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Expanding japanese encephalitis vaccination to selected endemic indonesia provinces: A cost-effectiveness analysis

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ABSTRACT

Introduction: A Markov model was used to evaluate the potential health and economic impact of introducing JE vaccine nationally and in selected endemic areas of Indonesia compared to no vaccination from government and societal perspectives over a child's lifetime horizon.

Methods: Costs were obtained from hospitalized JE suspected patient billing data from 2014 to 2019 in seven provinces. Local data burden data were derived from the literature. Analysis considered several scenarios, including national and sub-regional introduction in seven provinces via a one-time vaccination campaign in all children 1–15 years old followed by routine immunization among infants (RI), or RI alone without vaccination campaign.

Results and discussions: Across scenarios, JE vaccination was projected to range from cost-saving to cost-effective compared to no vaccination at a willingness-to-pay threshold of 0.5x gross domestic product per capita. Including a one-time campaign would avert nearly three times as many JE cases and deaths compared to RI alone while still providing good value for money.

1. Introduction

Japanese encephalitis virus (JEV) is the main cause of viral encephalitis in many countries of Asia [1]. Twenty-four countries in the WHO South-East Asia and Western Pacific Regions, including Indonesia, are endemic for JE with an estimated 67,900 cases per year across the countries [2,3]. JEV is in the genus Flavivirus and is transmitted to humans primarily by *Culex tritaeniorhynchus* mosquitoes, which have fed on viremic pigs or wading birds as intermediate viral amplifying hosts [4]. While only a small proportion of JE infections in humans produce encephalitis (<1%), those who develop encephalitis have an estimated case-fatality rate of 20–30% with 30–50% of survivors developing significant neurologic sequelae [2,4,5]. In Indonesia, for example, Maha et al found that half of all JE-surviving children from six provinces developed sequelae: 25% had severe sequelae with significantly impaired function that will likely make them dependent on others, 7% had moderate sequelae with mildly impaired function, and 18% had minor sequelae with mild effects on function or changes in behaviour [5].

JEV is transmitted in several Indonesian provinces. Epidemiologic data from 11 provinces in Indonesia, generated by local disease surveillance activities in 2016, found a total of 43 out of 326 human serum samples from individuals with JE symptoms were confirmed positive by IgM ELISA [6]. In 2016, the Ministry of Health's Special Research on Disease Vectors (Rikhus Vektora) demonstrated that JEV was present in 15 provinces by using gene amplification methods in three mosquito species. In addition to evidence of JE in *Culex tritaeniorhynchus*, *Culex vishnui*, and *Armigeres subalbatus mosquitoes*, the Indonesian National Institute of Health Research and Development (NIHRD) Laboratory for Vectors and Reservoirs tested 13,205 bats representing 55 different species and PCR evidence of JEV was found in 22 of the bat-species [7]. A recent review of JE studies in humans and animals in Indonesia presented evidence of JEV endemicity in 29 of the 34 provinces in Indonesia over a 5-plus decade period [4].

Several neighbouring countries namely China [17,19], Cambodia [18], and Philippines [10] have conducted similar studies and found cost-effective results of JE vaccination.

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In 2018, Indonesia successfully introduced JE vaccine into the Bali province where the disease has been formally studied and JE burden has been found consistently high [8,9]. JE immunization coverage based on valid records of denominators, ranging from 76.5 to 96.2 percent across Bali province [24]. Given the data suggesting JEV endemicity in much or all of Indonesia, an economic model designed by PATH [10] was used to estimate the costs, budget impact, health impact and cost-effectiveness of JE vaccination that can be used by the Indonesian government to assess the health and economic implications of introducing JE vaccine in the country more broadly.

2. Materials and methods

2.1. Model and design

We used a Markov model to estimate the potential impact of JE vaccination among children in Indonesia. The model was built using Microsoft Excel^{TM} (Redmond, WA) and simulates an individual child who either receives JE vaccination or no vaccination. Subsequently, the child can develop acute JE, asymptomatic JE, or no JE (Fig. 1). If the child develops acute JE, the child may experience mild/moderate/severe sequelae of JE and may die of either JE or non-JE causes.

The model was then used to quantify the costs and health outcomes over the child's lifetime horizon from the government and societal perspectives. Key health outcomes consisted of expected number of JE cases, expected deaths, and disability-adjusted life years (DALYs) with and without vaccination. Markov cycle lengths were one-year, and individual results were extrapolated to the population level. Fig. 1 illustrates the clinical pathways of a child with JE from acute phase to post-acute phase, and eventually death state. Costs were collected from seven hospitals in Indonesia. A patient is suspected to be JE patient if they were diagnosed as encephalitis, meningitis, or meningoencephalitis, and suspected as JE cases by his/her doctor. We searched eligible patients in the past five years (since the implementation of the National Health Insurance in 2014). The study took place in Provincial General Hospitals. Parameters used in the model are described in Table 1. All costs and health outcomes were discounted at the rate of 3.0%. Monetary units are presented in 2018 US dollars (USD). The results were presented in terms of incremental cost-effectiveness ratio (ICER), using the following formula:

$$\text{ICER} = \frac{total\ \ cost\ \ of\ \ new\ \ intervention - total\ \ cost\ \ of\ \ exisiting\ \ intervention}{total\ \ DALY\ \ of\ \ new\ \ intervention - total\ \ DALY\ \ of\ \ existing\ \ intervention}$$

2.2. Modelled immunization strategies

Total lifetime cost and health outcomes amongst four policy options were evaluated, two each for nationwide routine JE vaccine introduction ("National") and sub-national routine introduction in seven high-risk provinces where no JE vaccine had heretofore been introduced ("Sub-National"). Approximately 85% of JE cases in Indonesia are among children under 15-years-old, and therefore, we considered options that include one-time campaigns targeted to this age group. The options for the National scenario were:

- One-time vaccination campaign among 1–15 year old children in all 34 provinces followed by national routine immunization of infants for one birth cohort and three subsequent birth cohorts;
- National routine immunization only for infants over one birth cohort and three subsequent birth cohorts.

The options for the Sub-National scenario were:

- One-time campaign among 1–15 year old children in seven provinces followed by sub-national routine immunization for over one birth cohort and three subsequent birth cohorts;
- Routine immunization only for infants in the seven provinces over one birth cohort and three subsequent birth cohorts.

Evaluation immunization costs and impact across up to three birth cohorts were identified as the most relevant to Indonesian decision-makers. All scenarios were compared to the status quo of no vaccination.

2.3. Selection of study area and data collection

Based on the results of hospital sentinel surveillance for JE in children under 15 years of age in 2005–2006 [8] and in 2016 [6], seven high-risk provinces with suspected endemicity of Japanese Encephalitis were identified for the Sub-National scenario, namely: Riau Islands, West Kalimantan, Jakarta, Yogyakarta, West Nusa Tenggara, East Nusa Tenggara, and North Sulawesi. JE in Bali province has been well studied and is known to have high incidence but was not included in this assessment due to the province-wide introduction of JE vaccine in 2018 and prior estimates of cost-effectiveness [9].

We collected secondary, locally-specific estimates on disease incidence, vaccine delivery costs, and cost of illness, which were

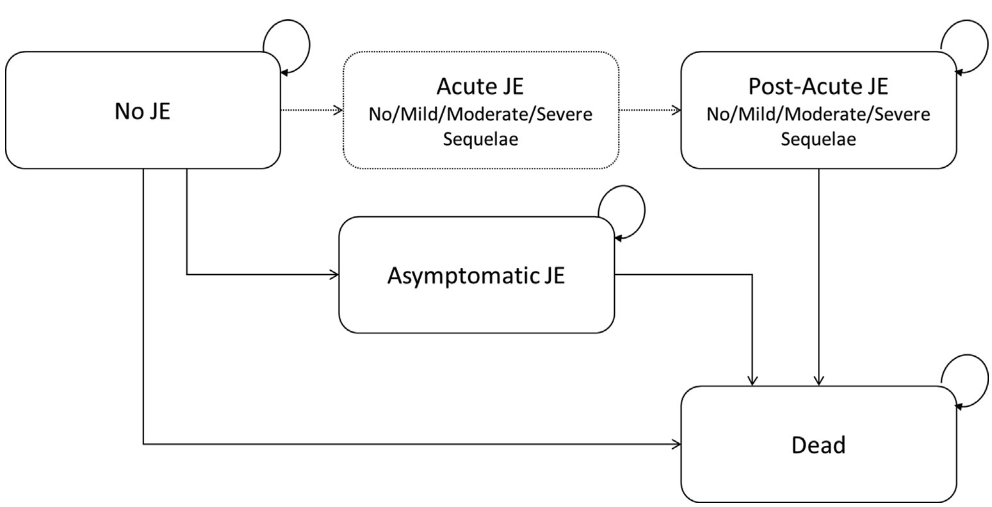

Fig. 1. Markov Model of Japanese encephalitis.

Table 1
Selected Input Parameters for JE Cost-Effectiveness Model.

Parameters	Base Case	Low	High	Source
JE Vaccine & Epidemiology				
Vaccine coverage: Routine Imm.	0.92	0.46	100%	Local Data (Indonesia), MoH Indonesia[11]
Vaccine coverage: Campaign	0.92	0.46	100%	Local Data (Indonesia), MoH Indonesia[11]
Vaccine efficacy	0.93	0.69	0.98	Li 2014[12], Pooled OR from 5 case-control studies evaluating the effectiveness of live attenuated SA14-14-2 virus vaccine
JE incidence (symptomatic) per 100,000	7.1	3.6	10.7	Kari 2006 [13]; range +/-50% of base case estimate
Case fatality ratio	0.23	0.1	0.3	Garjito 2018 [4]
Asymptomatic JE, times more common than acute	300	25	1000	Misra 2010[14]
Duration of acute JE event (weeks)	2.3	1.15	3.45	Local data (primary data from hospitals); range +/-50% of base case
Sequelae incidence	0.5	0.25	0.75	Maha 2009[5]; range +/-50% of base case
Sequelae severity breakdown				
Mild and/or transient				100%-(moderate + severe)
Moderate and permanent	0.14	0.07	0.21	Maha 2009[5]; range +/-50% of base case
Major and permanent	0.5	0.25	0.75	Maha 2009[5]; range +/-50% of base case
Probability of treatment for sequelae				
Mild and/or transient	0	0	0	Local Expert Opinion
Moderate and permanent	0	0	0	Local Expert Opinion
Major and permanent	0.75	0.375	1	Local Expert Opinion
Disability Weights				
Acute JE (per event)	0.133	0.148	0.308	Salomon JA et al. 2015 [15], disability weight for infectious disease acute episode – severe
Long term sequelae (annual)				
Mild	0.031	0.018	0.05	Salomon JA et al. 2015 [15], disability weight for motor and cognitive impairments – mild
Moderate	0.203	0.134	0.29	Salomon JA et al. 2015 [15], disability weight for motor and cognitive impairments – moderate
Severe	0.542	0.374	0.702	Salomon JA et al. 2015 [15], disability weight for motor and cognitive impairments – severe
Costs[ǂ]				
Vaccine cost (per dose)	$ 0.50	$ 0.25	$ 10.00	Assumption (high range estimate selected to capture price of choosing more costly vaccine)
Vaccine delivery costs, routine immunization	$ 0.80	$ 0.40	$ 1.20	In-country costing analysis; range: +/-50%
Vaccine delivery costs, campaign	$ 0.80	$ 0.40	$ 1.20	In-country costing analysis; range: +/-50%
JE related hospitalization costs (per JE event)	$ 1,444.00	$ 722.00	$ 2,166.00	In-country costing analysis; range: +/-50%
National surveillance costs	$ 5.00	$ 2.50	$ 7.50	In-country costing analysis; range: +/-50%
Annual sequelae costs				
Mild	$ -	$ -	$ -	Assumption
Moderate	$ 332.00	$ 166.00	$ 498.00	In-country costing analysis; range: +/-50%
Severe	$ 471.80	$ 235.90	$ 707.70	In-country costing analysis; range: +/-50%
Non-healthcare resources				
Transportation – patient	$ 2.14	$ 1.07	$ 3.21	Calculated based on local data[16]
Transportation – caregiver	$ 2.14	$ 1.07	$ 3.21	Calculated based on local data[16]
Caregiver time, severe sequelae, annual	$ 323.10	$ 82.56	$ 484.65	Base case: local data[16]; Low range: Assumed average stay of base case duration; with 1 day of caregiver time valued at median provincial minimum wage per day (calculated from reported monthly minimum wage assuming 21.7 working days per month); High range = 1.5xbase case
Other Parameters				
Annual increase in vaccine cost	5%	3%	8%	Assumption
Vaccine subsidy	100%	50%	100%	Assumed to be 100% from government perspective and 0% in societal perspective. Range provided is for government perspective.
Wastage	0.15	0.075	0.225	Ministry of Health[11]
Buffer	0.05	0.025	0.075	Ministry of Health[11]
Average useful lifetime of equipment (years)	10	5	15	Assumption

ǂ Note that costs presented here represent average costs nationally. Provincial-level costs also informed the model and are provided in the Supplemental Appendix; all costs are in 2018 USD.

used as inputs into the PATH JE economic model (Table 1) [10]. Cost of illness data were collected from hospital administrators, financial officers, clinicians, and others with knowledge about JE-related treatment costs and resource utilization in each identified province. Costs of vaccine delivery were collected from local, regional and/or national health officials, health facilities, and other stakeholders. We obtained ethical approval from the Institutional Review Board of the National Institute of Health Research and Development (NIHRD). Disability weights and epidemiological data were derived from the literature and expert opinion.

2.4. Uncertainty analysis

We ran one-way sensitivity analyses to identify key drivers of model outcomes using standard errors or reasonable ranges (low/high estimates in Table 1 and Fig. 2) for each input. We also conducted a probabilistic sensitivity analysis using Monte Carlo simulation in which all input parameters were assigned a probability distribution, and the model was run using values randomly sampled from their distribution simultaneously. The process was repeated over 10,000 simulations and the cost-effectiveness result

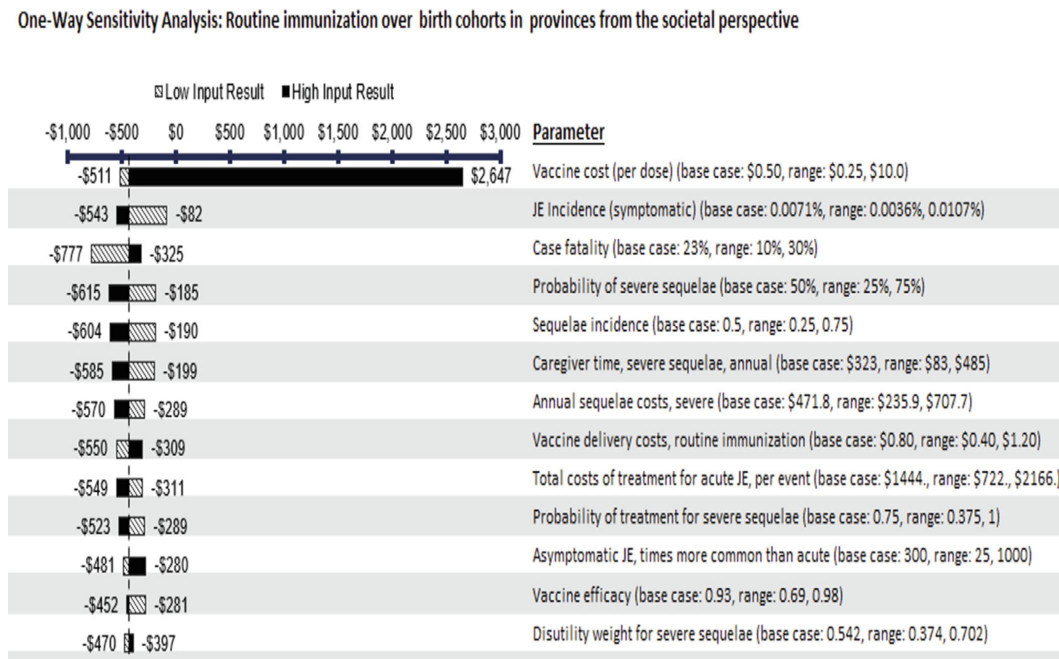

Fig. 2. One-way sensitivity analysis results JE vaccination via national routine immunization (34 provinces) over 3 birth cohorts from the societal perspectives.

(ICER value) from each simulation was recorded to assess the impact of joint parameter uncertainty on the model results and to calculate 95% credible ranges for results. Simulation results were compared to various willingness to pay thresholds and plotted on a cost-effectiveness acceptability curve to assess the potential likelihood that vaccination would be cost-effective compared to no vaccination.

3. Results

The projected costs and outcomes associated with each of the modelled JE vaccine delivery strategies are shown in Table 2. Compared to no vaccination, the model suggests that JE vaccination in all scenarios would avert more DALYs, at lower marginal costs or even save costs by offsetting the need for treatment downstream. We found that investment in JE vaccine in national routine program would be the most favorable scenario in terms of cost per DALY averted; compared to doing nothing, this strategy could prevent 11,149 JE cases, 2,564 JE deaths, and 78,349 DALYs over three birth cohorts and save an incremental $9.1 M from the government perspective and $33.7 M from the societal perspective over the cohorts' lifetime horizon after accounting for the long-term sequelae burden and associated costs with and without vaccination. Sub-national routine immunization in seven provinces was also projected to achieve cost savings of $586,505 (governmental) and $3.7 M (societal) while reducing the disease burden by 1,448 cases, 333 deaths, and 10,179 DALYs compared to no vaccination.

When a one-time campaign among children aged 1–15 years was included, either at a national or sub-national level, JE vaccination was no longer expected to be cost-saving but would have a greater impact on disease burden than routine immunization alone. At the national level, a one-time campaign followed by routine immunization among three birth cohorts was estimated to prevent 31,386 JE cases, 7,219 JE deaths, and 231,234 DALYs for an additional cost of $68.7 M from the government perspective and $39.8 M from the societal perspective. At the sub-national level, a one-time campaign plus routine immunization over three birth cohorts could prevent 4,099 JE cases and 943 JE deaths and incur an additional $10.2 M from the government perspective and $5.9 M from the societal perspective compared to no vaccination. While inclusion of a campaign would incur greater costs, the cost per DALY averted in these scenarios would be cost-effective with ICERs of $297 (government) and $172 per DALY averted one-time national campaign plus routine, and $322 (government) and $197 (societal) per DALY averted for sub-national campaign plus routine (see Fig. 2).

Results from the one-way sensitivity analyses indicate that vaccine cost per dose was the key driver of model outcomes across all scenarios due to the wide uncertainty range of this parameter ($0.25-$10 per dose). Other parameters that consistently impacted cost-effectiveness results across scenarios were incidence of JE and sequelae, case fatality ratio, probability of severe sequalae and subsequent costs of treatment, and vaccine delivery costs. Supplementary Appendix Fig. 1 shows the one-way sensitivity results, presented as a tornado diagram, for the scenario of national routine immunization over three birth cohorts from the societal perspective. As illustrated, when the high-range value for vaccine cost per dose was applied ($10), JE vaccination yields an ICER of $2,647 per DALY averted compared to being cost-saving at the baseline cost per dose ($0.50). Other parameters for this scenario slightly affect the ICER but do not change the directionality of results.

The scenario of National Routine Immunization covering children aged 1–15 years in the three-year period shows the most cost-effective intervention. Probabilistic sensitivity analysis shows that the model is robust to uncertainty (Supplementary Appendix Fig. 2). Additionally, when we compared ICER results for each scenario to a range of willingness-to-pay (WTP) per DALYs averted, the probability that JE vaccination would be cost-effective is over 90% when the WTP threshold is $500 per DALY averted or greater (Supplementary Appendix Fig. 3).

Supplementary Appendix Table 1 presents a comparison of Indonesian key parameters and the results of our analysis compared with neighbouring countries in Asia that evaluated JE vaccination; our analyses found similar cost-effective results as other countries.

Table 2
Projected costs and outcomes associated with routine and campaign-based JE immunization programs across various delivery strategies from the governmental and societal perspectives.

A. National Routine Immunization Only

	Over 1 birth cohort			Over 3 birth cohorts		
	With vaccination program	No vaccination	Difference with vaccination	With vaccination program	No vaccination	Difference with vaccination
Expected cases	606	3,963	(3,357)	2,005	13,154	(11,149)
Expected deaths	139	912	(772)	461	3,025	(2,564)
Expected DALYs	6,164	40,325	(34,162)	14,093	92,442	(78,349)
Expected costs, governmental perspective	$9,896,508	$12,507,879	$(2,611,371)	$38,781,637	$47,887,808	$(9,106,171)
Expected costs, societal perspective	$11,034,885	$20,064,234	$(9,029,348)	$43,140,044	$76,818,154	$(33,678,110)
Cost per DALY averted, governmental perspective	Cost-Saving (95% Credible Range: Cost-Saving to $222)			Cost-Saving (95% Credible Range: Cost-Saving to $246)		
Cost per DALY averted, societal perspective	Cost-Saving (95% Credible Range: Cost-Saving to $113)			Cost-Saving (95% Credible Range: Cost-Saving to $165)		

B. Sub-National Routine Immunization Only in 7 Provinces[ǂ] with Human JE Vectors Identified

	Over 1 birth cohort			Over 3 birth cohorts		
	With vaccination program	No vaccination	Difference with vaccination	With vaccination program	No vaccination	Difference with vaccination
Number of JE Cases	79	515	(436)	260	1,709	(1,448)
Expected deaths	18	118	(100)	60	393	(333)
Expected DALYs	801	5,239	(4,438)	1,831	12,010	(10,179)
Expected costs, governmental perspective	$1,258,031	$1,441,481	$(183,450)	$4,932,364	$5,518,870	$(586,505)
Expected costs, societal perspective	$1,405,623	$2,421,173	$(1,015,550)	$5,497,438	$9,269,730	$(3,772,292)
Cost per DALY averted, governmental perspective	Cost-Saving (95% Credible Range: Cost-Saving to $199)			Cost-Saving (95% Credible Range: Cost-Saving to $269)		
Cost per DALY averted, societal perspective	Cost-Saving (95% Credible Range: Cost-Saving to $132)			Cost-Saving (95% Credible Range: Cost-Saving to $135)		

C. One-Time National Campaign among 1–15 Year Olds and National Routine Immunization among Birth Cohort(s)

	Routine Immunization over 1 Birth Cohort			Routine Immunization over 3 Birth Cohorts		
	With vaccination program	No vaccination	Difference with Vaccination	With vaccination program	No vaccination program	Difference with vaccination
Number of JE Cases	4,167	27,761	(23,594)	5,566	36,952	(31,386)
Expected deaths	958	6,385	(5,427)	1,280	8,499	(7,219)
Expected DALYs	33,084	220,131	(187,047)	41,013	272,247	(231,234)
Expected costs, governmental perspective	$96,302,306	$21,035,573	$75,266,733	$125,187,435	$56,415,501	$68,771,934
Expected costs, societal perspective	$98,212,925	$33,736,653	$64,476,271	$130,318,083	$90,490,573	$39,827,510
Cost per DALY averted, governmental perspective	$402 (95% Credible Range: Cost-Saving to $785)			$297 (95% Credible Range: Cost-Saving to $619)		
Cost per DALY averted, societal perspective	$345 (95% Credible Range: Cost-Saving to $679)			$172 (95% Credible Range: Cost-Saving to $485)		

D. One-Time Sub-National Campaign among 1–15 Year Olds and Routine Immunization in 7 Provinces[ǂ] among Birth Cohort(s)

	Routine Immunization over 1 Birth Cohort			Routine Immunization over 3 Birth Cohorts		
	With vaccination program	No vaccination	Difference with vaccination	With vaccination program	No vaccination	Difference with vaccination
Number of JE Cases	545	3,632	(3,087)	727	4,826	(4,099)
Expected deaths	125	835	(710)	167	1,110	(943)
Expected DALYs	4,327	28,791	(24,464)	5,357	35,561	(30,204)
Expected costs, governmental perspective	$12,556,886	$2,432,028	$10,124,858	$16,231,219	$6,509,416	$9,721,802
Expected costs, societal perspective	$12,805,424	$4,084,233	$8,721,191	$16,897,239	$10,932,790	$5,964,449
Cost per DALY averted, governmental perspective	$414 (95% Credible Range: Cost-Saving to $734)			$322 (95% Credible Range: Cost-Saving to $604)		
Cost per DALY averted, societal perspective	$356 (95% Credible Range: Cost-Saving to $774)			$197 (95% Credible Range: Cost-Saving to $590)		

[ǂ]Seven provinces include those where local cost data collection was undertaken: Jakarta, Yogyakarta, Riau Island, West Kalimantan, West Nusa Tenggara, East Nusa Tenggara, and North Sulawesi.

4. Discussion

Results indicate that JE vaccination would be cost-effective from government and societal perspectives. While scenarios of routine immunization alone were cost-saving, inclusion of a one-time campaign would still be very cost-effective with ICERs of 4–19% GDP and would further reduce the JE disease burden among children. In all scenarios, the incremental cost per DALY averted is under the gross-domestic product (GDP) per capita for Indonesia in 2018 (US $3,972), with base case results ranging from cost-saving to $774 per DALY averted (highest ICER from 95% credible ranges). While 1xGDP has historically been used as a threshold

Table 3
Comparison of key parameters from other neighboring countries.

Variable	Location (year of publication)					
	Shanghai, China (Ding, 2003)[17]	Bali, Indonesia (Liu, 2008)[9]	Cambodia (Touch, 2010)[18]	Guizhou Province, China (Yin, 2012)[19]	Philippines (Vodicka, 2020)[10]	Indonesia (PATH 2019)
Incidence (age range)	35/100,000 (0–10 yrs) 18.2–68.9/100,000 (0–30 yrs)	6/100,000 (0–12 yrs)	11/100,000 (0–15 yrs)	35/100,000 (1–5 yrs)	1.8/100,000 (pooled incidence); 3.7/100,000 (Phil. all ages) **10.6/100,000 (0–14 years)**	7.1/100,000 (0–10 years) Range (3.55–10.65/100,000)
Model time frame (yrs)	30	11	15	65	Lifetime horizon; routine immunization over 20 birth cohorts	Lifetime horizon; routine immunization evaluated over 1, 3 and 20 birth cohorts
Cost, acute care	$1209/case[1]	$467/case[1]	$350/case[1]	$993/case[1]	Conservative: $2,675/case Utilization Based: $859/case	$1,444/case
Cost, long-term care	$3630/case[1]	$1813/case[2]	$79/case[1,3] ($316/case/yrs)	$1782/case/year[2]	$109–171/year	$332 for moderate sequelae $472 for severe sequelae
Case fatality ratio	25%	10%	13%	25%	30%	23% (Garjito 2018)
Prob. of long-term disability	30%	37%	30%	30%	28%	50% (Maha 2009)
Vaccine doses	2	2	1	2	1	1
Vaccine efficacy	≥ 95%	≥ 95%	96%	≥ 95%	93%	93%
Vaccine cost	$0.60/dose	$0.20/dose	$0.30/dose	$1.14/dose	$0.50/dose	$0.50/dose
Vaccination age	12 & 24 months	9 & 21 months	9 months	8 & 23 months		1st year of life for routine; 1–15 years for campaign

Variable	Location (year of publication)							
	Shanghai, China	Bali, Indonesia	Cambodia			Guizhou Province, China	Philippines	Indonesia
	(Ding, 2003)[17]	(Liu, 2008)[9]	(Touch, 2010) [8]			(Yin, 2012)[19]	(Vodicka, 2020) [10]	(PATH 2019)
Vaccination plan	Routine only	Routine only	**3 scenarios:** Campaign, 1–5 yrs Routine follows	Campaign, 1–10 yrs Routine follows	Routine only	Routine only	Routine (base case), 0–5 years; Campaign, 0–5 years	Routine only; Routine + 1 time campaign [evaluated national and in 7 provinces]
Total vaccination cost	$1.15/child/dose	$0.50/ child/dose	$2.30/child/dose	$2.30/child/dose	$1.80/ child/dose	$2.41/child/dose	Routine: $1.45/child/dose Campaign: $1.48/child/dose	Routine: $0.80/dose Campaign: $0.80/dose
Vaccine coverage	98% dose 1 98% dose 2	97% dose 1 94% dose 2	90%	90%	85%	95% dose 1 85% dose 2	82%	92%
Cost / averted DALY	($78)	$31	$34	$53	$22	$96	Routine, Govt:-$72 to $150 Routine, Soc:-$288 to $155 Campaign, Govt: -$66 to $155 Campaign, Soc.: -$278 to $165	Cost-effective to $414 from govt perspective Cost-effective to $356 from societal perspective
Cost-effective?	Yes (Cost-effective)	Yes	Yes	Yes	Yes	Yes		Potentially

to identify highly cost-effective interventions, this is no longer recommended by the WHO [20–22]. Recent predictive modeling of cost-effectiveness thresholds at the country-level based on empirical data suggests a potentially more realistic WTP threshold for Indonesia of less than 51% of GDP per capita per DALY averted [23]. Our ICER estimates fall below 20% of GDP, suggesting good value for money in Indonesia compared to these empirically-based WTP estimates. These findings are in line with the results from previous studies in other Asian countries that showed JE immunization to be a very cost-effective intervention, including prior such estimates in Bali Province [9,10,17,18,19].

Table 3 present comparison of Indonesian key parameters and the results of analysis with neighbouring countries in Asia that implement JE Vaccination; and shows similar cost-effective results.

This is the first study of JE vaccination cost-effectiveness for all endemic areas in Indonesia. As such, our findings provide valuable information to policy makers to consider investment in a national JE immunization program for children under 15 years old, in addition to establishing routine JE immunization for all infants. Importantly, sensitivity analysis demonstrated that vaccine price was a strong determinant of how cost-effective an immunization program could be in Indonesia. When the vaccine price was assumed to be very high at $10 per dose and all other parameters were held constant, the ICER estimate ranged from very cost-effective at 37% GDP ($1,449 with national routine immunization over one birth cohort) to potentially cost-effective at 103% GDP ($4,057 with a one-time campaign plus routine immunization in seven provinces over three birth cohorts). Therefore, selection of a highly efficacious yet low-cost vaccine product would make JE immunization a particularly good buy.

A key limitation in this study was the level of diagnostic uncertainty in surveillance data and lack of confirmatory testing for JE in most regions. While JE transmission was first identified in Lombok, West Nusa Tenggara (1960) and Surabaya, East Java (1968), JE serological testing for endemic provinces has been centralized in Jakarta (NIHRD). As such, the limited availability of confirmatory diagnostic testing for JE is partly due to laboratory test results requiring months to be returned because serum and cerebrospinal fluid must be sent from the local hospital or clinic to the Central Public Health Laboratory Ministry of Health in Jakarta for analysis. Therefore, we applied costs of suspected rather than confirmed JE cases in this analysis.

However, without confirmatory diagnosis, interviews with pediatricians indicated no standardized approach to classifying JE sequelae severity solely through clinical symptoms. Therefore, we adopted the criteria used to estimate sequelae incidence by severity from a 2009 study of JE encephalitis outcomes and disability among children in Indonesia by Maha et al in our model, noting that their estimates were based on a small sample of children with confirmed JE (N = 65) [5]. Another limitation in this study is the small number of suspected cases in each province where we collected data on costs of treatment, which led to wide variability in some parameters (e.g., hospital length of stay). Inherent uncertainty in our cost estimates were addressed via inclusion of wide ranges and evaluated through sensitivity analyses; we noted minimal impact of these ranges on key findings.

It can be concluded that investing in JE vaccination for national routine, and/or national routine following a one-time campaign is cost-effective from both the government and societal perspective. Our finding that even the broadest approach to JE vaccination in Indonesia is highly cost effective and supports JE vaccine introduction in several endemic Indonesian provinces, as stated in Indonesian Comprehensive Multi-Year Plan (CMYP) 2020 – 2024. The plan suggests introduction through a national campaign for children aged 1–15 years followed by routine JE immunization for children under 5 years old in selected priority provinces. Our results suggest that broadening the plan to include national routine immunization would also be highly cost-effective since the JE literature suggests endemicity across the Indonesian archipelago. Given the limitations noted in the study, however, updated national guidelines and clinical resources for a JE control program that provide for clear implementation of diagnosis, treatment, and surveillance of JE disease will be critical to establishing which areas might receive priority for JE vaccination if Indonesia chooses that approach rather than a national implementation. Establishing local capacity for diagnosis will still be needed, even with a national program, as local diagnosis will be essential to monitoring JE disease impact after implementation of vaccination. Establishing such a broad-based system also makes the vital function of assessing long-term vaccine impact after JE vaccine introduction. Finally, financial and operational feasibility for JE vaccine introduction need to be considered alongside cost-effectiveness evidence to ensure program sustainability over time.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2022.100179.

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