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Cost-effectiveness and budget impact analyses for the prioritisation of the four available rotavirus vaccines in the national immunisation programme in Thailand

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ABSTRACT

Background: Rotavirus is a major cause of diarrhoea in children less than five years old in Thailand. Vaccination has been shown to be an effective intervention to prevent rotavirus infections but has yet to be enlisted in the national immunisation programme. This study aimed to assess the cost-utility of introducing rotavirus vaccines, taking all WHO-prequalified vaccines into consideration.

Methods: A cost-utility analysis was performed using a transmission dynamic model to estimate, from a societal perspective, the costs and outcomes of four WHO-prequalified rotavirus vaccines: Rotarix®, RotaTeq®, ROTAVAC® and ROTASIIL®. The model was used to simulate the impact of introducing the vaccines among children aged < 1 year and compare this with no rotavirus vaccination. The vaccination programme was considered to be cost-effective if the incremental cost-effectiveness ratio was less than a threshold of USD 5,110 per QALY gained.

Results: Overall, without the vaccine, the model predicted the average annual incidence of rotavirus to be 312,118 cases. With rotavirus vaccination at a coverage of more than 95%, the average number of rotavirus cases averted was estimated to be 144,299 per year. All rotavirus vaccines were cost-saving. ROTASIIL® was the most cost-saving option, followed by ROTAVAC®, Rotarix® and RotaTeq®, providing average cost-savings of USD 32, 31, 23 and 22 million per year, respectively, with 999 QALYs gained. All vaccines remained cost-saving with lower QALYs gained, even when ignoring indirect beneficial effects. The net saving to the healthcare system when implementing any one of these vaccines would be between USD 13 and 33 million per year.

Conclusion: Rotavirus vaccines should be included in the national vaccination programme in Thailand. Implementing any one of these four WHO-prequalified vaccines would reduce government healthcare spending while yielding health benefits to the population.

1. Introduction

Rotavirus infection is one of the main causes of severe gastrointestinal illness globally in children under the age of 5 years. In 2013, the World Health Organization (WHO) estimated mortality worldwide due to diarrhoea attributable to rotavirus infection to be 215,000 deaths in children younger than 5 years. This accounted for 37% of deaths attributable to diarrhoea and 5% of all deaths in this age group [1]. Of these deaths, 63% were in countries in South Asia and sub-Saharan Africa [1,2]. A recent study of the global burden of rotavirus infection suggested there was a decreasing trend in the mortality due to rotavirus infection, estimated to be

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128,000 deaths in 2016 among children aged less than five years [3]. Rotavirus infections can range from being asymptomatic to causing severe illness and death [4]. Rotavirus is primarily spread via the faecal–oral route [5]. Clinical symptoms of rotavirus infection include fever, vomiting and diarrhoea in infants and young children. Children aged between three months and two years are most susceptible to severe infection. In adults the incidence of rotavirus infection is low, and symptoms are unlikely to be severe [4].

In Thailand, rotavirus is a major cause of diarrhoea in children aged less than five years, with a seasonal peak in infections occurring during the winter period (December to March) [6–8]. The prevalence of rotavirus infection is highest in infants aged 6 to 12 months and declines in older age groups [7]. The most recent study estimated the burden of rotavirus infection in Thailand to be 586,000 diarrhoea episodes in 2005, or about 12.5% of the total 4.8 million episodes [6]. Of these rotavirus diarrhoea cases, 131,000 (22.4%) required healthcare visits, and 56,000 (9.5%) were admitted to hospital. The proportion of rotavirus diarrhoea was lower in community settings than in hospitals [6]. The estimated mortality due to rotavirus diarrhoea among the Thai population is low, ranging from 0.23 to 2.2 deaths per 100,000 population [7,9,10]. The economic burden, from a societal perspective, of rotavirus diarrhoea among children aged less than five years was estimated to be $US 21 million (in 2009 values) [11].

Vaccination has been shown to be an effective intervention to prevent rotavirus infections, in a wide range of settings [12–15]. There are four oral rotavirus vaccines registered for use in Thailand: Rotarix® (monovalent live attenuated human G1P1A, GSK); RotaTeq® (pentavalent live attenuated bovine–human reassortant vaccine, MSD); ROTAVAC® (monovalent live attenuated rotavirus 116E, BHARAT); and ROTASIIL® (live attenuated bovine–human reassortant vaccine, Serum Institute of India). ROTAVAC® and ROTASIIL® were recently prequalified by WHO. None of these vaccines has yet been enlisted in the Thailand national immunisation programme. All four vaccine options show comparable efficacy; however, worldwide, their impact varies due to baseline differences in child and adult mortality rates among the general population [16]. Overall, the vaccines exhibit better efficacy in countries with lower child and adult mortality rates [15]. The use of a rotavirus vaccine could lead to a reduction in rotavirus infections among unvaccinated populations of both children and adults, via indirect effects or herd immunity; this has been reported in several countries [17–19].

Four previous cost-effectiveness studies have evaluated the introduction of rotavirus vaccines in the Thai setting [11,20–22]. The findings from these studies are somewhat diverse; three found vaccination to be cost-effective, while the fourth found vaccination was not cost-effective. These differences may have been due to the fact that these studies used different model structures (although all were static models) and different sources for parameter inputs, including surveillance data, cost of vaccine(s), cost of treatment for rotavirus infection, and vaccine efficacy/effectiveness. None of the previous studies incorporated all four WHO-prequalified rotavirus vaccines in their analysis nor did they account for any indirect effects or herd immunity arising from vaccine protection. To select the best vaccine option to include in a national immunisation programme, it is crucial to include all WHO-prequalified vaccines and their full economic impact in one analysis. Therefore, this study aimed to evaluate the cost-utility in Thailand of all WHO-prequalified rotavirus vaccines, using a transmission dynamic model to account for any herd protection arising as a result of the vaccination scheme and provide a budget impact analysis of the uptake of the vaccine(s) in routine immunisation programmes.

2. Material and methods

2.1. Overall approach

A cost-utility analysis using transmission dynamic and decision analytic models to estimate the costs and outcomes of the four rotavirus vaccines was performed. The model simulated the impact of introducing the different vaccines within the national immunisation programme among children aged < 1 year. Four rotavirus vaccines available in Thailand, Rotarix® (RV1), RotaTeq® (RV5),

Table 1
Parameter inputs used in the transmission dynamic model.

Parameter	Values (95% CIs)	Source
Population size (Thailand)	Population by age group	Office of the National Economic and Social Development Council [25]
Birth and death rates among the Thai population (age-specific)	Birth and death rates by age, 0–100 years 700,000 births per year	Office of the National Economic and Social Development Council [25]
Surveillance data for reported diarrhoea cases	1,700–2,000 per 100,000 population (year 2011–2015)	Report 506, reported diarrhoea cases during 2011–2015, Thailand
Rotavirus gastroenteritis positivity	28.01%	Literature review (see Supplementary Table A1)
Mixing contact patterns in Thailand	Contact rate by age	[26]
Asymptomatic rotavirus infections	11%	[51]
Duration of maternal protection	158 days	[27]
Duration of latency period	1 day	[27]
Vaccine efficacy (all outcomes for all vaccines)	75% (60–90%)	[12–14,16,39]
Vaccine protective duration with waning effect (mean, years).	5	[39]
Vaccine coverage	96.5%	DTP programme, Thailand [28]
Vaccine timeliness (time to full coverage, years)	1	Assumption
Infectivity of rotavirus infections		Estimated
(age 0–5)	0.635 (0.601–0.78)	
(age 6–14)	0.005 (0.004–0.006)	
(age 15–64)	0.003 (0.002–0.004)	
(age > 64)	0.004 (0.003–0.006)	
Proportion of hospitalised rotavirus cases	9% (7–10%)	Estimated
Amplitude	0.118 (0.042–0.205)	Estimated
Phase angle	15.223 (1.5–46.349)	Estimated

ROTAVAC® and ROTASIIL®, were evaluated and compared with base-case scenario of no immunisation programme. Age-specific sentinel surveillance data, representing the incidence of rotavirus infections derived from local epidemiological as well as clinical and economic data, were used to inform the model (See Table 1). Both costs and consequences in terms of Quality Adjusted Life Years (QALYs) were quantified, from a societal perspective, with a 3% discounting rate and reported in 2019 USD values [23]. The vaccination programme, its costs and its consequences were evaluated for a five-year timeframe. The incremental cost-effectiveness ratio (ICER) for each of the vaccine options was estimated. We used R software, version 3.3.3 (R Development Core Team, 2008) to run and analyze the model outputs and the deSolve package to solve the differential equations [24]. Model fitting was carried out using the Markov Chain Monte Carlo (MCMC) method, implemented using the Bayesian Tools R package on the Bayesian framework (see Supplementary Information). Output processing to obtain summary health economic results was also performed in R.

3. Transmission dynamic model

An age-structured dynamic epidemiological model was developed to estimate the age-specific incidence and outcomes of rotavirus diarrhoea in Thailand (Fig. 1A). Population size data as well as birth and death rates among the Thai population were obtained from the Office of the National Economic and Social Development Council [25]. This transmission model was based on an SEIR (susceptible-exposed-infective-recovered) structure, where the entire population was divided into five main compartments representing different stages of disease: maternal antibody protected (M), representing neonates or infants with innate maternal immunity; susceptible (S), representing individuals who have not been infected or are fully vulnerable to infection; exposed (E), representing those who have been infected but have not yet progressed to become infectious; infected (I), representing those who are infectious, including both asymptomatic and symptomatic cases; and recovered (R), representing people who have transient immunity after having recovered from infection or having been vaccinated effectively.

Interactions between age groups were accounted for by using an empirically derived matrix of contact patterns (the 'mixing matrix') to account for the fact that the probability of one infected person infecting one particular susceptible person will depend on their respective age groups and the degree of contact between them [26]. We ran the model from 2010 to 2024 and solved a large set of ordinary differential equations (ODEs) for the dynamic model. Age-specific sentinel surveillance was used and fitted with seasonal properties to estimate the transmission rate of rotavirus diarrhoea for each of the 18 specific age groups (0–1 month, 2–3 months, 4–5 months, 6–7 months, 8–9 months, 10–11 months, 12–13 months, 14–15 months, 16–17 months, 18–19 months, 20–21 months, 22–23 months, 2 years, 3 years, 4 years, 5–14 years, 15–64 years and $\geq$ 65 years). The total numbers of reported diarrhoea cases over time were obtained from the Bureau of Epidemiology, the Department of Disease Control, and the National Health Security Office (NHSO) to cover both hospital and community cases. These figures were combined with the average rotavirus positivity reported in the literature, obtained from our rapid review of research conducted in Thai settings, to estimate the number of rotavirus infection cases (Supplementary Table A1). The model accounted for a declining risk of infection and the duration and level of infectiousness following a first or second infection. Key assumptions for our model were as follows. First, the infectivity rate was assumed to be consistent over interval times but varied by age. Second, the human-to-human contact data for Thai population used in the model came from the survey in 2009 [26]. Third, the immunity status of each person was assumed to be the same and with an absence of any person fully resistant to infection. We assumed a lower susceptibility to infection among re-infected individuals, with factors of 0.65 and 0.4 for the second and later infections, respectively, based on previous estimates [27]. Finally, rotavirus-related deaths were assumed to be low enough that they would not affect population or infection dynamics, i.e. were negligible for transmission modelling purposes; hence, they were not explicitly represented in the model equations. Model fitting was carried out using a Bayesian framework; therefore, uncertainty in any of the transmission dynamic model parameters was expressed in terms of probability distributions. The posterior distribution for each estimated parameter was obtained by combining the uniform prior distribution and the likelihood of the observed data (age-specific sentinel surveillance).

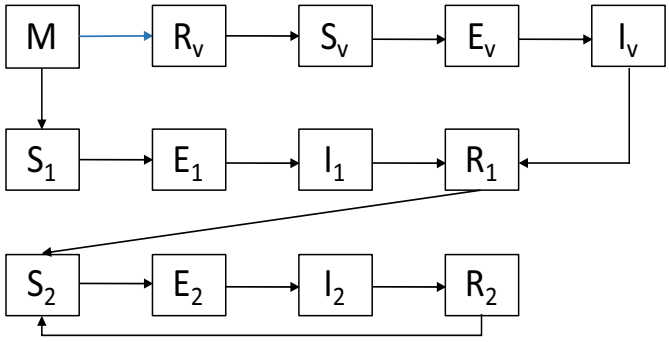
Vaccine protective efficacy was derived from systematic reviews and *meta*-analysis studies, enabling us to infer the overall efficacy of all rotavirus vaccines was comparable [12–14,16] (Supplementary Table A2). Rotavirus vaccine coverage was assumed to be the same as that of the diphtheria–tetanus–pertussis (DTP) vaccine, i.e. 96.5%, due to the similar schedule (at 2, 4 and 6 months of age) [28]. We applied wastage rates to each vaccine as reported by WHO and a detailed product profile from Gavi [29,30]. As any rotavirus vaccination schedule would be aligned within other vaccination programmes in Thailand and therefore use the existing pool of transportation facilities and human resources, we assumed there would be no additional cost for a new vaccine other than programme introduction costs. The vaccination period was assumed to be implemented from 1 January 2020 to 31 December 2024. Among children who were initially susceptible when vaccinated, it was assumed that the proportion successfully immunised (determined by the vaccine effectiveness) was removed from the susceptible class.

3.1. Cost-effectiveness analysis model

The estimated number of symptomatic rotavirus cases based on different scenarios, with and without a vaccination programme, were fed into a decision analytic model (Fig. 1B). Rotavirus diarrhoea cases were classified into three groups: severe diarrhoea, mild diarrhoea and self-care. The risk of severe and mild rotavirus diarrhoea was derived from the literature, NHSO data and assumptions [31,32]. We assumed no death due to rotavirus infection, reflecting findings from the NHSO dataset (ICD-10-CM A08.0) [32] (Table 2).

All costs were assigned in accordance with the age group. Direct medical costs for hospitalised cases and outpatient cases were obtained from NHSO, while the costs for self-care cases were obtained from the literature [31,32]. Direct non-medical costs and indirect costs were derived from previous surveys and accounted for transportation, extra food and other costs [31,33]. Caregivers' expenses or productivity losses due to taking care of children were applied in the baby and children age groups, while productivity losses due to absence from work were accounted for in adults. All direct medical costs obtained from the NHSO database were converted from charges to costs with a cost-to-charge ratio of 1.63 [33]. The ratio between outpatient department (OPD) and self-care cases was assumed to be 1:1, as there is no such information available for Thailand. With this assumption, the fraction of total diarrhoea cases that sought healthcare was estimated to range between 58% and 73% from all age groups; this corresponded with data in the literature showing that 65% of diarrhoea cases in low- and middle- income countries sought healthcare [34]. The duration of illness due to severe rotavirus infection was quantified based on the length of stay during admission for

A) The transmission dynamic model (SEIR) with age structure .



M = maternal antibody protected

S = susceptible

E = exposed (latency period)

I = infected with rotavirus (asymptomatic and symptomatic diarrhoea)

R = recovery from rotavirus infection (partially immune) or having immunity by vaccination

**i) The subscripted numbers represent primary and secondary infections.*

ii) The vaccinated population is represented by the subscripted 'v' compartment, where the vaccinated individuals will go straight from M to R_v, shown by the blue arrow.

B) The decision analytic model structure (decision tree) for cases of rotavirus infection .

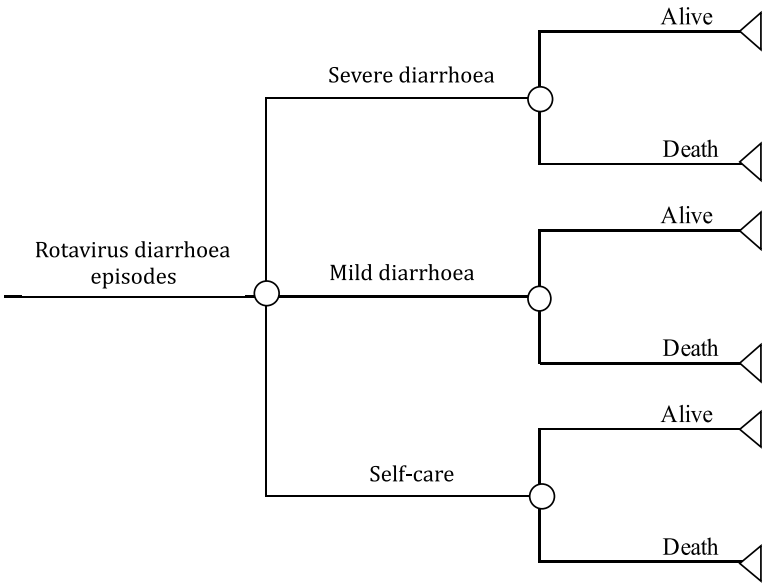


Fig. 1. Model structure. (A) The transmission dynamic model (SEIR) with age structure. M = maternal antibody protected S = susceptible E = exposed (latency period) I = infected with rotavirus (asymptomatic and symptomatic diarrhoea) R = recovery from rotavirus infection (partially immune) or having immunity by vaccination *i) The subscripted numbers represent primary and secondary infections. ii) The vaccinated population is represented by the subscripted 'v' compartment, where the vaccinated individuals will go straight from M to R_v, shown by the blue arrow. (B) The decision analytic model structure (decision tree) for cases of rotavirus infection. *Severe diarrhoea refers to hospitalised rotavirus diarrhoea cases. Mild diarrhoea refers to non-hospitalised (OPD and self-care) rotavirus diarrhoea cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Parameter inputs used in the decision analytic cost-effectiveness model. (OPD, outpatient department).

Parameter	Value (95% CI)	Distribution	Source
Risk of severe diarrhoea (age 0–5) (hospitalised)	0.53 (0.52–0.54)	Beta	[32], assumption
Risk of mild diarrhoea (age 0–5) (OPD)	0.20 (0.19–0.21)	Beta	[31,32]
Risk of mild diarrhoea (age 0–5) (self-care)	0.27 (0.25–0.28)	Beta	[31]
Risk of severe diarrhoea (age 6–14) (hospitalised)	0.22 (0.19–0.24)	Beta	[32], assumption
Risk of mild diarrhoea (age 6–14) (OPD)	0.39 (0.36–0.42)	Beta	[31,32]
Risk of mild diarrhoea (age 6–14) (self-care)	0.39 (0.36–0.42)	Beta	Assumption
Risk of severe diarrhoea (age 15–64) (hospitalised)	0.16 (0.14–0.18)	Beta	[32], assumption
Risk of mild diarrhoea (age 15–64) (OPD)	0.42 (0.39–0.45)	Beta	[32], assumption
Risk of mild diarrhoea (age 15–64) (self-care)	0.42 (0.39–0.45)	Beta	Assumption
Risk of severe diarrhoea (age $\geq$ 65) (hospitalised)	0.35 (0.26–0.44)	Beta	[32], assumption
Risk of mild diarrhoea (age $\geq$ 65) (OPD)	0.32 (0.24–0.41)	Beta	[32], assumption
Risk of mild diarrhoea (age $\geq$ 65) (self-care)	0.32 (0.24–0.41)	Beta	Assumption
Costs (in USD, 2019)			
Cost-to-charge ratio	1.63	n/a	[33]
Costs of severe cases (hospitalised)			
Babies (age 0–5 years)			
Direct medical costs	251.39 (56.45–827.46) USD	Gamma	[32]
Direct non-medical and indirect costs (transportation, food, caregivers)	113.31 (100.46–126.16) USD	Gamma	[31]
Children (age 6–14 years)			
Direct medical costs	267.70 (59.08–749.96) USD	Gamma	[32]
Direct non-medical costs (transportation and food)	4.17 (3.99–4.36) USD	Gamma	[33]
Indirect costs (productivity losses of caregivers)	25.68 (9.58–57.49) USD	Gamma	[32,35]
Adults (age 16–64 years)			
Direct medical costs	270.45 (35.96–605.10) USD	Gamma	[32]
Direct non-medical costs (transportation and food)	4.17 (3.99–4.36) USD	Gamma	[33]
Indirect costs (productivity losses)	19.26 (0–49.35) USD	Gamma	[32,35]
Elderly (age $\geq$ 65 years)			
Direct medical costs	293.83 (37.41–932.49) USD	Gamma	[32]
Direct non-medical costs (transportation and food)	4.17 (3.99–4.36) USD	Gamma	[33]
Indirect costs (productivity losses of caregivers)	22.90 (9.58–85.28) USD	Gamma	[32,35]
Costs of OPD cases			
Babies (age 0–5 years)			
Direct medical costs	5.14 (1.64–16.70) USD	Gamma	[32]
Direct non-medical and indirect costs (transportation, food, caregivers)	18.94 (11.47–26.40) USD	Gamma	[31]
Children (age 6–14 years)			
Direct medical costs	7.47 (2.05–54.00) USD	Gamma	[32]
Direct non-medical costs (transportation and food)	4.17 (3.99–4.36) USD	Gamma	[33]
Indirect costs (productivity losses of caregivers)	9.58 (0–19.16) USD	Gamma	Assumption, [35]
Adults (age 16–64 years)			
Direct medical costs	8.71 (2.24–32.05) USD	Gamma	[32]
Direct non-medical costs (transportation and food)	4.17 (3.99–4.36) USD	Gamma	[33]
Indirect costs (productivity losses)	9.58 (0–19.16) USD	Gamma	Assumption
Elderly (age $\geq$ 65 years)			
Direct medical costs	16.08 (1.60–178.22) USD	Gamma	[32]
Direct non-medical costs (transportation and food)	4.17 (3.99–4.36) USD	Gamma	[33]
Indirect costs (productivity losses of caregivers)	9.58 (0–19.16) USD	Gamma	Assumption, [35]
Costs of self-care cases			
Babies (age 0–5 years)			
Direct medical costs, direct non–medical costs and indirect costs (transportation, food, and caregivers)	3.91 (0.5–7.3) USD	Gamma	[31]
Children (age 6–14 years)			
Direct medical costs	7.23 (6.7–7.7) USD	Gamma	[52]
Direct non-medical costs (transportation and food)	n/a	Gamma	

Table 2 (*continued*)

Parameter	Value (95% CI)	Distribution	Source
Indirect costs (productivity losses of caregivers)	9.58 (0–19.16) USD	Gamma	Assumption, [35]
Adults (age 16–64 years)			
Direct medical costs	7.23 (6.7–7.7) USD	Gamma	[52]
Direct non-medical costs (transportation and food)	n/a	Gamma	
Indirect costs (productivity losses)	9.58 (0–19.16) USD	Gamma	Assumption, [35]
Elderly (age ≥ 65 years)			
Direct medical costs	7.23 (6.7–7.7) USD	Gamma	[52]
Direct non-medical costs (transportation and food)	n/a	Gamma	
Indirect costs (productivity losses of caregivers)	9.58 (0–19.16) USD	Gamma	Assumption, [35]
Vaccine costs			
Rotarix®, single dose (liquid)	8.78 USD	n/a	Information from National List of Essential Medicine (Thailand) submission
RotaTeq®, single dose (liquid)	5.85 USD	n/a	Information from National List of Essential Medicine (Thailand) submission
ROTAVAC®, five doses per vial (frozen)	1.00 USD	n/a	Manufacturer's price (India)
ROTASIIL®, single dose (lyophilised)	1.00 USD	n/a	Assumption
Vaccine wastage rate			
Rotarix®, single dose (liquid)	1%	n/a	WHO [30]
RotaTeq®, single dose (liquid)	1%	n/a	WHO [30]
ROTAVAC®, five doses per vial (frozen)	30%	n/a	Gavi Product Details [29]
ROTASIIL®, single dose (lyophilised)	5%	n/a	Gavi Product Details [29]
Logistics costs (per additional dose)	0.15 (0.12, 0.19) USD	Gamma	[36]
Cost of adverse events (acute diarrhoea) (per vaccinated person)	0.38 (0.31, 0.46) USD	Gamma	[31]
Cost of intussusception (per case)	195.0 (156.0, 234.0) USD	Gamma	[33]
Utility due to rotavirus diarrhoea			
Children (age 0–5 years)			
Severe rotavirus diarrhoea	0.595 (0.584–0.606)	Beta	[37]
Non-severe rotavirus diarrhoea	0.685 (0.678–0.686)	Beta	[37]
Other age groups (age ≥ 6 years)			
Severe rotavirus diarrhoea	0.615 (0.604–0.626)	Beta	[37]
Non-severe rotavirus diarrhoea	0.698 (0.697–0.699)	Beta	[37]

severe cases, while those with mild infections were assumed to have one day absent from work [32]. The minimum wage per day was applied to the duration of illness to estimate productivity losses [35]. Vaccination costs, comprising the costs of the vaccine, administration and logistics (including supply chain management, storage, transportation and vaccine delivery), were derived from the manufacturers' data and the literature [36]. Costs due to adverse events (of acute diarrhoea) were adopted from a previous study conducted in Thailand [31]. Health-related quality of life values (utility) of the three health states (severe, mild and self-care cases) were also obtained from a previous study conducted in Thailand [37]. We assumed the utility values of rotavirus infection in adults were equivalent to those of caregivers who take care of children infected with rotavirus. The vaccination programme was considered to be cost-effective if the ICER was less than a threshold of USD 5,110 per QALY gained (160,000 Thai baht), as recommended by the Health Economic Working Group under the subcommittee for the development of the National List of Essential Medicine [38].

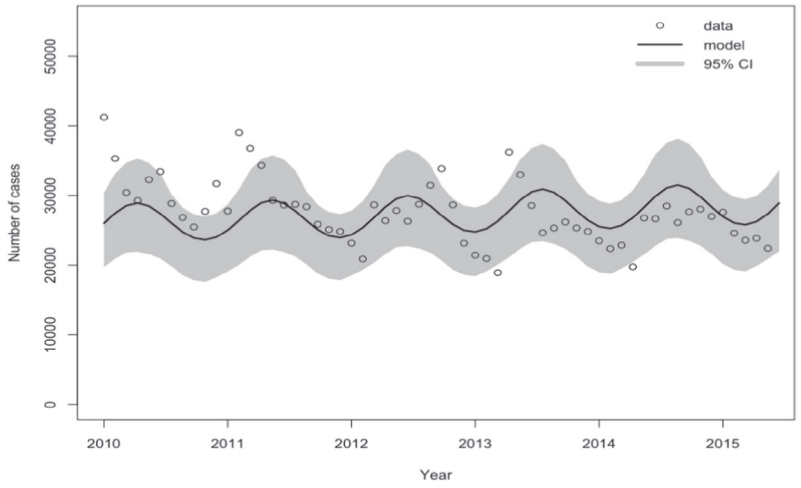
3.2. Sensitivity analysis

One-way sensitivity analyses, with upper and lower values for vaccine efficacy as well as the lower incidence of rotavirus infection (half of the estimated annual incidence), were performed to examine the magnitude of their effect on the results. Two-way sensitivity analyses were conducted to identify the optimum price of the ROTASIIL® and ROTAVAC® vaccines, using different assumptions about their protective efficacy. In addition, a scenario analysis was performed to determine whether vaccination with ROTAVAC® or ROTASIIL® had either lower protective efficacy (at 60%) or caused more intussusception among infants, compared with Rotarix® or RotaTeq®, under base case conditions. The lower efficacy was derived from the lower bound efficacy estimated by a *meta*-regression analysis of randomised controlled trials across the medium-mortality settings at 24-month follow-up [39]. The incidence of intussusception was assumed to be 1 per 15,000 recipients, about half of the reported incidence with ROTASHIELD® (1 per 5,000 to 10,000 recipients) with an age-unrestricted schedule, a previously available rotavirus vaccine that was withdrawn due to safety concerns [40]; the cost of intussusception management was also taken into account [33]. Finally, a probabilistic sensitivity analysis (PSA) was performed using Monte Carlo simulation, repeating the analysis with a thousand runs and sampling from a set of parameter probability distributions.

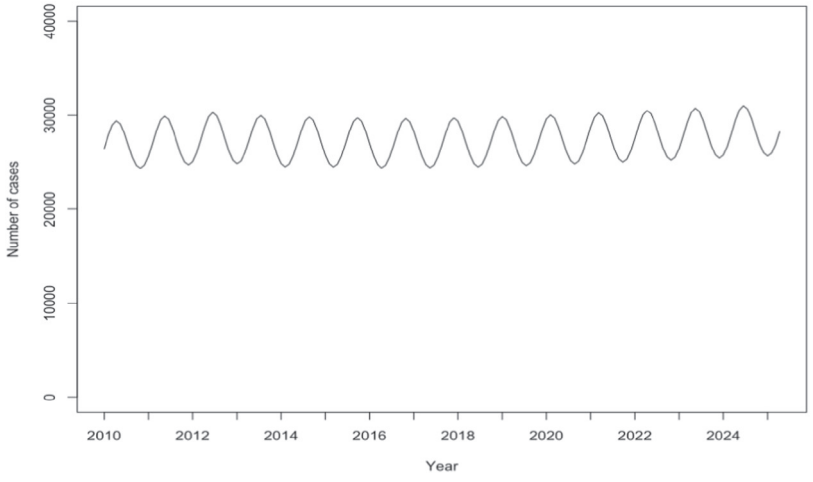
3.3. Budget impact analysis

The financial consequences, from the governmental perspective, for the national implementation of a rotavirus vaccine within a five-year timeframe was assessed. All relevant information, including vaccine cost per dose, number of doses, cost of logistics, adverse event management, and expected losses from wastage, were incorporated to estimate their impact on the budget. Annual

A) Model fitting from data of rotavirus incidence in Thailand, 2010 to 2015.



B) Predicted rotavirus incidence in Thailand from 2010 to 2024.



C) Expected transmission dynamics following implementation of a vaccination programme in Thailand.

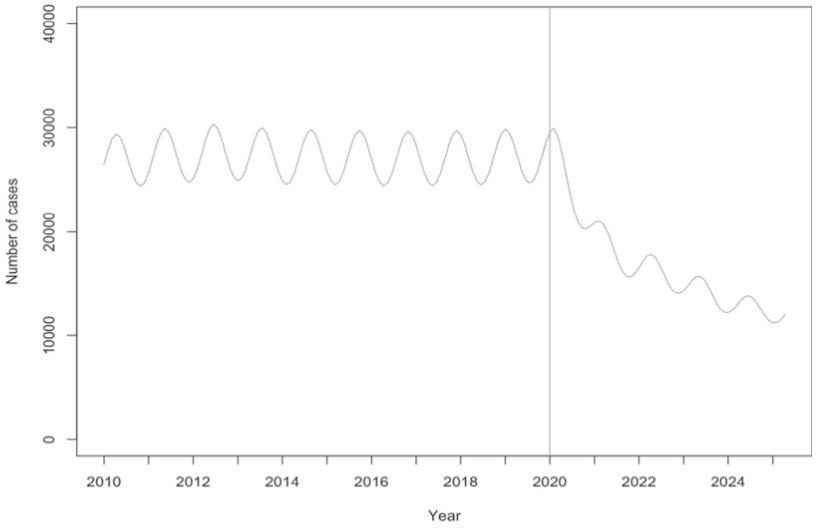


Fig. 2. Model fitting and prediction. (A) Model fitting from data of rotavirus incidence in Thailand, 2010 to 2015. (B) Predicted rotavirus incidence in Thailand from 2010 to 2024. (C) Expected transmission dynamics following implementation of a vaccination programme in Thailand.

vaccine costs, administrative costs, healthcare costs and the total net budget were estimated without discounting.

4. Results

4.1. Epidemiology

Overall, without the vaccine, the transmission dynamic model predicted the annual incidence of rotavirus to be 308,138 cases per year (in 2020) and 316,099 cases per year (in 2024) (Fig. 2A and 2B). Age-specific incidence was estimated to range from 98 to 3,570 cases per 100,000 population. The incidence was the highest in the 0–5 years age group (414–3,570 cases per 100,000 population) followed by the 6–14 years age group (111 cases per 100,000 population), the 15–64 years age group (108 cases per 100,000 population), and the over-65 years age group (98 cases per 100,000 population) (Supplementary Fig. S1).

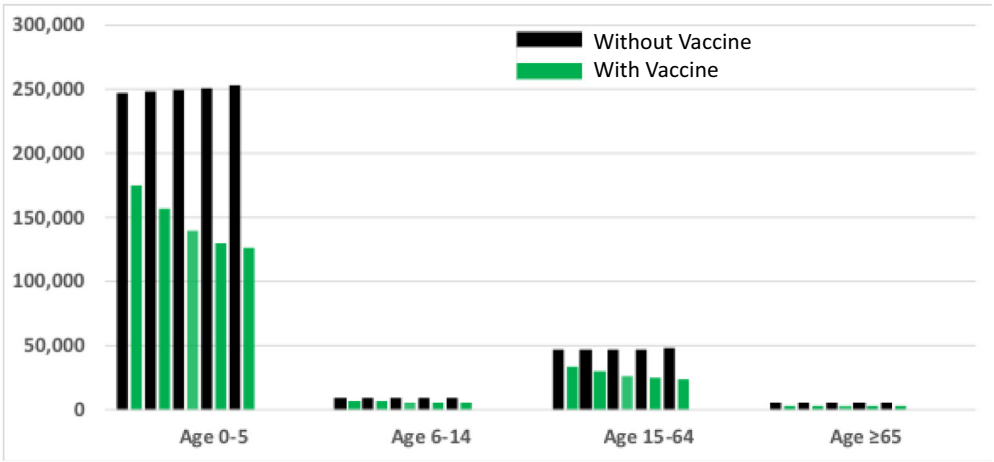
With rotavirus vaccination, the transmission dynamic model predicted rotavirus infections will decrease from 218,789 to 158,100 cases per year from 2020 to 2024, providing an average of 144,299 cases averted per year. Of these, 67,427 cases averted, or 46.7%, would have required hospitalisation (Supplementary Fig. S2 and S3). Of the total cases averted, 84,144 (58.3%) were due to direct effects in vaccinated individuals, whereas 60,155 (41.7%) cases were averted by indirect protection (Fig. 3B). The greatest reduction was seen in the 0–5 years age group, ranging between 89,349 and 150,038 cases averted per year.

4.2. Economic evaluation

4.2.1. Base case results

In the base case analysis, all rotavirus vaccines were cost-saving compared with no immunisation. All vaccine options provided the same health benefits, with 998.7 QALYs gained. ROTASIIL® was the most cost-saving option, followed by ROTAVAC®, Rotarix® and Rota-

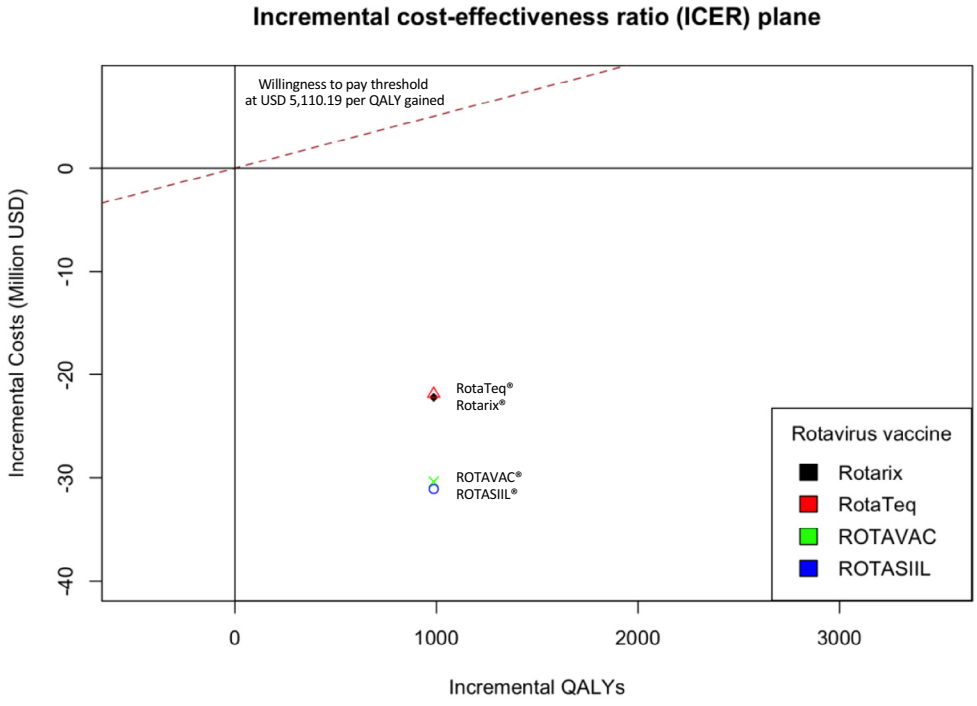
A) Number of cases averted by vaccination by age group, 2020 to 2024.



B) Average number of rotavirus cases averted per year, 2020 to 2024.

Fig. 3. Number of rotavirus cases averted by age group and vaccine effect. (A) Number of cases averted by vaccination by age group, 2020 to 2024. (B) Average number of rotavirus cases averted per year, 2020 to 2024.

A) Incremental cost-effectiveness ratio (ICER) plane showing the results of the four vaccine options compared with no vaccine (base case). (Exchange rate, USD 1 = 31.31 Thai baht).



B) Probabilistic sensitivity analysis (PSA) results showing all 1,000 iterations of each vaccine option compared with no vaccine (base case).

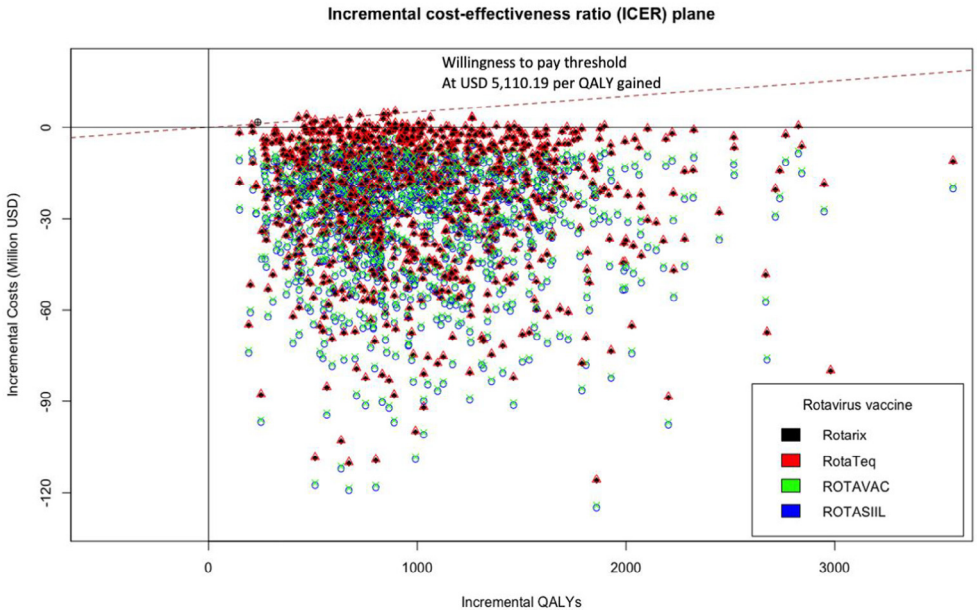


Fig. 4. Base case results. (A) Incremental cost-effectiveness ratio (ICER) plane showing the results of the four vaccine options compared with no vaccine (base case). (Exchange rate, USD 1 = 31.31 Thai baht). (B) Probabilistic sensitivity analysis (PSA) results showing all 1000 iterations of each vaccine option compared with no vaccine (base case).

Teq®. The total average annual cost-saving due to the vaccination programme was estimated to be between USD 22.39 and 31.62 million (Fig. 4A). An extended head-to-head comparison analysis was not required due to the fact that all vaccines were cost-saving and the magnitude of the savings could be ranked directly. When considering only direct benefits, all vaccines were still cost-saving but with

fewer QALYs gained (Supplementary Table S5). The probabilistic sensitivity analysis (PSA) and cost-effectiveness acceptability curves (CEACs) all consistently showed ROTASIIL® to be the best option (Fig. 4B and Supplementary Fig. S4).

4.2.2. Sensitivity analysis

As would be expected, the sensitivity analyses for all vaccines indicated increased cost-savings with more QALYs gained in the higher efficacy situation (90%) and less cost-saving with fewer QALYs gained in the lower efficacy situation (60%) (Supplementary Table S6 and Fig. S5). In addition, other than RotaTeq®, all vaccines remained cost-effective even when a 50% reduction in the overall incidence of rotavirus infection in Thailand was applied (although with fewer QALYs gained), while ROTAVAC® and ROTASIIL® remained cost-saving. However, when considering only direct effects, Rotarix® and RotaTeq® were no longer considered cost-effective, while ROTAVAC® and ROTASIIL® were still cost-saving (Supplementary Table S7). Two-way sensitivity analyses, varying the cost of either ROTASIIL® or ROTAVAC® and their efficacy, showed that both ROTASIIL® and ROTAVAC® remained cost-effective even if their protective efficacy was as low as 30%. The cost of ROTASIIL® and ROTAVAC could be as high as USD 12 per dose (USD 36 per course) and USD 9 per dose (USD 27 per course), respectively, and remain cost-effective, if they provide at least 50% protective efficacy (Supplementary Fig. S6).

In the scenario analysis where a head-to-head comparison was performed, by setting the lower bound efficacy of ROTASIIL® to 60%, with or without adverse events of intussusception, ROTASIIL® remained optimal compared with the other three vaccines (Table 3A). Likewise, when compared with ROTAVAC® (referring to a situation where ROTASIIL® is not available), ROTAVAC was still optimal compared with the other two vaccines (Table 3B) (Supplementary Fig. S7–S10).

4.2.3. Budget impact analysis

Over 5 years, implementing universal rotavirus vaccination in Thailand would cost between USD 5 and 15 million per year, with the vaccine alone costing USD 2 to 12 million per year. The vaccination costs will reduce over time due to the decreasing birth rate in Thailand. Any of the vaccines would result in lower healthcare costs by avoiding rotavirus cases. The healthcare costs with vaccination will be reduced to USD 39 to 49 million per year compared with USD 77 to 79 million per year if there is no vaccination. The net savings to the healthcare budget when vaccinating with any one of these options would be between USD 20–29 million per year (Supplementary Table S8).

5. Discussion

We compared all WHO-prequalified rotavirus vaccines, accounting for any indirect effects, if these vaccines were to be incorporated into the nationwide immunisation programme. All vaccines were found to be cost-saving. The recently developed ROTASIIL® vaccine was found to offer the best value for money, providing comparable effectiveness to the other vaccines but with the lowest costs, followed by ROTAVAC®, Rotarix® and RotaTeq®. The cost savings were due to the substantial reduction in the rotavirus burden among infants, who are directly protected by vaccination, as well as benefits from indirect protection among adults and especially the elderly. Our findings showed the indirect effects of rotavirus vaccination i.e. 60,155 (41.7%) cases averted by indirect protection are consistent with those of a recent systematic review and *meta*-analysis that found the pooled indirect rotavirus vaccine efficacy to be 48% (95% confidence interval (CI): 39–55%) and a previous modelling study from the UK suggesting the indirect effect to be 43% [41,42]. The results remained robust when assuming the incidence of rotavirus infection is reduced by half of the estimated annual cases, when the protective efficacy of the vaccine is as low as 50%, and when accounting only for the direct benefits to those vaccinated.

This study is the first economic evaluation comparing all four WHO-prequalified rotavirus vaccines licensed for use in Thailand; previous studies only evaluated either Rotarix® or RotaTeq® [11,20–22]. Our findings showed that all four vaccines are cost-saving, whereas three previous studies [20–22] showed vaccination with either Rotarix® or RotaTeq® to be cost-effective, and another study found these two vaccines were not cost-effective [11]. These differences can be mainly explained by the different

Table 3
Sensitivity analysis results assuming ROTASIIL® and ROTAVAC® had lower protective efficacy (at 60%), with and without adverse events of intussusception. A) Using ROTASIIL® as a comparator. B) Using ROTAVAC® as a comparator.

Intervention	Total cost (USD, 2019)	QALYs lost	Incremental cost	Incremental QALYs	ICER
Compared with ROTASIIL® without intussusception					
ROTASIIL® (as comparator)	49,613,820.89	1,348.7			–
Rotarix®	52,961,404.66	1,189.4	3,347,583.78	159.3	21,014.34
RotaTeq®	53,299,566.56	1,189.4	3,685,745.67	159.3	23,137.14
ROTAVAC®	50,325,990.90	1,348.7	712,170.01	0.0	Not cost-effective
Compared with ROTASIIL® with intussusception					
ROTASIIL® (as Comparator)	49,729,656.44	1,348.7			–
Rotarix®	52,961,404.66	1,189.4	3,231,748.23	159.3	20,287.18
RotaTeq®	53,299,177.48	1,189.4	3,569,521.05	159.3	22,407.54
ROTAVAC®	50,441,826.45	1,348.7	712,170.01	0.0	Not cost-effective

Intervention	Total cost (USD, 2019)	QALYs lost	Incremental cost	Incremental QALYs	ICER
Compared with ROTAVAC® without intussusception					
ROTAVAC® (as comparator)	50,325,990.90	1,348.7			–
Rotarix®	52,961,404.66	1,189.4	2,635,413.76	159.3	16,539.83
RotaTeq®	53,299,566.56	1,189.4	2,973,575.66	159.3	18,662.12
Compared with ROTAVAC® with intussusception					
RotaVAC® (as comparator)	50,441,826.45	1,348.7			–
Rotarix®	52,961,404.66	1,189.4	2,519,578.22	159.3	15,816.54
RotaTeq®	53,299,177.51	1,189.4	2,857,351.07	159.3	17,936.92

costs of vaccines and hospitalisation used in our model. We used the lowest costs of vaccines (USD 17.57 per course for both Rotarix® and RotaTeq®), whereas the other studies applied vaccine costs ranging from USD 25.55 to 106.55 per course (16–70% lower than costs used in other studies). Moreover, the costs of treating hospitalised rotavirus infection cases adopted from the NHSO database (USD 483.33 per case) were two- to four-times higher than the costs used in previous studies (ranging from USD ~ 100 to 240 per case). These factors made the implementation of these vaccines more favourable, according to our findings. In addition, our findings of the overall hospitalisation rate among rotavirus cases (46.7%), where we derived input values from national Thai data, differ from the rate reported by a local study where data were collected from two provinces in Thailand, which found 27.3% of cases in infants aged 0 to 5 years were hospitalised [10]. We confirmed in our sensitivity analysis that this lower hospitalisation rate was unlikely to affect our conclusion on the cost-savings the vaccines could provide (Supplementary Table S9).

Our study has several strengths compared with previous studies [11,20–22]. First, we used a transmission dynamic model to estimate the baseline incidence of rotavirus infections using age-specific surveillance data for diarrhoea cases, combined with information about rotavirus positivity rates from a rapid review we conducted to gather the most recent evidence. This allowed for improved prediction of the consequences of implementing rotavirus vaccines as part of the national immunisation programme. This study broadened the scope of the analysis to estimate the overall burden of rotavirus infection and fully captured the benefits of a national rotavirus vaccination programme among both the vaccinated and non-vaccinated population. In addition, we derived the cost of treatments for rotavirus infection, in both hospitalised cases and outpatient cases, from the NHSO database (2015 to 2018). This information reflects the actual healthcare costs due to rotavirus infection in the Thai health system. Finally, we compared all rotavirus vaccine options, and our findings will support policymakers as they consider these WHO-prequalified vaccines for possible inclusion in the national immunisation programme.

This study has several limitations. Due to the fact that there is limited evidence of efficacy for ROTAVAC® and ROTASIIL® in low-mortality countries (stratum B) such as Thailand, and most evidence originates from high-mortality countries (stratum C) such as India, the assumption that these vaccines have an efficacy comparable with that of Rotarix® and RotaTeq® may be incorrect [39]. Our sensitivity analyses, however, still showed the results to be robust with lower efficacies of the vaccines, which remained cost-effective even with protective efficacy as low as 50%. Moreover, the healthcare-seeking rate among older children and adults that we have assumed could potentially be overstated, which may have some implications for the estimated cost-savings. However, this is unlikely to change our conclusions, as our sensitivity analysis showed all vaccines remained cost-saving even when the overall incidence was reduced by half (see Supplementary Table S7). In addition, we adopted the utility values of two health states, mild and severe gastroenteritis, from literature based on research conducted among the Thai population, assuming the utility values provided by caregivers were representative of all adult patients with rotavirus infection [37]. Although the utility values directly assessed by adults themselves may differ from those as assessed by caregivers, this would have little impact because rotavirus infection events are short (2 to 16 days) [32]. Finally, patients with symptoms such as sore throat, common cold, or acute diarrhoea are able to purchase antimicrobial drugs at pharmacies in Thailand. Therefore, an immunisation programme could potentially provide additional benefits by avoiding the unnecessary use of antibiotics as a result of decreasing the number of suspected diarrhoea cases, reducing antimicrobial consumption and resistance in the longer term [43]. Ideally, this consequence would be incorporated in the analysis; however, quantifying this benefit in monetary terms remains difficult, as shown by several attempts in the literature [44–46]. As a result, our study provides conservative estimates by not taking this into account.

If a rotavirus vaccine is to be added to the national immunisation programme, several features of the vaccine must be considered to support the policy decision-making process. First, some of these vaccines require specific conditions, such as a cold chain. Rotarix®, RotaTeq® and ROTASIIL® must be kept at 2 °C to 8 °C, while ROTAVAC® must be stored under sub-zero cold-chain conditions. ROTASIIL® also requires additional workload to reconstitute it with a diluent, as it is supplied in a lyophilised form. The shelf-lives of these vaccines also vary, with implications for wastage. Rotarix®, RotaTeq® and ROTASIIL® can be kept for up to 24 months at 2 °C to 8 °C, while ROTAVAC® can only be kept for 6 months at 2 °C to 8 °C or 60 months at less than −20 °C [29]. In addition, for the more recent vaccines manufactured in India, i.e. ROTAVAC® and ROTASIIL®, where healthcare providers have less experience in dealing with adverse reactions, closer monitoring may be needed, although there is no evidence in India to suggest that these vaccines increase the risk of intussusception [12]. Preparedness, in terms of procuring the appropriate equipment and training the healthcare workforce for vaccine delivery, should be taken into account when making any decisions about including rotavirus vaccinations in the national immunisation programme.

Each of the four rotavirus vaccines was developed using different techniques and with different rotavirus serotypes, although available evidence suggests that three of these vaccines, Rotarix®, RotaTeq® and ROTAVAC®, provide protective efficacy against heterotypic strains [47,48]. This is verified by the fact that these vaccines provide comparable efficacy and that no dominant strain appears during the post-vaccination period [48,49]. This suggests that implementing any one of these vaccines would result in a similar reduction in rotavirus infections without changing the dominant serotype in Thailand. However, it may be the case that the vaccine procured is changed each year due to variations in prices, supply shortages or other technical purchasing issues, resulting in the use of a mixture of these vaccines. Information about the implications of mixed vaccine use is still limited in the literature, especially for vaccines manufactured in India. One study in the USA showed that incomplete doses and mixed used of RotaTeq® and Rotarix® could provide some level of protection among infants [50]. Further investigation of this issue may be required before implementing a mixed-use policy.

6. Conclusion

All rotavirus vaccine options explored here represent good value for money. Implementing any one of these four vaccines would reduce healthcare costs and provide health benefits to the population. This would be the case even when considering only the direct effects of the vaccination programme. Issues such as vaccine availability, logistics and delivery systems are further elements for policymakers to contemplate prior to enlisting a rotavirus vaccine in the national essential medicine list. These findings are being used to support the policy decision-making process in Thailand.

7. Authors' contributions

N.L. and W.M. designed the study, planned the analyses, collected the data, conducted the literature search and statistical analyses, created the tables and figures, interpreted the results and

wrote the manuscript. W.P. and K.P. contributed to the study design, analysis plan, preparation of outputs, interpretation of results, as well as writing and revising the manuscript. B.S.C., Y. L., L.J.W. and Y.T. provided essential data inputs and helped with the interpretation of results and revising the manuscript. All authors approved the final submitted version.

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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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.01.051.

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