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

Soewarta Kosen a,⇑, Levina Chandra Khoe b, Endang Indriasih c, Ingan Tarigan c, Retno Widyastuti Iriawan c, Rozana Ika Agustiya c, G William Letson d, Elisabeth Vodicka d

a Health Systems Specialist, Taman Kebon Jeruk W4 No. 34, Jakarta 11630, Indonesia
b Department of Community Medicine, School of Medicine University of Indonesia, Indonesia
c National Institute of Health Research & Development, Ministry of Health, Indonesia
d Program Appropriate Technology for Health (PATH), Seattle, USA

A R T I C L E   I N F O

Article history:
Received 12 August 2021
Received in revised form 29 May 2022
Accepted 31 May 2022
Available online 13 June 2022

Keywords:
Japanese encephalitis
Expanding JE vaccination
Cost-effectiveness
Indonesia

A B S T R A C T

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.

https://doi.org/10.1016/j.jvacx.2022.100179
2590-1362/© 2022 The Authors. Published by Elsevier Ltd.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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\textsuperscript{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:

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

2.2. Modeled 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 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...
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

---

**Table 1**

| 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 | Gajitho 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 | 0.14 | 0.07 | 0.21 | Maha 2009[5]; range +/-50% of base case |
| Moderate and permanent | 0 | 0 | 0 | Local Expert Opinion |
| Major and permanent | 0 | 0 | 0 | Local Expert Opinion |
| Probability of treatment for sequelae | | | | |
| Mild and/or transient | 0.75 | 0.375 | 1 | Local Expert Opinion |
| Moderate and permanent | | | | |
| Major and permanent | | | | |
| **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** | | | | |
| 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 | $332.00 | $498.00 | $166.00 | In-country costing analysis; range: +/-50% |
| Moderate | $471.80 | $707.70 | | |
| Severe | $471.80 | $707.70 | | |
| **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 | $235.90 | $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) | | | | |

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.
(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 sequelae 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    | No vaccination      | Difference with vaccination |
| Expected cases                       | 606                 | 3,963               | (3,357) |
| Expected deaths                      | 139                 | 912                 | (772) |
| Expected DALYs                       | 6,164               | 40,325              | (34,162) |
| Expected costs, governmental perspective | $9,896,508          | $12,507,879        | ($2,611,371) |
| Expected costs, societal perspective | $11,034,885         | $20,064,234        | ($9,029,348) |
| Cost per DALY averted, governmental perspective | $345 (95% Credible Range: Cost-Saving to $774) | $197 (95% Credible Range: Cost-Saving to $590) |
| Cost per DALY averted, societal perspective | $414 (95% Credible Range: Cost-Saving to $734) | $322 (95% Credible Range: Cost-Saving to $604) |
| Cost per DAILY averted, societal perspective | $356 (95% Credible Range: Cost-Saving to $774) | $197 (95% Credible Range: Cost-Saving to $590) |

| B. Sub-National Routine Immunization Only in 7 Provinces\(^1\) with Human JE Vectors Identified | Over 1 birth cohort | Over 3 birth cohorts |
|-----------------------------------------------------------------------------------------------|---------------------|---------------------|
|                                                                                           | With vaccination    | No vaccination      | Difference with vaccination |
| Number of JE Cases                                                              | 79                  | 515                 | (436) |
| Expected deaths                                                               | 18                  | 118                 | (100) |
| Expected DALYs                                                               | 801                 | 5,239               | (4,418) |
| Expected costs, governmental perspective                                       | $1,258,031          | $1,441,481         | ($183,450) |
| Expected costs, societal perspective                                             | $1,405,623          | $2,421,173         | ($1,015,550) |
| Cost per DALY averted, governmental perspective                                 | Cost-Saving (95% Credible Range: Cost-Saving to $199) |
| Cost per DALY averted, societal perspective                                      | Cost-Saving (95% Credible Range: Cost-Saving to $132) |

| 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    | No vaccination      | Difference with vaccination |
| Number of JE Cases                                                              | 4,167               | 27,761              | (23,594) |
| Expected deaths                                                               | 958                 | 6,385               | (5,427) |
| Expected DALYs                                                               | 33,084              | 220,131             | (187,047) |
| Expected costs, governmental perspective                                       | $96,302,306         | $21,035,573        | $75,266,733 |
| Expected costs, societal perspective                                             | $98,212,925         | $33,736,653        | $64,476,271 |
| Cost per DALY averted, governmental perspective                                 | $402 (95% Credible Range: Cost-Saving to $785) |
| Cost per DALY averted, societal perspective                                      | $345 (95% Credible Range: Cost-Saving to $679) |

| D. One-Time Sub-National Campaign among 1–15 Year Olds and Routine Immunization in 7 Provinces\(^1\) among Birth Cohort(s) |
|-----------------------------------------------------------------------------------------------|---------------------|---------------------|
| Routine Immunization over 1 Birth Cohort | Routine Immunization over 3 Birth Cohorts |
|                                                                                           | With vaccination    | No vaccination      | Difference with vaccination |
| Number of JE Cases                                                              | 545                 | 3,632               | (3,087) |
| Expected deaths                                                               | 125                 | 835                 | (710) |
| Expected DALYs                                                               | 4,327               | 28,791              | (24,464) |
| Expected costs, governmental perspective                                       | $12,556,886         | $2,432,028         | $10,124,858 |
| Expected costs, societal perspective                                             | $12,805,424         | $4,084,233         | $8,721,191 |
| Cost per DALY averted, governmental perspective                                 | $414 (95% Credible Range: Cost-Saving to $734) |
| Cost per DALY averted, societal perspective                                      | $356 (95% Credible Range: Cost-Saving to $774) |

\(^1\)Seven provinces include those where local cost data collection was undertaken: Jakarta, Yogyakarta, Biau 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)    | Shanghai, China 35/100,000 (0–10 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) |
|                         | Bali, Indonesia 6/100,000 (0–12 yrs) 11/100,000 (0–15 yrs) 18.2–68.9/100,000 (0–30 yrs) |
|                         | Cambodia 11/100,000 (0–15 yrs) 18.2–68.9/100,000 (0–30 yrs) |
|                         | Guizhou Province, China 35/100,000 (1–5 yrs) 10.6/100,000 (0–14 yrs) |
|                         | Philippines (Vodicka, 2020) 1.8/100,000 (pooled incidence); 3.7/100,000 (Phil. all ages) |
|                         | Indonesia (PATH 2019) 7.1/100,000 (0–10 years) 7.1/100,000 (0–10 years) |

| Model time frame (yrs)   | 30 11 15 65 30 |
|                          | 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 | $467/case | $350/case | $993/case |
|                          | $3630/case | $1813/case | $79/case | $1782/case/year |
|                          | Utilization Based: $859/case $109–171/year |

| Cost, long-term care     | $1209/case | $467/case | $350/case | $993/case |
|                          | $3630/case | $1813/case | $79/case | $1782/case/year |
|                          | Utilization Based: $859/case $109–171/year |

| Case fatality ratio      | 25% 10% 13% 25% 30% |
| Prob. of long-term disability | 30% 37% 30% 30% 28% |

| Vaccine doses            | 2 2 1 2 1 |
| Vaccine efficacy         | ≥ 95% ≥ 95% 96% ≥ 95% 93% |
| Vaccine cost             | $0.60/dose $0.20/dose $0.30/dose $1.14/dose $0.50/dose |
| Vaccination age          | 12 & 24 months 9 & 21 months 9 months 8 & 23 months |

| Vaccination plan         | Routine only Routine only 3 scenarios: Campaign, 1–5 yrs Routine follows $2.30/child/dose Routine only Routine only Routine (base case) 0–5 years; Campaign, 0–5 years Routine only Routine (base case) 0–5 years; Campaign, 0–5 years |
| Total vaccination cost   | $1.15/child/dose $0.50/child/dose $2.30/child/dose $1.80/child/dose $2.41/child/dose $1.45/child/dose $0.80/child/dose |
| Vaccine coverage         | 98% dose 1 98% dose 2 ($78) 97% dose 1 94% dose 2 $31 $34 $53 $22 |
| Cost / averted DALY      | $34 $34 $53 $22 |
| Cost-effective           | Yes (Cost-effective) Yes Yes Yes Yes Yes Potentially |

Note: Cost-effective? indicates whether the vaccination program is cost-effective from a societal perspective.
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 ($4,857 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.

Acknowledgements

The study was supported by PATH, Seattle, WA 98107, USA. The funding for PATH support was graciously supplied as part of grant #3328 from the Margaret A Cargill Philanthropies, which supported this activity as part of a larger grant to PATH for technical assistance in Japanese encephalitis vaccine introduction into Myanmar and Bali, Indonesia.

Appendix A. Supplementary material

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

References

[1] WHO. Japanese Encephalitis: Key Facts. At https://www.who.int/mediacentre/factsheets/feverpdf/en/20encephalitis%20virus%20(JEV)%20is%207%20every%20year. Last Updated: September 2019 [accessed August 2020].

[2] Campbell G, Hills S, Fischer M, Jacobson J, Hoke C, Hombach J, et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ 2011;89(10):766–74. https://doi.org/10.2471/BLT.10.085233.

[3] World Health Organization. Japanese Encephalitis Vaccines: WHO Position Paper – February 2015. Weekly Epidemiological Rec 2015;9(90):69–88.

[4] Garjito TA, Widiartti, Anggraeni YM, Alfiah S, Tunggul Satoro TB, Farchanny A, et al. Japanese encephalitis in Indonesia: An update on epidemiology and transmission ecology. Acta Trop 2018;187:240–7. https://doi.org/10.1016/j.actatropica.2018.08.017.

[5] Maha MS, Monaiga VA, Hills SI, Widjaya A, Sasmito A, Hariati R, et al. Outcome and extent of disability following Japanese encephalitis in Indonesian children. Int J Infect Dis 2009;13(6):e389–93. https://doi.org/10.1016/j.ijid.2009.01.009.

[6] Burn E. Vector borne diseases and zoonotic policy in Indonesia. National Seminar on Rikhus Vectora Final Report; 2017, 17–19 December 2017, Yogyakarta.

[7] Results of Special Research on Disease Vector in Indonesia 2014–2017, National Institute of Health Research and Development, Jakarta, Indonesia [Unpublished].

[8] Maha MS, Monaiga VA, Hills SI, Jacobson JA, Widjaya A, Suwondo A, et al. Confirmation of Japanese encephalitis as an endemic human disease through sentinel surveillance in Indonesia. Am J Trop Med Hyg 2008;79(6):963–70. https://doi.org/10.4269/ajtmh.2008.79.963.

[9] Liu W, Clemens JD, Kari K, Xu Z-Y. Cost-effectiveness of Japanese encephalitis (JE) immunization in Bali, Indonesia. Vaccine 2008;26(35):4456–60. https://doi.org/10.1016/j.vaccine.2008.06.056.

[10] Vodicka E, Zimmermann M, Lopez AL, Silva MW, Gorgolon I, Koheli T, et al. Japanese encephalitis vaccination in the Philippines: A cost-effectiveness analysis comparing alternative delivery strategies. Vaccine 2020;38(13):2833–40. https://doi.org/10.1016/j.vaccine.2020.02.018.
[11] Ministry of Health, Government of Indonesia. Report on Immunization Program; 2018.

[12] Li X, Ma S-J, Liu X, Jiang L-N, Zhou J-H, Xiong Y-Q, et al. Immunogenicity and safety of currently available Japanese encephalitis vaccines: A systematic review. Hum Vaccines Immunother 2014;10(12):3579–93. https://doi.org/10.4161/hvi.2014.9801097.

[13] Kari K, Liu W, Gautama K, Mammen MP, Clemens JD, Nisalak A, et al. A hospital-based surveillance for Japanese encephalitis in Bali, Indonesia. BMC Med. 2006;4(1). https://doi.org/10.1186/1741-7015-4-8.

[14] Misra UK, Kalita J. Overview: Japanese encephalitis. Prog Neurobiol 2010;91(2):108–20. https://doi.org/10.1016/j.pneurobio.2010.01.008.

[15] Salomon JA, Haagsma JA, Davis A, de Noordhout CM, Polinder S, Havelaar AH, et al. Disability weights for the Global Burden of Disease 2013 study. Lancet Glob Heal 2015;3(11):e712–23. https://doi.org/10.1016/S2214-109X(15)00009-8.

[16] Indonesia Health Technology Assessment. Economic evaluation of Cetuximab for metastatic colorectal cancer patients; 2017.

[17] Ding D, Kilgore PE, Clemens JD, Wei L, Zhi-Yi X. Cost-effectiveness of routine immunization to control Japanese encephalitis in Shanghai, China. Bull World Health Organ 2003;81(5):334–42. http://www.ncbi.nlm.nih.gov/pubmed/12856051.

[18] Touch S, Suraratdecha C, Sannang C, Heng S, Gazley L, Huch C, et al. A cost-effectiveness analysis of Japanese encephalitis vaccine in Cambodia. Vaccine 2010;28(29):4593–9.

[19] Yin Z, Beeler Asay GR, Zhang Li, Li Y, Zuo S, Hutin YJ, et al. An economic evaluation of the use of Japanese encephalitis vaccine in the expanded program of immunization of Guizhou province, China. Vaccine 2012;30(37):5569–77.

[20] Bertram MY, Lauer JA, De Joncheere K, Edejer T, Hutubessy R, Kiény M-P, et al. Cost–effectiveness thresholds: pros and cons. Bull World Health Organ 2016;94(12):925–30. https://doi.org/10.2471/BLS.15.164419.

[21] Lefevre AA, Kim DD, Cohen JT, Neumann PJ. Use and Misuse of Cost-Effectiveness Analysis Thresholds in Low- and Middle-Income Countries: Trends in Cost-per-DALY Studies. Value Heal 2018;21(7):759–61. https://doi.org/10.1016/J.JVAL.2017.12.016.

[22] Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: Alternative approaches. Bull World Health Organ 2015;93(2):118–24. https://doi.org/10.2471/BLT.14.138206.

[23] Woods B, Revill P, Sculptor M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. Value Heal 2016;19(8):929–35. https://doi.org/10.1016/j.jval.2016.02.017.

[24] Sagung Savitri AA, Cintya Yuliatni PC, Dwi Ariawan IM, Kartika Sari KA. Coverage evaluation of Japanese encephalitis Supplementary Immunization Activities (JE SIA) in Bali Island. Faculty of Medicine University of Udayana; 2018.

Soewarta Kosen, Member of Scientific Research Commission – NIHRD; M.D. (1976), School of Medicine – University of Indonesia; M.P.H. (1982), Institute of Public Health – University of the Philippines System; Dr. P.H. (1990), The Johns Hopkins School of Public Health. Public Health Officer (1976 – 1990), Senior Health Researcher, NIHRD (1990-2015), Independent Consultant (2015 – now). Research interests: health systems, immunization, health policy. Member of the Indonesian Medical Association and Indonesian Public Health Association.