general practitioners and hepatologists resulted in the following distribution: mild, i.e. only treated by the general practitioner (GP): 50%; moderate, i.e. referred by the GP to the hepatologist: 30% of all symptomatic infections; severe, i.e. requiring hospitalization: 19.9%; and only 0.1% resulted in fulminant hepatitis. This distribution comes close to that reported by Hadler and Purcell[9]. No chronic hepatitis A carrier states are assumed but biphasic infections (relapses) do occur. Because it has been suggested that relapse rates vary inversely with the severity of the infection, we have assumed relapse rates of 9, 7 and 2% after a mild, moderate and severe HAV infection respectively[10,11].

Estimated costs of treatment

Calculations of expected costs of treating HAV infections are based on a questionnaire sent to GPs and hepatologists and an analysis of the records of hospitalized patients. Medical care cost data are presented in US$ but reflect Belgian 1991 health-care price levels. Details of the costings can be found in Tormans *et al.*[12] Average costs of treating mild, moderate and severe hepatitis were estimated at US$330, 420 and 2144 respectively. Due to a lack of case records for patients with fulminant hepatitis A, we have arbitrarily estimated that the costs of treating these patients would be tenfold the costs of treating severe hepatitis. Costs of treating relapsing hepatitis were estimated at US$420. The time span for the model is 10 years and all costs in future years were discounted to their present value using a discount rate of 5%.

INTERVENTION STRATEGIES

Vaccination

This strategy aims at active immunization of the entire target group with HAV vaccine. However, because the vaccine is administered in two doses and a booster (at 0, 1 and 12 months), compliance – and therefore also protection – may be less than complete. We have assumed that 100% will receive the first dose, but only 60% will come for the second dose and 50% for the booster (see *Table 1*). The rate and duration of protection with only one dose, with two doses and with the full schedule are estimates based on the currently available evidence on seroconversion rates[13,14].

The costs of vaccination are estimated to be US$24 for one dose plus US$15 administration costs.

Screening and vaccination

To avoid injecting expensive vaccine into immune individuals, screening for HAV antibodies can be considered. The HAV antibody screening test has high sensitivity (99%) and specificity (99%) rates[15]. Assuming that two visits to a physician are needed to obtain blood and interpret the test results, the total cost of screening per case is estimated at US$43. Compliance to the vaccination schedule for those found susceptible after screening is assumed to be identical to the compliance of those vaccinated without prior screening (see above).

Passive immunization

At present, the recommended prevention strategy for persons travelling to high endemic regions is passive immunization with immunoglobulin. The protection rate is estimated to be 85%[16–18] and protection lasts for 3 months. Also, as estimated for active immunization, compliance may be incomplete in the sense that individuals may not always be willing or able to obtain an immunoglobulin injection before each trip. We have estimated compliance at $\approx$ 50% by assuming that the entire target group receives passive immunization for the first five years but not for the next five years. Unit costs for passive immunization, i.e. the purchase and administration of one dose, is estimated at US$41.

RESULTS

For each of the three strategies, the expected number of infections and the expected costs incurred have been calculated using the baseline assumptions. Comparison to the 'doing nothing' strategy allows the computation of

each strategy's cost-effectiveness, i.e. the net medical costs per infection prevented. *Table 2* illustrates that the total costs are lowest when no preventative action is taken, but that, on average, 27.7 per 1000 travellers will acquire an HAV infection. Vaccination of all 1000 travellers reduces this number to 12.6 per 1000 at a total net medical expense of US $89 321. It is mainly the imperfect compliance that prevents the infection rate from reaching zero. Screening before vaccination leads to a marginally higher infection rate (12.8 per 1000), mainly because of the 1% false-positive individuals that remain susceptible but are not vaccinated. Also the costs for screening and vaccinating only susceptibles turn out to be higher than for immediate vaccination of the entire group. Finally, passive immunization of travellers yields the highest overall cost and the highest infection rate of the three prevention strategies. The elevated numbers are due to the lower protection rate associated with the immunoglobulin (85%) and to the compliance problem suspected to occur after the fifth year.

Given these costs and effects, it is not surprising that the vaccination strategy yields the lowest cost per infection prevented (US$4880). With the screening strategy, it costs US$5621 to prevent an HAV infection, while the cost-effectiveness ratio for passive immunization is about six times that of the vaccination strategy (US$29 932). Obviously, these baseline results are critically dependent on some of the data assumptions made in the model. The following section explores the sensitivity of these results to changes in the baseline data assumptions.

Sensitivity analysis

Table 3 presents the effects of the vaccination strategy on the cost-effectiveness ratio (CER) when some of the basic assumptions are varied. First, it is shown that the CER increases when exposure to HAV risk is reduced and vice versa. The costs of preventing HAV infections increase when the travel frequency or the duration of the stay abroad is reduced. Second, it is obvious that vaccination becomes more cost-effective when compliance is higher or the price of the vaccine is lower. The CER is relatively insensitive to the costs of treating HAV infections. Even a tripling of the baseline cost estimates does not reduce the CER in a meaningful way (only 24%). Of greater importance are the estimated prevalence of immunity (which increases the waste of vaccine in non-susceptibles) and the attack rate for a particular travel destination (which increases the risk of infection). It is clear that the availability of more reliable or more specific estimates on each of the parameters can substantially improve the confidence in the baseline cost-effectiveness results.

Table 2 Cost-effectiveness of HAV prevention: baseline results

Strategy	Infections per 1000 travellers	Cost (US$)	Cost effectiveness ratio[a] (US$)
Doing nothing	27.7	15 576	–
Vaccination	12.6	89 321	4 880
Screening and vaccination	12.8	99 389	5 621
Passive immunization	21.9	196 091	29 932

[a] The cost effectiveness ratio (CER) is defined as the costs incurred to prevent one HAV infection under each intervention strategy, compared to doing nothing

Table 3 Sensitivity analysis: costs per infection prevented by the vaccination strategy compared to doing nothing

Variable	Low value		High value	
	Input data	cost (US$)	Input data	Cost (US$)
Frequency of travel	19 days for 1 year	7138	19 days for 10 years	4880
Duration of stay	1 week for 10 years	6460	6 months for 10 years	888
Booster compliance	0%	14052	100%	3732
Vaccine price	$US16	3760	US$32	6000
Treatment costs	Baseline	4880	Baseline × 3	3729
Prevalence of immunity	0%	2698	75%	12518
Attack rate abroad	3%	5255	6%	2906
Indirect costs	US$65 per day lost	3453	US$194 per day lost	602
Secondary attack rate	0%	4880	100%	2236

Model extensions

The indirect costs and secondary attack rate data in *Table 3* illustrate the effects of two extensions of the basic model. So far we have only been concerned with the direct costs of intervention, i.e. the medical care costs of prevention and treatment. There are, however, also indirect costs associated with HAV infections in terms of work-related losses due to illness. From the responses of GPs and hepatologists, we have estimated the average number of work loss days due to mild, moderate and severe infection. *Table 3* shows the cost-effectiveness ratios for vaccination when these work days lost are priced by a low estimate (US$65) and a high estimate (US$194). Assuming a high cost per day lost, the cost savings as a result of vaccination do not outweigh the costs of prevention.

A second extension of the model deals with the issue of horizontal transmission. It seems fair to argue that the vaccination of these 1000 travellers also prevents an (unknown) number of secondary infections through horizontal transmission to personal contacts. In the baseline model, this secondary attack rate was implicitly assumed to be 0%. It is shown that the CER from vaccination is reduced by > 50% when the secondary attack rate is assumed to be 100%, i.e. when it is assumed that every HAV infected traveller will, on average, transmit the infection to one other person.

Threshold analysis

The cost-effectiveness ranking of the prevention alternatives can vary with the input data assumptions. In particular, the comparison of screening versus vaccination is very sensitive to the prevalence of HAV antibodies in the target population. *Figure 4* shows the cost-effectiveness of both alternatives as a function of the prevalence of immunity. It can be seen that above the immunity threshold level of 55%, screening becomes more cost-effective than vaccination, keeping all other assumptions constant. This kind of threshold analysis can be useful in the search for the most cost-effective HAV prevention strategy for different target groups.

CONCLUSIONS

By means of a decision-tree-based model, the cost-effectiveness was analysed of three HAV prevention strategies

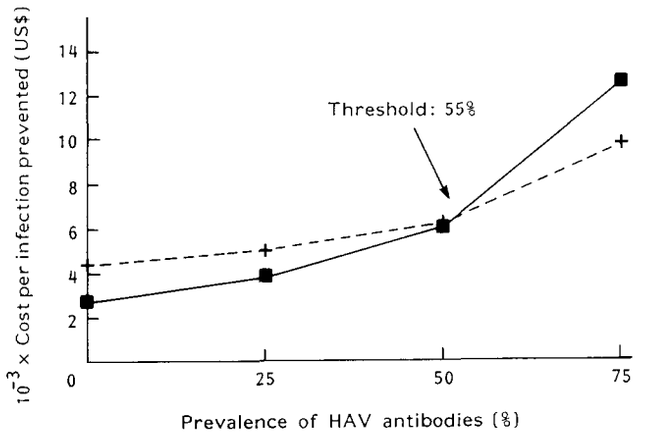

Figure 4 Threshold analysis for the prevalence of HAV antibodies. Target group: 1000 travellers. ■——■, Vaccination; +—+, Screening and vaccination.

for travellers to countries with high endemicity was analysed. Vaccination proved to be more cost-effective than the currently recommended passive immunization. However, vaccination does not save health-care costs. Under the baseline assumptions, the net cost per infection prevented is estimated at US$4880. The baseline cost-effectiveness ratios vary substantially with input data assumptions about travel behaviour, compliance with the immunization schedule and risk exposure, but are relatively insensitive to HAV infection treatment costs. Extending the model, by taking into account indirect costs and secondary attack rates through horizontal transmission, reduces the cost per infection prevented but does not make prevention a cost-saving item. Screening for HAV antibodies and then vaccinating susceptibles only becomes a more cost-effective strategy at high prevalence rates of immunity.

Further investigation is required on some of the crucial input parameters to the model to increase the reliability of the outcomes and to extend its usefulness to the evaluation of HAV prevention strategies for other risk groups than travellers.

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