COST-BENEFIT ANALYSIS OF HEPATITIS A VACCINATION IN THAILAND

Anchalee Teppakdee[1], Araya Tangwitoon[1], Danai Khemasuwan[1], Kawin Tangdhanakanond[1], Nuttanun Suramaethakul[1], Jiruth Sriratanaban[2] and Yong Poovorawan[3]

[1]3rd Year Medical Student, [2]Department of Preventive Medicine, [3]Viral Hepatitis Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University and Hospital, Bangkok 10330, Thailand

Abstract. We constructed a decision model to simulate costs and benefits for persons in the context of hepatitis A prevention. Three strategies were compared: i) no intervention; ii) vaccination against hepatitis A without screening; iii) vaccination against hepatitis A for those susceptible after screening for anti-HAV. We divided the population into 3 age groups : 3-11 years, 12-18 years and 19-40 years. Data regarding the cost of treatment and vaccination were obtained from the King Chulalongkorn Memorial Hospital. Relevant probabilities were obtained from published literature and expert opinion. At the present incidence of hepatitis A infection, in all age groups examined, the net benefits of a universal no-intervention strategy were higher than those of either vaccination (intervention) strategy. The cost of vaccination without screening in the 3-11-year and 12-18-year groups would equal the benefit if the incidence rates amounted to approximately 138 and 212 infected individuals per 100,000, respectively, that of vaccination with screening at incidence rates of about 200 and 260 infected persons per 100,000, respectively. In the 19-40-year group, the cost incurred by vaccination either with or without screening would equal the benefit at an incidence rate above 450 infected individual per 100,000. For the benefits to outweigh the estimated vaccination costs at present the vaccine is still too expensive. The cost of vaccination without screening in the 3-11-year group would equal the benefit if the cost of vaccine was about 586 baht/2 doses (293 baht/dose), and about 500 baht/2 doses (250 baht/dose) in the 12-18-year group. Likewise, because of the cost of vaccine, it would not be cost-beneficial in the 19-40-year group both with and without screening, and neither would it be in the 3-11-year and 12-18-year groups including screening. According to current standards, under the conditions of the present study the benefit of hepatitis A vaccination administered to the general population between the age of 3 and 40 years in Thailand does not justify the expenses incurred. Major changes in hepatitis A incidence, anti-HAV seroprevalence, vaccine cost or the treatment outcome would be required to potentially render either intervention strategy cost beneficial.

INTRODUCTION

During the past decade, the incidence and prevalence of hepatitis A infection in Thailand have significantly decreased due to improvements in hygiene and sanitary conditions. However, when outbreaks do occur children and adolescents, often lacking immunity to the disease, are the worst-affected groups. Hepatitis A infection in children is normally asymptomatic; in adults, whose naturally-acquired immunity puts them at much lower risk of infection, symptoms can be severe and may lead to complications such as prolonged cholestasis and fulminant hepatitis (Poovorawan *et al*, 1987; Friedland *et al*, 1991; Corpechot *et al*, 1994). Compared with healthy individuals, patients with underlying diseases, especially chronic hepatitis or liver cirrhosis has a greater tendency to develop potentially-fatal fulminant hepatitis if they contract hepatitis A infection (Yao, 1991; Pramoolsinsap *et al*, 1999). There is no specific treatment for hepatitis A: clearance of the virus depends on a patient's

Correspondence: Prof Yong Poovorawan, Viral Hepatitis Research Unit, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University and Hospital, Bangkok 10330, Thailand.
E-mail: Yong.P@chula.ac.th

immune response. Because of the potentially adverse effects of hepatitis A infection, the application of preventive measures ought to be considered: one effective strategy is vaccination against hepatitis A infection (Werzberger *et al,* 1992; Innis *et al,* 1994)

Modern inactivated vaccines, which provoke a potent immune response, are used for prophylaxis. The efficacy of these vaccines after the complete 2-3-dose course exceeds 94% (Werzberger *et al,* 1992; Innis *et al,* 1994) and is sufficient to prevent both symptomatic and asymptomatic hepatitis A infections; four weeks after the first vaccine dose, most patients have antibody titers high enough to prevent infection (Poovorawan *et al,* 1996; 1998).

However, hepatitis A vaccine is expensive, a fact provoking the challenging questions, "Is it worth while to universally vaccinate people against hepatitis A infection?" and, "which age groups of a given population should be vaccinated?"

The objective of this study was to determine the cost-benefit balance of hepatitis A vaccination strategies for the general population of Thailand using a social perspective. In order to answer these questions and make subsequent decisions regarding the respective vaccination strategies we simulated Markov model by using incidence data from the Ministry of Public Health of Thailand, direct and indirect cost from patient aged between 3-40 years old who came to King Chulalongkorn Memorial Hospital.

MATERIALS AND METHODS

Study population

Based on the parameters of vaccine cost and seroprevalence of anti-HAV, we divided the population studied into 3 age groups: group 1 (3-11-year-olds); group 2 (12-18-year-olds); group 3 (19-40-year-olds).

For each group we conducted descriptive cost benefit studies of HAV vaccine by applying three strategies, the first including those not having received the vaccine, the second those vaccinated without subsequent screening for anti-HAV, and the third those vaccinated as well as screened.

We collected data from 23 hepatitis A patients admitted to King Chulalongkorn Memorial Hospital between 1990 and 1999 in order to calculate the direct cost; additional data, from the intensive care unit, allowed us to estimate the cost per patient with acute liver failure. Data on indirect cost were collected from 185 patients in the out-patients' department and the emergency wards.

Probabilities and assumption of probability

Probabilities were obtained from the published literature and an expert's opinion. Wherever possible, this expert's opinion was anchored to related published data. Probabilities pertaining to hepatitis A are shown in Table 1.

In this study, we used the adjusted incidence and assumed that it was the true incidence of hepatitis A in Thailand. The incidence of all types of hepatitis A reported to the Ministry of Public Health amounts to a mere 15% of the true national incidence (Division of Epidemiology, 1994). Underreported cases comprise 85% of the true incidence and 28.8% of undiffertiated hepatitis patients (Division of Epidemiology, 1994) infected by hepatitis A virus. The reported cases of hepatitis A infection in the 3-11-year, 12-18-year and 19-40-year groups were 76/13,276,761 (0.57/100,000), 64/8,122,191 (0.79/100,000) and 104/22,229,150 (0.47/100,000) respectively. Reported cases of hepatitis of all types amounted to 14,759 cases in the entire population; including the underreported cases, this figure increases to (100/15)x14,759 = 98,393 cases; for hepatitis A patients, including the underreported cases the future becomes (28.8/100)x98,393 or 28,337 cases.

The reported cases of hepatitis A infection in Thailand in all age are 295, 76 in the 3-11-year group, 64 in the 12-18-year group and 104 cases in the 19-40-year group. Hence, the

Table 1
Hepatitis parameters.

	Age at infection (in years)		
	3-11	12-18	19-40
Symptomatic cases[a] (per 100,000 population)	55	76	45
Cases (by treatment)			
#Out patients (% symptomatic cases)[b]	91.5	90.76	85
#In patients (% symptomatic cases)[c]	8.5	9.24	15
- without complication	8.1515	8.75	13.995
- with prolonged cholestasis[d]	0.34	0.4618	0.9005
- with fulminant hepatitis A[e]	0.0084	0.0279	0.1045
#Dead (% symptomatic cases)[f]	0.0025	0.0112	0.0523
#Natural immunity (Seroprevalence) (%)[g]	9.4	15	70

[a] Division of Epidemiology, 1994.
[b] O'Cornnor *et al*, 1994; Shah *et al*, 2000; Willner *et al*, 1998.
[c] O'Cornnor *et al*, 1994; Shah *et al*, 2000; Willner *et al*, 1998.
[d] Poovorawan *et al*, 1987.
[e] Friedland *et al*, 1991; Shah *et al*, 2000; Takahashi and Shimizu, 1991.
[f] Shah *et al*, 2000; Takahashi and Shimizu, 1991.
[g] Innis *et al*, 1991; Kiatseree, 1996; Kosuwan *et al*, 1996; Poovorawan *et al*, 1997; Poovorawan, 2001.

total number of hepatitis A patients (including the underreported cases) in the 3-11-year group must be (0.57/295)x28,337 = 54.98/100,000 cases, in the 12-18-year group must be (0.79/295)x28,337 = 75.69/100,000 cases and in the 19-40-year group must be (0.47/295)x28,337 = 44.94/100,000 cases. Therefore, we adjusted the incidence rate of hepatitis A in the 3-11-year group from 0.57/100,000 to 55/100,000, in the 12-18-year group from 0.79/100,000 to 76/100,000, and in the 19-40-year group from 0.49/100,000 to 47/100,000. In this study, we used the adjusted incidence and assumed that it was the true incidence of hepatitis A in Thailand. As most patients have been infected during adolescence, they have naturally acquired immunity and thus, the antibody levels detected in patients infected with hepatitis A increase with age.

The seroprevalence of anti-HAV among different age groups in Thailand has been reported in many studies (Innis *et al*, 1991; Kiatseree, 1996; Kosuwan *et al*, 1996; Poovorawan *et al*, 1997; 2001). We used the average of them which are 9.4, 15 and 70 in 3-11, 12-18 and 19-40 years old respectively to calculate in this model as shown in Table 1.

Hepatitis A serology screening was assumed employing an ELISA antibody test (the cost was shown in Table 1), with both high sensitivity and specificity. In this study, the false negative and false positive rates are assumed to be zero.

The protective efficacy of hepatitis A vaccine range is between 94-100% (Innis *et al*, 1994; Werzberger *et al*, 1992). We applied a clinical baseline at 96%. Side effects resulting from the vaccine are rare and unlikely to seriously impact quality of life, and were thus assumed to be mild and never fatal (Poovorawan *et al*, 1996; 1998). Hence, we did not include the treatment cost of these side effects to the direct cost in this study.

Cost assignment and assumption

Costs for treatment of hepatitis A patients include costs for laboratory tests and treatment; the latter depending on disease severity. In case of complications, most patients were referred to the hospital for treatment. The data we collected originated from patients admitted to King Chulalongkorn Memorial Hospital. Treatment costs for hospitalized patients include charges for room and diet. As the costs for each patient's room vary we employed a unit cost (Kamolrattanakul *et al*, 1995) of 333.69 baht/day for patients between 3 and 18 years of age and of 253.19 baht/day for those between 19 and 40 years of age, with the cost for diet already included. Except for complications arising, the symptoms of hepatitis A patients are not severe and hence, most attend as outpatients.

The cost for patients with acute liver failure was estimated as the cost for intensive care treatment as shown in Table 2. Inferred from the cost for the screening test and vaccination at King Chulalongkorn Memorial Hospital, the cost for the screening test amounts to 250 baht, and that for the vaccine to 1,840 baht per 2 pediatric dosage (for children), and 2,860 baht per 2 dosage (adult dosage) for adults above 19 years of age respectively. These costs included the administration cost of vaccine. Costs of hepatitis A were also treated as an inpatients. This treatment cost also includes loss of productivity (based on net income per capita) and the transportation cost. The work-days loss was the period of hospitalization and the duration of resting at home on the day of vaccination (1 day); in the 3-11 years group, the work-days loss could be calculated from their parents. We assumed that the age of working population is between 20-60 years old. In this study, we calculated the productivity cost by using GDP x (60 - the age of death). The costs of transportation and work-days loss was collected from 185 outpatients who came within Bangkok to King Chulalongkorn Memorial Hospital and emergency ward patients estimated for a 3-week interval between May 8 and May 26, 2000.The sample size employed for expense calculation amounts to 4.18 persons (5 persons). Sample size was determined using the formula:

$$N = \frac{(1.96)^2\ pq}{(0.1)^2}$$

with

N = sample size
p = 0.011 (Innis *et al*, 1991) (annual infection rate of acute hepatitis A in Thailand)
q = 1 - p

Table 2
Cost estimates of hepatitis A vaccine, medical treatment and indirect cost for simulation model.

Cost (baht)	3-11 yrs old	12-18 yrs old	19-40 yrs old
Vaccine cost (per dose)	920	920	1,430
Serology test (per test)	250	250	250
Medical cost/visit			
Out patients	2,556.25	2,556.25	2,556.25
Hepatitis A without complication	2,909.45 (21 days)	3,491.34 (21 days)	3,940.95 (21 days)
Hepatitis A with cholestasis	11,914.53 (91 days)	11,914.53 (121 days)	10,617.68 (132.5 days)
Hepatitis A with fulminant liver failure	99,975.35 (53 days)	100,557.24 (53 days)	98,269.85 (53 days)
Indirect cost			
Transportation	113.19	95.89	142.2
Work day loss	236[a]	236[a]	236
Others	0	4.55	2.13

[a]work day loss of patient's parents

We included both direct and indirect costs in the treatment cost per episode of hepatitis A without complication, with complication (cholestasis or fulminant hepatitis A) and outpatients with hepatitis A. The indirect cost was calculated using the average income per capita to determine loss of productivity. Persons with naturally acquired immunity or those already infected with hepatitis A virus will retain life-long protective immunity.

Assignment of outcome and benefit

The outcome measures were the expenses incurred by morbidity and/or mortality from hepatitis A infection in per groups of the intervention strategies employed. In case of death from hepatitis A infection, we estimated the mortality cost based on the per capita income. In case of HAV infection, each strategy incurs a specific cost depending on the patient's symptoms per episode and the loss of productivity.

Benefits from the vaccination are the potential saving of their incurred costs. The net benefit is calculated from the cost of no-intervention strategy minus the cost of vaccination strategy both with and without screening. As hepatitis A is a short-lived illness resolved by spontaneous recovery and devoid of the risk to proceed towards a chronic state, the patients can be followed up until complete recovery within one year.

The Markov model

In this study, we applied the Markov model to analyze the cost benefit of hepatitis A vaccination strategies using the statistical software "STATA 5.0" (Intercooled Stata 5.0 for Windows 95 Copyright© 1985-1997).

The Markov model is one of the decision analysis tools widely used in studies of health management, especially in the context of protracted time horizon and recurrent risk of a particular disease and hence, is very useful for studying the cost benefit of vaccination programs (Das, 1999; O' Connor *et al*, 1999). For the general application of the Markov model, we assigned the states of health involved in the study and the transitional probability, which is the probability to change from one state to another in a given period of time. Transitional probabilities from one state to another were obtained from the available information. This model is static due to the constant of independent variables in any cycles.

Applying this model, we can simulate events comparing the 2 intervention strategies *vs* no-intervention strategy in the general population of Thailand. The model is run for several cycles to simulate the natural history of the problem and at the end of each cycle, cumulative reward values in terms of outcome measures are calculated. The follow up period of the model was infinity, *ie* the model would run until the cohorts entering into this model died. The average life expectancy of a healthy person is 70.23 years (Ministry of Public Health, 1995). Size of each cohort was the number of Thai population in each age group in 1994. However, the proportion of the numbers of each state was calculated in the model.

At any given time, an individual may be in one of the following 7 health conditions: (1) susceptible to hepatitis A; (2) infected with hepatitis A (in patient, IP); (3) infected with hepatitis A with prolonged cholestasis (IP); (4) infected with hepatitis A with fulminant hepatitis A (IP); (5) infected with hepatitis A (out patient, OP); (6) immune; (7) dead. Vaccine immunity is a result of successful vaccination, whereas natural immunity is acquired as a consequence of hepatitis A infection. Although 95-97% of hepatitis A vaccinees developed immunity, 3-5% (Keeffe, 1996) did not. It was assumed that death from hepatitis A infection would only occur in the hospital as a consequence of fulminant hepatitis. Death from other causes is the all-cause mortality for both sexes in Thailand.

Patients infected with hepatitis A may be symptomatic or asymptomatic. Those with symptomatic hepatitis A can be treated as outpatients or hospitalized patients, depending on severity. Hospitalized patients may develop complications in the form of prolonged cholestasis (Poovorawan *et al*, 1987) and fulminant hepatitis A (Friedland *et al*, 1991; Takahashi and Shimizu, 1991). Patients developing fulminant hepatitis A may die since liver transplantation is not widely performed in Thailand. In this study, we did not include the option of liver transplantation for patients with fulminant hepatitis A.

We divided the sample population into 3 age groups, those between 3 and 11 years, 12 and 18 years, and those between 19 and 40 years of age and studied the cost benefit in each group. Each person enters the model in either an immune or a susceptible state. In the no intervention strategies, we derived incidence of immune state in each age group from the actual seroprevalence. And both vaccination with and without strategies, we derived incidence of immune state in each age group from the efficacy of hepatitis A vaccine (96%). Susceptible persons become immune as a consequence of naturally acquired hepatitis A.

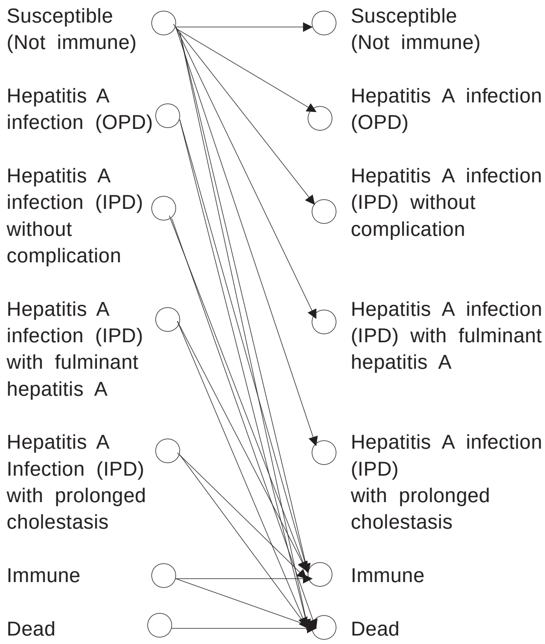

Fig 1–Markov decision model.

Assumption of the study

Since the 3-11-year-old patients do not have an income of their own, their parents are always responsible for the expenses and suffer an impairment of their income.

In this study, the patients below the age of 3 years usually have passive immunity from their mothers and almost all patients above the age of 40 years are immune to hepatitis A. Both groups do not require vaccination and therefore, we did not include them in the present study. Since the cost for medical treatment of hepatitis A patients at King Chulalongkorn Memorial Hospital does not vary between age groups, we applied the same cost for the entire population studied.

Cost-benefit ratio

Cost-benefit ratio was determined by the benefit of vaccination program (cost of treatment in no-intervention strategy minus by cost of treatment in vaccination strategies) divided by the cost of the program (the cost of vaccine, with and without serological testing cost and administration cost).

RESULTS

This study has shown that based on the present incidence of hepatitis A infection, vaccination either with or without screening would not be cost-beneficial. The results obtained were different between age groups. Based on the current incidence, the most cost-beneficial strategy for all age groups was no intervention (Table 3).

As shown in Fig 2, one-way sensitivity analysis was performed on the incidence rate. There are 5 points per line, with the first point at the incidence decreasing 10 times from the actual one, the second at the incidence decreasing 5 times from the actual one, the third at the actual incidence, the fourth at the incidence increasing 5 times from the actual one, and the fifth and last at the incidence increasing 10 times from the actual one.

In the 3-11-year group, the cost of vaccination without screening would equal the benefit if the incidence rate amounted to approximately 138 infected individuals per

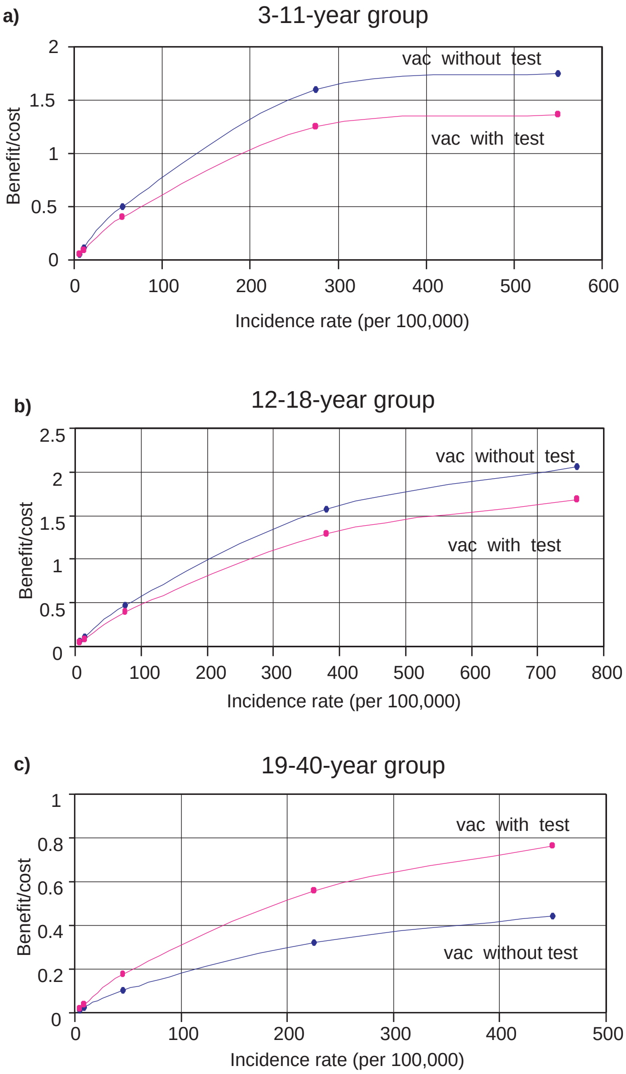

Fig 2–Sensitivity analysis was performed on incidence rate. Comparison between cost benefit ratio and the incidence rate in the program of vaccination with and without screening among different age groups.

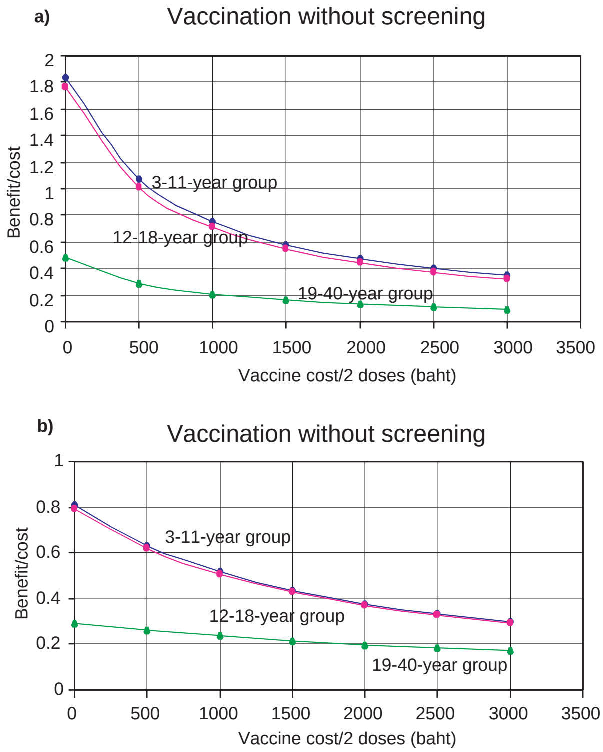

Fig 3–Sensitivity analysis was performed on vaccine cost. Comparison between cost benefit ratio and the cost of vaccine in the program of vaccination with and without screening among different age groups.

100,000, that of vaccination with screening at an incidence rate of about 200 infected persons per 100,000. Similarly, in the 12-18-year group, the cost incurred by vaccination without screening would equal the benefit if the incidence rate amounted to approximately 212 infected individuals per 100,000, that of vaccination with screening at an incidence rate of about 260. In the 19-40-year group, the cost incurred by vaccination either with or without screening would equal the benefit at an incidence rate above 450 infected individuals per 100,000. We conclude that in the first 2 groups, vaccination without screening is more cost-beneficial than with screening. However, in the last group (19-40-year), vaccination with screening is much more cost-beneficial than without screening.

For the benefits to outweigh the estimated vaccination costs, at present the vaccine is still too expensive. Fig 3 shows the relation of the cost of vaccine and cost-benefit ratio on hepatitis A vaccination with and without screening.

The cost of vaccination without screening in the 3-11-year group would equal the benefit if the cost of vaccine was about 586 baht/2

Table 3
The cost-benefit among different aged groups compared with different method of intervention.

Age group	Cost of no intervention	Cost of vaccination without screening	Cost of vaccination with screening	Benefit of vaccination without screening	Benefit of vaccination with screening
3-11 yrs	1,339.48	2,597.68	3,307.45	-1,258.2	-1,967.97
12-18 yrs	1,245.76	2,571.5	3,117.45	-1,325.74	-1,871.69
19-40 yrs	420.94	3,676.79	2,152.99	-3,255.85	-1,732.05

doses (293 baht/dose), and about 500 baht/2 doses (250 baht/dose) in the 12-18-year group. In the 19-40-year group both with and without screening, it is still not cost-beneficial and neither is it if vaccination with screening is performed in the 3-11- and 12-18-year groups.

DISCUSSION

As a consequence of the improvement in hygiene and sanitary conditions in conjunction with Thailand's progress from a developing to a newly industrialized country the incidence of hepatitis A virus infections has gradually declined. In case of occasionally occurring outbreaks the infection follows a much milder, usually asymptomatic course among infants and children as compared to adolescents and adults. This fact has become obvious when comparing the results as to the cost/benefit ratio of hepatitis A vaccination performed within the three different age groups this study has been conducted upon. Hepatitis A vaccine has been proven to prevent the infection with an efficacy amounting to between 94% and 100%. Yet, although any potentially severe infectious disease ought to be prevented, particularly in countries undergoing a gradual improvement of their economy the cost/benefit aspect of the preventive measures applicable ought to be considered in order to arrive at feasible priorities in the context of policy making. Taking the example of the rather expensive hepatitis A vaccine, in a country such as Thailand the cost/benefit ratio certainly has to be evaluated and weighed against the background of the altogether declining incidence of HAV infections. In practical, universal vaccination is unable to cover all population. The studying in universal hepatitis B vaccination, in Thailand the coverage rate is just 82.3% after EPI. (Poovorawan *et al,* 2001).

As a case of reference, administration of hepatitis A vaccine to Thai individuals between the age of 3 and 40 years was not cost-beneficial due to several factors, *eg* incidence of hepatitis A, cost of vaccine and cost of logistics associated with vaccination. Unless the vaccine cost can be drastically lowered, the no-intervention strategy is the one economically most reasonable.

The medical costs applied in this study were obtained from King Chulalongkorn Memorial Hospital, which might be cheaper than others. Thus, if hepatitis A patients were treated in other hospitals, such as private hospitals or health care facilities, the cost benefit analysis of hepatitis A vaccine might yield different results.

As for the data on hepatitis A incidence, we estimate hepatitis A to be significantly underreported by approximately 85%. Hence, we employed sensitivity analysis in order to establish an incidence representative for determining the vaccination benefit.

Based on the current study, if we increase the incidence of hepatitis A to 5- and 10-times that of the current incidence, vaccination will become more cost-beneficial within all age groups. On the other hand, if we decrease the incidence of hepatitis A to 5- and 10-times that of the current incidence, the cost-benefit will equally decrease.

The cost-benefit of this sensitivity analysis was determined by two factors. The first one is the virulence of hepatitis A and the other is natural immunity (both received from symptomatic and asymptomatic infection), which represent cost of treatment and incidence rate of the disease, respectively.

Although the virulence of the disease increases with age, for the benefit to equal the cost the incidence rate in the 19-40-year group ought to undergo a more pronounced increase than in the lower age groups, since the majority within this age group will have acquired natural immunity on the one hand, and the vaccine administered in a dosage applicable for adults is more expensive, on the other.

To compare the cost/benefit ratio and the vaccine cost in the 3-11- and 12-18-year groups, cost and benefit in vaccination without screening groups are equal (ratio = 1) when the vaccine costs are 293 and 250 baht, respectively. In the 19-40 aged group, it is still not cost-beneficial although the vaccine cost was reduced to zero. Since most people in the 19-40-year group have already acquired immunity against hepatitis A and the indirect cost of vaccination in this age group exceeds the potential benefit we should only vaccinate high risk individuals of this age group

In Thailand, outbreaks of hepatitis A may occur occasionally. Hence, sustained high incidence rates in endemic areas combined with low vaccine costs might render HAV vaccination cost beneficial under certain circumstances.

Accordingly, the present study concurs with the conclusions arrived at in previous reports on the cost/benefit ratio of HAV vaccine, in that the vaccine has been suggested to be administered only to some selected groups at high risk to contact the virus, such as travellers to endemic areas, inmates of institutions, members of the armed forces, chronic liver disease patients as well as severely immunocompromised individuals.

ACKNOWLEDGEMENTS

The authors would like to thank the expert advisor Prof Pirom Kamolratanakul, Department of Preventive and Social Medicine, Chulalongkorn University and Hospital, for his invaluable contributions. We also would like to thank the entire staff of the Department of Pharmacology, Department of Microbiology, King Chulalongkorn Memorial Hospital for supporting this project. This work was supported within the group research from Thailand Research Fund, Senior Research Scholar. Finally, we also would like to thank Professor P Van Damme for critical reviewing and Ms P Hirsch for editing the manuscript.

REFERENCE

Corpechot C, Cadranel JF, Hoang C, *et al*. Cholestatic viral hepatitis A in adults. clinical, biological and histopathological study of 9 cases. *Gastroenterol Clin Biol* 1994; 18: 743-50.

Das A. An economic analysis of different strategies of immunization against hepatitis A virus in developed countries. *Hepatology* 1999; 29: 548-52.

Division of Epidemiology, Ministry of Public Health. Annual Epidemiological Surveillance Report, 1994.

Friedland IR, Zuckerman M, Kala UK, Parbhoo KB. Fulminant hepatitis in children: report of 12 cases. *Ann Trop Paediatr* 1991; 11: 210-2.

Innis BL, Snitbhan R, Hoke CH, Munindhorn W, Laorakpongse T. The declining transmission of hepatitis A in Thailand. *J Infect Dis* 1991; 163: 989-95.

Innis BL, Snitbhan R, Kunasol P, *et al*. Protection against hepatitis A by an inactivated vaccine. *J Am Med Assoc* 1994; 271: 1328-34.

Kamolrattanakul P. *et al*. Unit cost in provider prospective. *Thai Med Counc Bull* 1995; 8: 101-10.

Keeffe EB. Special target groups for hepatitis A vaccination. In: Rizzeto M, Pursell RH, Gerin JL, Verme G, eds. Viral hepatitis and liver disease. Satellite symposium on recent achievements and future direction for hepatitis A vaccination. Rome, Italy, 1996: 928-30.

Kiatseree F. Prevention of viral A hepatitis in the Thai population. *Siriraj Hosp Gaz* 1996; 48: 806-16.

Kosuwan P, Sutra S, Kosalaraksa P, Poovorawan Y. Seroepidemiology of hepatitis A virus antibody in primary school children in Khon Kaen Province, northeastern Thailand.: *Southeast Asian J Trop Med Public Health* 1996; 27: 650-3.

Ministry of Public Health, Human Resources Planing Division, Office of the National Economic and Social Development Board. Public Health Statistic AD Bangkok, 1995: 17.

O' Connor JB, Imperiale TF, Sirger ME. Cost-effectiveness analysis of hepatitis A vaccination strategies for adults. *Hepatology;* 1999; 10: 1077-81.

Poovorawan Y, Suwankul P, Tatiyakavee K, Sakulramrung R. Prolong cholestasis in children with hepatitis A infection. *Chula Med J* 1987; 11: 55-62.

Poovorawan Y, Theamboonlers A, Safary A. Single dose hepatitis A vaccination: comparison of different doses in adolescents. *Vaccine* 1996; 14: 1092-4.

Poovorawan Y, Theamboonlers A, Vimolket T, *et al*. Impact of hepatitis B immunisation as part of the EPI. *Vaccine* 2001; 19: 943-9.

Poovorawan Y, Theamboonlers A, Vimolket T, Dumas R, Milcamps B, Forrat R. Immunogenicity and safety of a new inactivated hepatitis A vaccine in Thai young adults. *Southeast Asian J Trop Med Public Health* 1998; 29: 779-85.

Poovorawan Y, Vimolkej T, Chongsrisawat V, Theamboonlers A, Chumdermpadetsuk S. The declining pattern of seroepidemiology of hepatitis A virus infection among adolescents in Bangkok, Thailand. *Southeast Asian J Trop Med Public Health* 1997; 28; 154-7.

Pramoolsinsap C, Poovorawan Y, Hirsh P, Busagorn S, Attamasirirul K. Acute hepatitis A superinfection in HBV carriers or chronic liver disease related to HBV or HCV. *Ann Trop Med Parasitol* 1999; 93: 745-51.

Shah U, Habib Z, Kleinman RE. Liver failure attributable to hepatitis A virus infection in a developing country. *Pediatrics* 2000; 105: 436-8.

Takahashi Y, Shimizu M. Aetiology and prognosis of fulminant viral hepatitis in Japan: a multicentre study. The study group of fulminant hepatitis. *J Gastroenterol Hepatol* 1991; 6: 159-64.

Werzberger A, Mensch B, Kuter B, *et al*. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med* 1992; 327: 453-7.

Willner IR, Uhl MD, Howard SC, Williams EQ, Riely CA, Water B. Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. *Ann Intern Med* 1998; 128: 111-4.

Yao G. Clinical spectrum and natural history of viral hepatitis A in a 1998 Shanghai epidemic. In Hollinger FB, Lemon SM, Margolis HS, eds. Viral hepatitis and liver disease. Baltimore: Williams and Wilkins, 1991: 76-78.