Economic evaluations of non-traditional vaccinations in middle-income countries

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CHAPTER 7

Cost-effectiveness of hepatitis A vaccination in Indonesia

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Abstract

Objective

This study aims to assess the cost-effectiveness of hepatitis A vaccination in Indonesia, including an explicit comparison between one-dose and two-dose vaccines.

Methods

An age-structured cohort model based on a decision tree was developed for the 2012 Indonesia birth cohort. Using the model, we made a comparison on the use of two-dose and one-dose vaccines. The model involves a 70-year time horizon with 1-month cycles for children less than 2 years old and annually thereafter. Monte Carlo simulations were used to examine the economic acceptability and affordability of the hepatitis A vaccination.

Results

Vaccination would save US$ 3,795,148 and US$ 2,892,920 from the societal perspective, for the two-dose and one-dose vaccine schedules, respectively. It also would save 8,917 and 6,614 discounted quality-adjusted-life-years (QALYs) for both schedules. With the vaccine price of US$ 3.21 per dose, the implementation of the hepatitis A vaccine from the societal perspective would yield incremental cost-effectiveness ratios (ICERs) at US$ 7,421 and US$ 4,933 per QALY gained for the two-dose and one-dose vaccine schedules, respectively. Considering the 2012 gross-domestic-product (GDP) per capita in Indonesia of US$ 3,557, the results indicate that hepatitis A vaccination would be a cost-effective intervention, both for the two-dose and one-dose vaccine schedules. Vaccination would be 100% affordable at budgets of US$ 71,408,000 and US$ 37,690,000 for the implementation of the two-dose and one-dose vaccine schedules, respectively.

Conclusions

The implementation of hepatitis A vaccination in Indonesia would be a cost-effective health intervention under the market vaccine prices. Given the budget limitations, the use of a one-dose vaccine schedule would be more realistic to be applied than a two-dose schedule. The vaccine price, mortality rate and discount rate were the most influential parameters impacting the ICERs.

Introduction

Approximately 1.4 million cases of hepatitis A virus (HAV) infection occur annually worldwide and almost half of those cases are reported in Asia [1]. HAV is primarily transmitted from person to person by the fecal-oral route and the ingestion of contaminated foods or drinks [2]. As the World Gastroenterology Organization (WGO) reported that poor hygiene and poor sanitation pose the greatest risk related to HAV infection [3], the incidence rate of HAV infection in a country is inversely related to its wealth [2]. In Asia, the endemicity levels of HAV infection vary considerably between countries [4]. Several countries still have a high endemicity level (*e.g.,* India, Bangladesh and Pakistan), other countries are intermediate in level (*e.g.,* Uzbekistan, Kazakhstan and Azerbaijan) or low (*e.g.,* Indonesia, China and Thailand) [5]. In particular, three high-income countries in Asia (Japan, South Korea and Singapore) are classified into the very low endemicity level [5].

Despite the relatively low endemicity of HAV infection in Indonesia, a substantial proportion of adolescents and adults may be susceptible to infection due to social developments, such as globalization, migration and travel patterns [6]. Additionally, as a middle-income country with continuously improving sanitation, it has been reported that fewer children in Indonesia are infected by HAV in early childhood than earlier [7]. Yet, this condition paradoxically may lead to a higher disease incidence, since HAV disease primarily manifests itself in older age groups. In the context of hepatitis A prevention, it has been emphasized that the most effective way is through vaccination, which has been implemented in several countries and has reduced hepatitis A cases significantly [8]. In Indonesia, where transmission occurs primarily from person to person in the general community and hepatitis A outbreaks periodically happen, control of hepatitis A also may be achieved through a widespread vaccination program.

Until now, an economic evaluation on hepatitis A vaccination has not yet been conducted in Indonesia. It is important to know whether potential favorable cost-effectiveness may exist within the context of the Indonesian government perspective to justify full inclusion of the hepatitis A vaccine into the national immunization program (NIP). The objective of this study is to assess the cost-effectiveness of hepatitis A vaccination in Indonesia, including an explicit comparison between one-dose and two-dose vaccine schedules.

Methods

Model

In this study, we applied a birth cohort of 4,200,000 infants [9] in an age-structured cohort model based on a decision tree. The model involves a 70-year time horizon (the average life expectancy in Indonesia) [10] with 1-month cycles for children less than 2 years old and annually thereafter. Differing from several previous studies in Asia [11-13], we made a comparison on the use of a two-dose versus a one-dose vaccine schedule. The model was run in Microsoft Excel 2010 and @Risk 4.5.4 was used in probabilistic sensitivity analysis (see Figure 1).

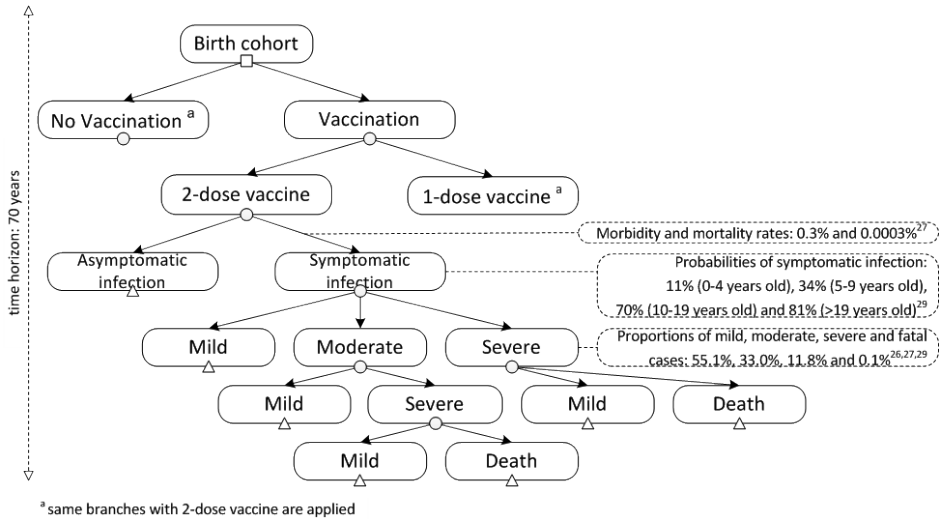

Fig. 1. Decision analytic model

Incidence of HAV infection

We classified HAV infection into four levels of severity which are generally used for global assessments: mild (home treatment), moderate (general practitioner treatment), severe (hospitalization) and fatal cases [14]. From the World Bank's report in 2006 on economic impacts of sanitation in Indonesia [15] and considering the annual incidence of HAV infection declining linearly at an average annual rate of 2% as the result of socioeconomic improvement [11], we obtained the number of hepatitis A cases in 2012 (mild, moderate, severe and fatal cases) by considering the morbidity and mortality rates of 0.3211% and 0.0003% [15]. We estimated the total number of severe cases by applying the ratio of hospitalization (severe) and outpatient visit (mild-moderate) at 11.8%:88.2% according to a study by Zhuang *et al.* [11]. For the number of severe cases in each age group, we applied

data from a study on hepatitis A cases at one of biggest public hospitals in Indonesia during 2011 [16]. Furthermore, we estimated that moderate cases would make up 37.5% and mild cases 62.5% from outpatient visit cases based on a study by Buma *et al.* [14]. Several data from previous studies related to the age-specific probabilities of symptomatic infection [17], hospitalization rate [16] and case fatality rate [11] were used to estimate mild-moderate, severe and fatal cases in various age groups. For economic consequences, we only consider symptomatic infections since asymptomatic infections were assigned no costs and excluded from further follow-up for disease outcomes [11]. As the liver transplant in acute hepatitis patients with fulminant liver failure is very rare in Indonesia, we did not take this into account (see Figure 2).

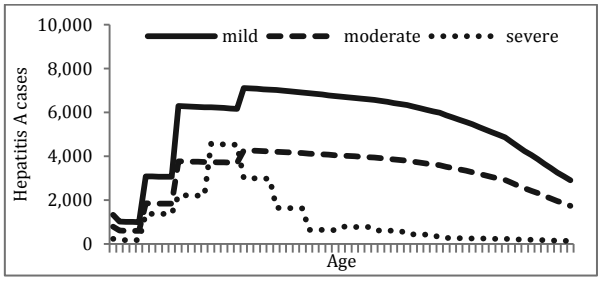

Fig. 2. Age-specific hepatis A-associated case

Vaccine characteristics

Hepatitis A vaccine would be given in a two-dose schedule at 12 and 18 months of age and in a one-dose schedule at 12 months of age. We applied vaccine efficacy at 93% and 95 % for the first and second dose, based on vaccine immunogenicity and safety studies [18-20]. Furthermore, we assumed that with the two-dose vaccine schedule, vaccine protection would annually decline by 0.31% within the first 10 years and 0.62% thereafter according to the expert panel opinion [21]. In the one-dose vaccine schedule, vaccine protection would annually decline by 1.62% within the first 10 years and 2.67% thereafter [21]. Vaccine coverage in this study was assumed to be 80% for both the two-dose and one-dose vaccine schedules, according to a previous hepatitis B study conducted in Indonesia (see Table 1) [22].

QALY (quality-adjusted-life-year) losses

To estimate QALY losses, we applied data from several previous studies with estimated durations of illness at 16, 21 and 33 days for mild, moderate and severe cases, respectively [10], and disutility scores at 0.43 for the state lived with hepatitis A [23]. Based on those

data, we estimated QALY losses, *e.g.,* mild cases at 0.01885 (16 x 0.43 / 365 days) [24]. We applied the same method for estimating QALY losses for moderate and severe cases. We did not consider caregiver QALY losses in our study (see Table 1).

Table 1
Parameters used in the model

Parameters	Baseline	Distribution	References
Vaccine coverage	80%	Normal (95%CI; 76.64-83.36%)	[37]
Vaccine efficacy			
1st dose	93%	Normal (95%CI; 89.10-96.90%)	[13]
2nd dose	95%	Normal (95%CI; 91.01-98.99%)	
Annual loss of vaccine protection			
1-dose schedule (1-10 years)	1.62%	NA	[36]
1-dose schedule (> 10 years)	2.67%		
2-dose schedule (1-10 years)	0.31%		
2-dose schedule (> 10 years)	0.62%		
Probability of symptomatic infection			
0-4	11%	NA	[31]
5-9	34%		
10-19	70%		
20+	81%		
Hepatitis A hospitalization rate			
0-4	1.05%	NA	[32]
5-9	8.42%		
10-14	13.68%		
15-19	28.42%		
20-24	18.95%		
25-29	10.53%		
30-34	4.21%		
35-39	5.26%		
40-44	4.21%		
45-49	3.16%		
50+	2.11%		
Hepatitis A case fatality rate			
1-14	0.030%	NA	[13]
15-39	0.054%		
40+	0.436%		
Hepatitis A cases			
Mild	381,347	Normal (95%CI; 380,137-382,556)	[13,29-32];
Moderate	228,808	Normal (95%CI; 227,871-229,745)	calculated
Severe	81,590	Normal (95%CI; 81,030-82,150)	
Death	679	Normal (95%CI; 628-730)	
Age-dependent hepatitis A related proportion of mild, moderate, severe and fatal cases		Dirichlet	[13,29-32]; calculated
Utility losses			
Mild	0.01885	Triangular	[13,29,38];
Moderate	0.02474	(using 25% lower and upper)	calculated
Severe	0.03888		
Death	1.00000		
Total healthcare costs per case (US$)			
Mild	8.77	Gamma (5.06-15.81)	[30,39];
Moderate	17.53	Gamma (25.20-55.80)	calculated
Severe	25.82	Gamma (59.50-114.30)	
Total societal costs per case (US$)			
Mild	11.31	Gamma (9.24-25.03)	[27,33];
Moderate	20.08	Gamma (34.10-71.60)	calculated
Severe	36.24	Gamma (124.50-215.80)	
Vaccination cost (US$)			
Vaccine price (per dose)	3.21	Triangular	[37,39]
Administration cost (per dose)	0.36	(using 25% lower and upper)	[9,39]
Discount rate	3%	0-5%	[13]

NA: not applicable

Hepatitis A costs

Differing from two previous studies in South East Asia Region (SEAR) [12,25], the analysis in this study was viewed from two perspectives: healthcare and societal. We only considered direct medical cost in the healthcare perspective, while in the societal perspective, we considered both direct and indirect costs. We derived our cost estimations from a 2006 study on estimated unit costs related to HAV infection due to poor sanitation in Indonesia [15]. Healthcare costs due to HAV infection related mild, moderate and severe cases were estimated from informal outpatient care (home treatment), formal outpatient care (general practitioner treatment) and formal inpatient care (hospitalization) sources, respectively [15]. For societal costs, we additionally took direct non-medical costs (*e.g.,* transportation) and indirect costs (*e.g.,* productivity loss) into account [9]. Vaccine price and administration cost per dose were applied at US$ 3.21 [22] and US$ 0.36 [9], respectively, based on previous studies in Indonesia. All results from the analyses were converted to 2012 US$ by using purchasing power parities (PPPs) [26] and all costs were discounted with a yearly rate of 3% (see Table 1).

Analytic methods

$$\text{ICER} = \frac{\text{Total cost of with vaccination} - \text{Total cost of without vaccination}}{\text{Total QALY gained without vaccination} - \text{Total QALY gained with vaccination}}$$

The incremental cost-effectiveness ratio (ICER) was calculated to measure the outcomes from both perspectives in relation to the World Health Organization's (WHO's) definition on cost-effectiveness of universal vaccinations according to the gross-domestic-product (GDP) per capita: (i) highly cost-effective (less than one GDP per capita); (ii) cost-effective (between 1 and 3 times GDP per capita); and (iii) cost-ineffective (more than 3 times GDP per capita) [27]. We performed both univariate and probabilistic sensitivity analyses (PSA). Univariate sensitivity analyses were performed to investigate the effects of different input parameters primarily by varying each parameter with ± 25% while keeping other parameters constant. PSA were performed by running 5,000 Monte Carlo simulations. The results of the PSA were presented in CEACs by using two thresholds: 2 times GDP per capita and 3 times GDP per capita. We evaluated affordability of vaccinations related to the required budget (vaccination and treatment costs) from the healthcare perspective, based on the distribution of incremental costs and health gains from the same 5,000 Monte Carlo simulations.

Results

Baseline analyses

Assuming a vaccine coverage of 80% and vaccine efficacies of 93% (first dose) and 95% (second dose), vaccination of 4,200,000 infants [9] would reduce HAV infection by 452,834 and 322,207 cases when using two-dose and one-dose vaccine schedules, respectively. In particular, the two-dose vaccine schedule would reduce hepatitis A cases by 247,694 (65.0%), 148,670 (65.0%), 56,064 (68.7%) and 406 (59.8%) for mild, moderate, severe and fatal cases, respectively. The one-dose vaccine schedule would reduce hepatitis A cases by 174,157 (45.7%), 104,579 (45.7%), 43,224 (53.0%) and 247 (36.3%) for mild, moderate, severe and fatal cases, respectively. Hepatitis A vaccination would save 8,917 and 6,614 discounted QALYs for the two-dose and one-dose vaccine schedules, respectively. Furthermore, it also would save US$ 3,795,148 and US$ 2,892,920 from the societal perspective for both schedules, respectively (see Table 2.a). The cost-effectiveness values from all perspectives are shown in Table 2.b. With a vaccine price of US$ 3.21 per dose, the implementation of hepatitis A vaccine from the healthcare perspective would yield ICERs at US$ 7,510 and US$ 5,025 per QALY gained for the two-dose and one-dose vaccine schedules, respectively. From the societal perspective, it would yield ICERs at US$ 7,421 and US$ 4,933 per QALY gained for both schedules. Considering the 2012 GDP per capita in Indonesia of US$ 3,557 [28], the results confirmed that hepatitis A vaccination using the two-dose and one-dose vaccine schedules would be cost-effective interventions since the ICERs were between 1 and 3 times GDP per capita [27]. Additionally, the ICERs of the two-dose over the one-dose schedule were US$ 14,648 and US$ 14,568 per QALY gained from the healthcare and societal perspectives, respectively.

Table 2.a
Results from all vaccination strategies

Vaccine	Without Vaccination	With Vaccination	Difference
Two-dose vaccine schedule			
Number of cases [a]	692,424	239,590	452,834
Mild	381,347	133,653	247,694
Moderate	228,808	80,138	148,670
Severe	81,590	25,526	56,064
Death	679	273	406
Cost of illness			
Healthcare perspective [b,c]	$ 4,441,405	$ 1,437,763	$ 3,003,642
Societal perspective [b,c]	$ 5,604,793	$ 1,809,645	$ 3,795,148
Cost of vaccination program			
Acquisition cost [b]	0	$ 62,859,401	($ 62,859,401)
Administration cost [b]	0	$ 7,107,260	($ 7,107,260)
Total vaccination cost [b]	0	$ 69,966,661	($ 69,966,661)
QALYs lost [b]	13,896	4,980	8,917
One-dose vaccine schedule			
Number of cases [a]	692,424	370,217	322,207
Mild	381,347	207,190	174,157
Moderate	228,808	124,229	104,579
Severe	81,590	38,366	43,224
Death	679	432	247
Cost of illness			
Healthcare perspective [b,c]	$ 4,441,405	$ 2,155,823	$ 2,285,582
Societal perspective [b,c]	$ 5,604,793	$ 2,711,873	$ 2,892,920
Cost of vaccination program			
Acquisition cost [b]	0	$ 31,914,096	($ 31,914,096)
Administration cost [b]	0	$ 3,608,398	($ 3,608,398)
Total vaccination cost [b]	0	$ 35,522,494	($ 35,522,494)
QALYs lost [b]	13,896	7,348	6,859

[a] Undiscounted
[b] Discounted
[c] Costs are excluding vaccination cost

Table 2.b
Cost effectiveness results

Cost effectiveness of vaccination	One-dose	Two-dose
Vs no vaccination		
Net cost per QALY gained (healthcare) [a]	US$ 5,025	US$ 7,510
Net cost per QALY gained (societal) [a]	US$ 4,933	US$ 7,421
Vs one-dose vaccine schedule		
Net cost per QALY gained (healthcare) [a]		US$ 14,648
Net cost per QALY gained (societal) [a]		US$ 14,568

[a] Discounted

Univariate, probabilistic sensitivity and affordability analyses

The effects of varying input parameters on the ICERs are shown in a tornado chart (see Figure 3). For the schedule using two administrations, the result confirmed that the vaccine price, mortality rate and discount rate provide most impact on the ICERs. The cost-effectiveness acceptability curves (CEACs) from the societal perspective showed that at the

threshold ICER of US$ 7,114 (2 times GDP per capita), the probability for the implementation of hepatitis A vaccination to be cost-effective would be 38.18% and 100% for two-dose and one-dose vaccine schedules, respectively. If a threshold ICER of US$ 10,671 (3 times GDP per capita) were used, the probability for the implementation of hepatitis A vaccination to be cost-effective would be 100% for both vaccine schedules (see Figure 4.a). The affordability curves related to the required budget for vaccination from the healthcare perspective, are shown in Figure 4.b. At budgets of US$ 71,408,000 and US$ 37,690,000 for the implementation of the two-dose and one-dose vaccine schedules, the implementation of hepatitis A vaccination would be 100% affordable.

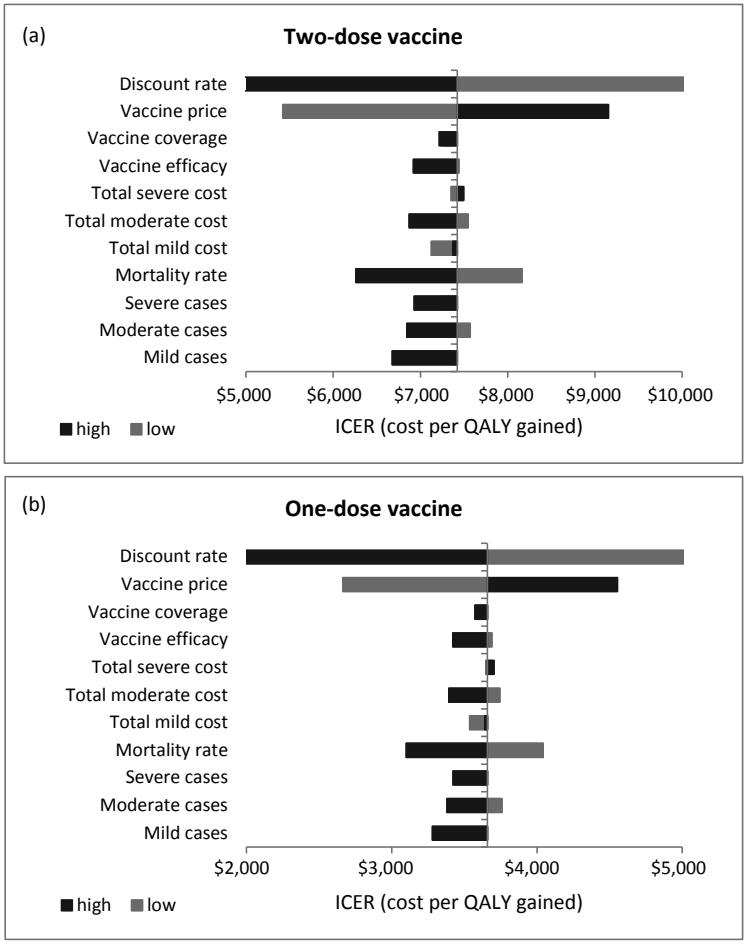

Fig. 3. Univariate sensitivity analyses from societal perspective

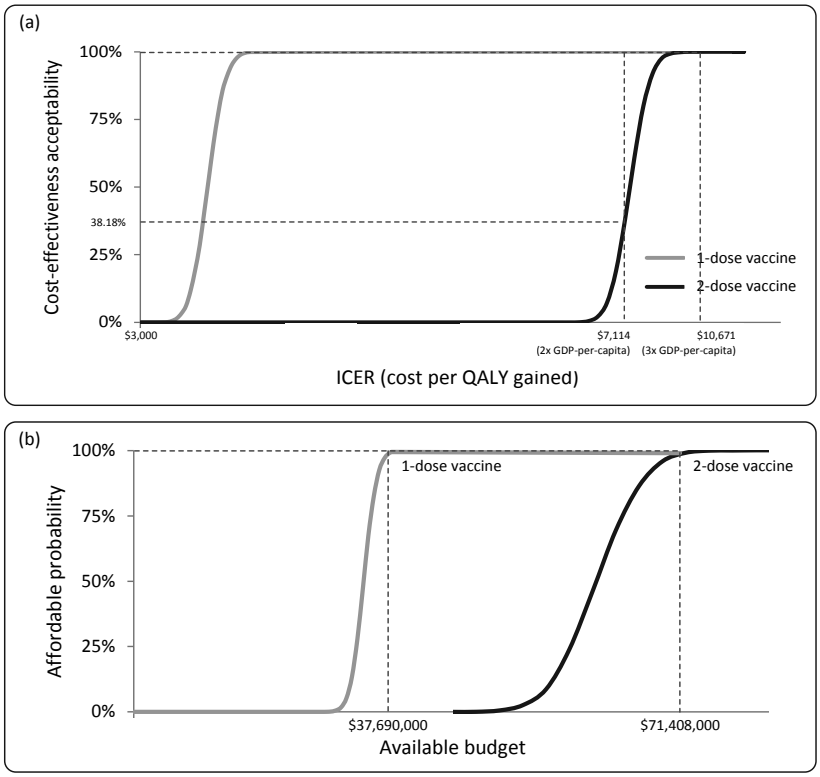

Fig. 4. (a) Cost-effectiveness acceptability curves from the societal perspective
(b) Affordability curves from the healthcare perspective

Discussion

As a consequence of the improvement in hygiene and sanitary conditions, which are coupled with the economic rising of Indonesia from a low-income country into a middle-income country, the incidence of HAV infection has gradually declined. Without vaccination, HAV causes 692,424 cases in Indonesia where the disease acquisition occurs in adulthood rather than childhood as a typical of hepatitis A case in a low endemicity country [29]. Applying a vaccine coverage at 80%, vaccination of a birth cohort of 4,200,000 would reduce HAV-cases by 452,834 and 322,207 for vaccination with the two-dose and one-dose vaccine schedules, respectively. The cost-effectiveness analyses yielded ICERs from the societal perspective at US$ 7,421 and US$ 4,933 per QALY gained for both vaccine schedules. Our finding that the implementation of universal hepatitis A immunization could be cost-effective even in a low endemicity country, such as Indonesia, is linear with a previous study [11]. It could be emphasized that incidence was only one of the major determining factors for the cost-effectiveness of universal hepatitis A vaccination. Even in very low endemic countries, such

as Canada and certain parts of the United States, universal vaccination could be a cost-effective intervention [30]. However, in other very low endemic countries, for instance in Belgium and Australia, it was shown that two-dose universal childhood hepatitis A vaccination was not cost-effective, using dynamic and static models, respectively [31,32]. These results are mainly influenced by estimated disease incidence, vaccine price, the schedule and the inclusion of societal cost [30]. In particular, another finding that the implementation of the one-dose vaccine schedule would be more cost-effective intervention compared to the two-dose vaccine schedule is in line with a previous study in Argentina [33]. This further warrants future attention on the implementation of the one-dose vaccine schedule, especially to control community-wide outbreaks since a single dose of hepatitis A vaccine has been proven an effective strategy if vaccination was started early and applied with high coverage. Additionally, compared to the two-dose vaccine schedule, the one-dose vaccine schedule is cheaper and easier to be implemented. Yet, in high-risk groups (such as children with chronic liver disease and immune-compromised individuals) for hepatitis A, a two-dose vaccine schedule is still preferred [8]. In the context of the health economic perspective, however, the implementation of the one-dose vaccine schedule would be more realistic to be implemented in Indonesia. Related to the sensitivity analyses, the results in this study reconfirmed the results from several previous studies that the vaccine price [12,34,35], mortality rate [36], and discount rate [30,34,37,38] were the most influential parameters impacting the ICERs in the implementation of hepatitis A vaccination. However, the dominant role of the vaccine price might lead the small difference between the ICERs from the healthcare and societal perspectives [25].

This study is the first economic evaluation study on hepatitis A immunization in Indonesia. Yet, we do not present the first economic analysis on that matter in SEAR. Compared to the previous studies in Thailand [12,13], our study has some significant differences in the process of analysis. Firstly, we explicitly compared the two-dose and one-dose vaccine schedules in a cost-effectiveness study in order to investigate the difference on the cost-effectiveness results by performing the ICERs of both vaccines over without vaccination, while two previous studies used only one vaccine schedule in their cost-benefit analyses. We also performed the ICERs of the two-dose over one-dose vaccine schedules. Secondly, we adopted both the healthcare and societal perspectives in our study. However, the healthcare perspective is relevant for assisting decision makers in the health sector only, while the societal perspective is often preferred to reflect the full public health impact. Thirdly, we performed an age-structured cohort model based on a decision tree by dividing the outpatient cases into two different levels: mild (requiring home treatment) and moderate

cases (requiring general practitioner treatment), and considering the annual decline of infection incidence and the annual loss of vaccine protection that would render results that are more precise and valid.

Nevertheless, several limitations were found in this study. The first and main limitation is that we use a static model rather than a dynamic model, which has the ability to incorporate the effect of herd immunity. In general, the static model tends to over-estimate the cost-effectiveness result. Notably, there would be an even more favorable cost-effectiveness if we took herd immunity into account. Next to the ability to incorporate the epidemiology of hepatitis A and the development of herd immunity, the disadvantage of a dynamic model is the requirement for data, which are currently scarce in Indonesia. Particularly, the age specific force of infection is difficult to be estimated as it requires serial seroprevalence data and social contact data. The second limitation is the lack of vaccine efficacy data for different levels of severity: mild, moderate, severe and death. Even though we applied different vaccine efficacy for the first dose and second dose, we applied the same vaccine efficacy for all levels of severity, thus the vaccine efficacy might be over or underestimated. The third limitation is the lack of specific local data related to the proportion of incidence for all levels of severity. In this study, we derived those numbers from international data. Yet, we varied these estimates extensively in multiple sensitivity analyses. Finally, we applied treatment costs from a 2006 study on estimated unit costs related to HAV infection due to poor sanitation in Indonesia and these costs were inflated to 2012 price levels. Obviously, hepatitis A vaccination would be more cost-effective when the treatment costs are higher, and *vice versa*.

Our study provides information for policy makers in Indonesia to justify full inclusion of the hepatitis A vaccine into the NIP. With the market price of US$ 3.21 per dose, vaccinating using both the two-dose and one-dose vaccine schedules could be a cost-effective intervention according to the WHO's criteria for cost-effectiveness. Furthermore, when we took uncertainties into account, the implementation of universal hepatitis A immunization would not be affordable when the budget does not exceed US$ 71,408,000 and US$ 37,690,000 for the two-dose and one-dose vaccine schedules, respectively. In fact, the Indonesian government spent approximately US$ 68 million for NIP activities in 2011 [39]. Compared to the total Indonesian government health budget for the whole mandatory immunization program (hepatitis B, BCG (bacille Calmette-Guérin), diphtheria-pertussis-tetanus, measles and polio), the required investment by the Indonesian government for universal hepatitis A vaccination would be unrealistic without external support. A solution could be to reduce the vaccine price through financial aids from international organizations.

However, saving funds could enhance implementation of further vaccination programs in a country with limited vaccination budget, such as Indonesia. In particular, the implementation of the one-dose vaccine schedule could be considered since it has been proven to be the most cost-effective intervention in this study. Using the combined hepatitis A/B vaccine instead of monovalent vaccine could be considered to reduce the administration costs since the combined hepatitis A/B vaccine has been proven as a highly immunogenic and well-tolerated in a previous study [40]. Hopefully, this study helps the Indonesian government in making regulation to reduce the incidence of HAV infection in Indonesia, in line with WHO's goal on the implementation of universal vaccination.

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