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Cost analysis of two strategies for preventing hepatitis A virus infection in Spanish travellers to developing countries

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SUMMARY

Our objectives were to assess the prevalence of anti-hepatitis A (HAV) antibodies in Spanish travellers to developing countries and to carry out a cost analysis to allow the comparison of two vaccination strategies. Adult subjects were selected from among travellers to developing countries. Information was obtained on age, sex, destination, previous vaccination against HAV and having received immunoglobulin. Blood specimens were obtained for anti-HAV antibody determination. A total of 485 travellers were studied. The prevalence of anti-HAV antibody was 30·5% (95% CI 26–35). Antibody prevalence was inversely correlated with age: 9·8% in 18–25 years of age, rising to 75·4% in those 41–55 years of age. Cost analysis determined that the critical value of prevalence for vaccination with HAV vaccine was 37·5%. It was concluded that the youngest Spanish travellers lack anti-HAV antibodies. Vaccination without screening in those $\leqslant 35$ years of age and screening before vaccination for those > 35 years, are the preferred alternatives.

INTRODUCTION

Hepatitis A virus (HAV) infections occur worldwide, and prevalence is strongly tied to levels of socio-economic development and standards of hygiene [1]. Hepatitis A is a risk for travellers to developing countries, even those staying in luxury resorts [2]. Immunization with HAV vaccine is recommended for all non-immune travellers from industrialized countries who visit developing countries [3, 4]. Mediterranean countries in Europe have classically been considered areas of moderate endemicity for HAV, where infection occurs mainly in children and young adults [1]. However, epidemiological surveys carried out in recent years in these countries have shown a decrease in the prevalence of antibodies against HAV and a change in the epidemiological pattern of HAV infection [5]. In Spain, the prevalence of anti-HAV antibody has dramatically decreased during the last 15 years, resulting in a growing proportion of children and young adults who are susceptible to infection [6, 7].

Cost analysis can be used to evaluate different alternatives for immunization against hepatitis A. In situations where the expected prevalence of protected individuals in a population is high, a strategy based on pre-vaccination testing and vaccination of only those who are found to be susceptible can be more efficient than vaccinating everyone without screening [8]. In situations of low prevalence, vaccination alone is preferable. These considerations can be applied to persons who live in countries of intermediate HAV endemicity and who plan to travel to developing

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countries where HAV infections are highly endemic. The aim of this study was to assess the prevalence of anti-HAV antibodies in persons residing in Spain, a country of intermediate HAV endemicity, before they travelled to high-endemicity regions, and to carry out a cost analysis to allow the comparison of two interventions for preventing HAV in these individuals.

METHODS

The study population was drawn from healthy adults between 18 and 55 years of age, who were seen in the Adult Vaccination Centre, Hospital Clinic, Barcelona. The study protocol was approved by the Research Ethics Committee of Hospital Clinic, Barcelona. Written informed consent to participate was obtained from all participants. All persons who planned international travel to regions highly-endemic for HAV (Eastern Europe, Central and South America, Africa and Asia), who were within the defined age range and who agreed to participate were included in the study. Those who previously had been vaccinated against hepatitis A, and those who had received immunoglobulin during the previous year were excluded from the study. Information on age, sex and country of destination was recorded by the investigator. On the same visit, four drops of whole blood (spots of at least 15 mm diameter) were obtained by finger-stick, collected on filter paper (Scheiler and Schuell 2992, Acefe SA, Barcelona, Spain), air-dried and stored at +4 °C for later antibody determination.

Laboratory methods

Blood spots were eluted with 1 ml of 0·115% saline solution plus 1·5% bovine albumin for 12 h at room temperature. Eluates were tested for the presence of anti-HAV antibody by a commercial ELISA assay (Imx, Abbott Laboratories, Chicago, IL, USA) [9, 10]. Antibody determinations were performed in the laboratory of the Department of Public Health, School of Health Sciences, University Rey Juan Carlos, Madrid Spain.

Statistical analysis

The sample size needed for the study was calculated based on published data on the prevalence of anti-HAV antibodies in the age group of the population being studied (29%), and aimed at an absolute precision for the results of three percentage points with a confidence level of 95% [11]. The minimum number of subjects required was determined to be 473 subjects. Mean age in years (±S.D.) and sex distribution at enrolment were calculated. The overall prevalence of anti-HAV antibody in the study population, as well as in different age groups (18–25, 26–30, 31–35, 36–40 and 41–50 years) were calculated. All statistical analyses were carried out using Epi-Info 6·5 software (CDC, Atlanta, GA, USA).

Cost analysis

Two strategies for the prevention of hepatitis A infection were compared: (1) vaccination against HAV of all persons in the target group ('vaccination' strategy), and (2) testing for hepatitis A antibody followed by vaccination only of antibody-negative persons ('screening' strategy). In the 'vaccination' strategy, all travellers were assumed to be vaccinated with only one dose of HAV vaccine. In the 'screening' strategy, it was assumed that subjects were tested for antibodies to hepatitis A, and those who were found to be anti-HAV negative would be vaccinated. The Critical Value of Prevalence (defined as the prevalence of anti-HAV that makes the cost-efficiency of 'vaccination' equal to that of 'screening') was calculated to compare these two alternatives [8]. The economic decision would favour 'vaccination' when the prevalence of anti-HAV antibody is lower than this Critical Value, and 'screening' when the prevalence is higher [8].

The Critical Value of Prevalence was calculated by taking into account clinical, epidemiological and economic information on hepatitis A [8, 12–17]. Costs included those costs associated with interventions (e.g. cost of serologic testing and the vaccine), as well as the costs of treating patients who would contract hepatitis A. Costs corresponded to 1997 prices and were updated to 1999 with the corresponding inflation rates for the health sector. The health care payer perspective has been used for the analysis, and only direct health care cost have been included. According to published data, the mean cost for a case of hepatitis A in Spain was $588·9 [8, 12, 13]. This cost was calculated by taking into consideration that 90% of infected adults would develop symptomatic infections. Of these, 50% would be mild, 30% would be moderate, 19·9% would be severe and 0·1% would be fulminant hepatitis [8, 14–16]. For non-immune

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Table 1. *Prevalence of anti-HAV antibody and the preferred strategy for preventing hepatitis A in international travellers from Spain*

Age group (years)	Prevalence of anti-HAV			Preferred strategy for preventing Hepatitis A†
	No.	%	95% CI*	
18–25	133	9·8	6–17	Vaccination
26–30	119	17·6	12–26	Vaccination
31–35	108	31·5	23–41	Vaccination Pre-vaccination testing§
36–40	66	57·6	45–69	Pre-vaccination testing
41–55	53	75·5	61–86	Pre-vaccination testing
Total	479	30·5	26–35	—

*95% confidence interval.
†The two strategies are either to vaccinate all international travellers to developing countries without prior screening for anti-HAV antibody (vaccination) or to screen first and to vaccinate only those who are antibody negative (screening).
§Screening is more efficient if it is assumed that with the vaccination strategy all persons receive two doses.

persons of average susceptibility, the attack rate of symptomatic hepatitis A during a 1-month stay in a developing country was estimated to be three cases per 1000 person months of travel. This rate applied to short-term vacationers and business persons staying in western-style accommodation [2]. However, the attack rate was estimated to be 20 per 1000 person months for backpackers and other persons who would be exposed daily to poor hygienic conditions [2]. It is known that one dose of hepatitis A vaccine induces protective levels of anti-HAV antibody in 95% of adults and these levels persist for at least 3 years [14]. A booster dose will elicit seroprotective levels in 99% of adults and these levels persist for a minimum period of 10 years [14]. The baseline value for compliance with the booster dose was considered to be 60% [14]. The cost of vaccination was calculated by considering an average wholesale price of $35 for one dose of hepatitis A vaccine and a cost of $5 for its administration [8, 17]. The cost of screening for anti-HAV antibody was considered to be $15 [8, 17].

The Critical Value of Prevalence (P) was calculated by using the following equation [8]: $P = S/V - Ad$, where the Value of Averted Disease (Ad) is equal to $(1-Pv)DAEC$; Pv is the Predictive Value of a Positive Test; D is the Mean Disease Cost; A is the Attack Rate; E is the Vaccine Protection Rate and C is the Compliance. The vaccination cost (V) is equal to $(Cd+Va)C$, where Cd is the cost of a dose of vaccine, Va is the cost of its administration and C is compliance. Vaccination cost for one dose and two doses would be $(Cd1+Va1)C1$ and $(Cd1+Va1)C1+(Cd2+Va2)C2$, respectively. S is the cost of screening for anti-HAV.

RESULTS

A total of 485 travellers (18–55 years of age) were recruited between September 1998 and September 1999. Their mean of age (±S.D.) was 30·8 (7·1) years and 50·4% were male. Seventy-five percent were younger than 36 years of age. Forty-one percent planned to travel to Central and South America, 41% to Asia, 17% to Africa and the rest to East Europe. Six subjects were excluded: four had previously been vaccinated against HAV and two had received immunoglobulin. The prevalence of anti-HAV antibody in the five age groups is shown in Table 1. Overall, only 19% (68/360) of those younger than 36 years of age were anti-HAV positive. No significant differences in prevalence were found between sexes.

A Predictive Value of Positive Test (Pv) of 97·5% was calculated, by taking into account the overall anti-HAV prevalence found in the study population (30%), and the documented sensitivity and specificity of the anti-HAV antibody determination by ELISA in blood spots dried on filter paper (91% sensitivity and 99% specificity) [9]. The Critical Value of Prevalence for vaccination with one dose of HAV vaccine was calculated to be 37·5% when the expected attack rate was 0·3%. Table 1 also shows the recommended strategy for preventing HAV infection in the different age groups. Vaccination without screening will be the preferred alternative for persons $\leqslant 35$ years in age.

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Table 2. *Sensitivity analysis for the critical value of prevalence* (P) *for HAV vaccination of international travellers from Spain*

	P (%)	
Variable	One dose	Two doses
Study results	37·5	23
Vaccination cost		
+10%	34	21
−10%	42	26
Screening cost		
+10%	41	26
−10%	33	21
Attack rate		
0·05%*	37	23
2%	38	23
Compliance for the booster dose		
90%	—	20
75%	—	21
45%	—	26

*Conservative estimate based on date of the general population in Spain [8].

However, the 'screening' strategy is the preferred alternative for persons > 35 years in age. When a completed vaccination with two doses of HAV vaccine (to guarantee long term protection) was considered, the Critical Value of Prevalence was 23·4%.

Sensitivity analysis has been performed to check the effect on the critical value of prevalence of variations in some of the variables included in the analysis (Table 2). The critical value of prevalence was sensitive to variations in vaccination cost, screening cost and compliance with the second dose of vaccine, it showed very low sensitivity to variations in the attack rate. Hence economic decisions on vaccination strategy depend mainly on vaccination and screening costs.

DISCUSSION

Hepatitis A infection is a risk for all travellers to developing countries [2]. Since hygienic and sanitary conditions are not expected to improve dramatically in these countries for several years, hepatitis A virus infection will continue to be a problem [2]. The current prevalence of hepatitis A antibody in Spanish travellers is lower than that found in samples of the Spanish population of similar age [6, 7]. Since the presence of anti-HAV antibody is associated with factors such as socioeconomic level and standards of hygiene, this lower prevalence likely reflects the higher socioeconomic status of international travellers [1]. This low prevalence is more dramatic among travellers less than 31 years of age: only 10% of those 18–25 years in age and 18% of those 26–30 years in age, were found to be protected against hepatitis A. Moreover, these younger individuals are more likely either to settle for long periods in developing countries or travel under 'precarious' conditions (e.g. backpacking).

This study was carried out to explore the basis for deciding which of two alternatives for preventing HAV infections should be chosen by travel clinic physicians. With the availability of single-dose inactivated vaccines, the possibilities for effective and efficient prevention have increased substantially [14]. The World Health Organization (WHO) has included hepatitis A in its programme for the development of new vaccines and has recommended that health economic studies should be carried out to evaluate different alternatives for immunization against hepatitis A [18]. However, cost-effectiveness analysis can be an expensive method to assess the efficiency of vaccination strategies, as it requires precise clinical, epidemiological and economic information [8]. In most cases, this information is not available or resources are insufficient to carry out such a cost-effectiveness analysis. Given these limitations, the method used in this study can be helpful. Our results show that for vaccination with only one dose of HAV vaccine, a critical value of prevalence of 37·5% should be considered. This is lower than the 55% rate found in another study of travellers from northern Europe to high-endemic countries, primarily because the cost for the screening was assumed to be $43 [19]. In an earlier study from Spain, a critical value of prevalence of 22% was obtained, but this study considered that three doses of an hepatitis A vaccine would be required [8]. Sensitivity analysis showed that the value of prevalence was sensitive mainly to variations in vaccination and screening costs. It was also sensitive to variations in compliance to vaccination, as this variable is directly related to the vaccination cost.

This study may have certain limitations. Some costs and benefits were not included, especially working hours lost because of the illness, or gained as a consequence of the different alternatives to immunization. These cost have been estimated to be 2–3 times the cost of treating the disease [20]. Nonetheless, our results indicate that vaccination with one dose of HAV vaccine (without screening) of persons aged $\leqslant 35$ years and the 'screening' strategy for those aged

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$>$ 35 years, are the preferred alternatives for Spanish travellers to developing countries. However, when two doses of vaccine are to be given, the 'vaccination' strategy for travellers aged $\leqslant$ 30 years and 'screening' strategy for those aged $>$ 30 years will be preferred.

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