FOURTEENTH INTERNATIONAL

ROTAVIRUS SYMPOSIUM

MARCH 14–16 **2023** BALI INDONESIA

Learn more on www.sabin.org

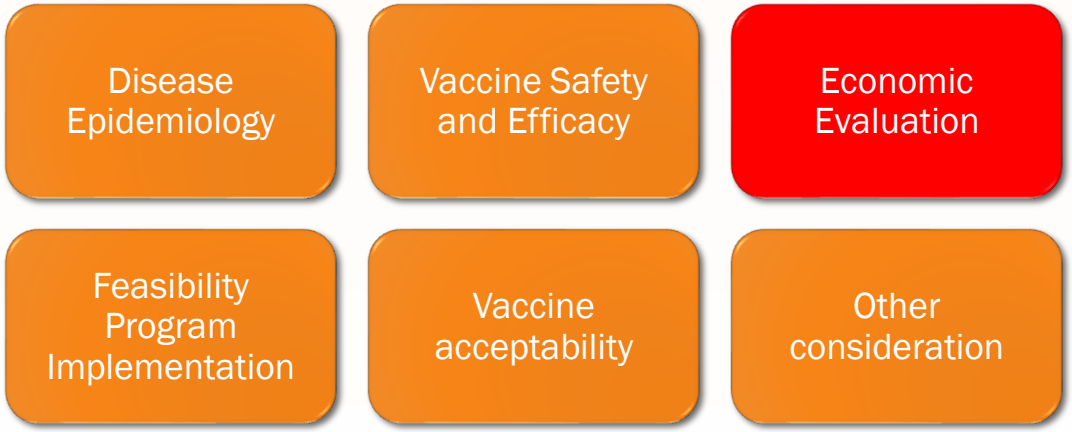
COST EFFECTIVENESS OF ROTAVIRUS VACCINE IN INDONESIA

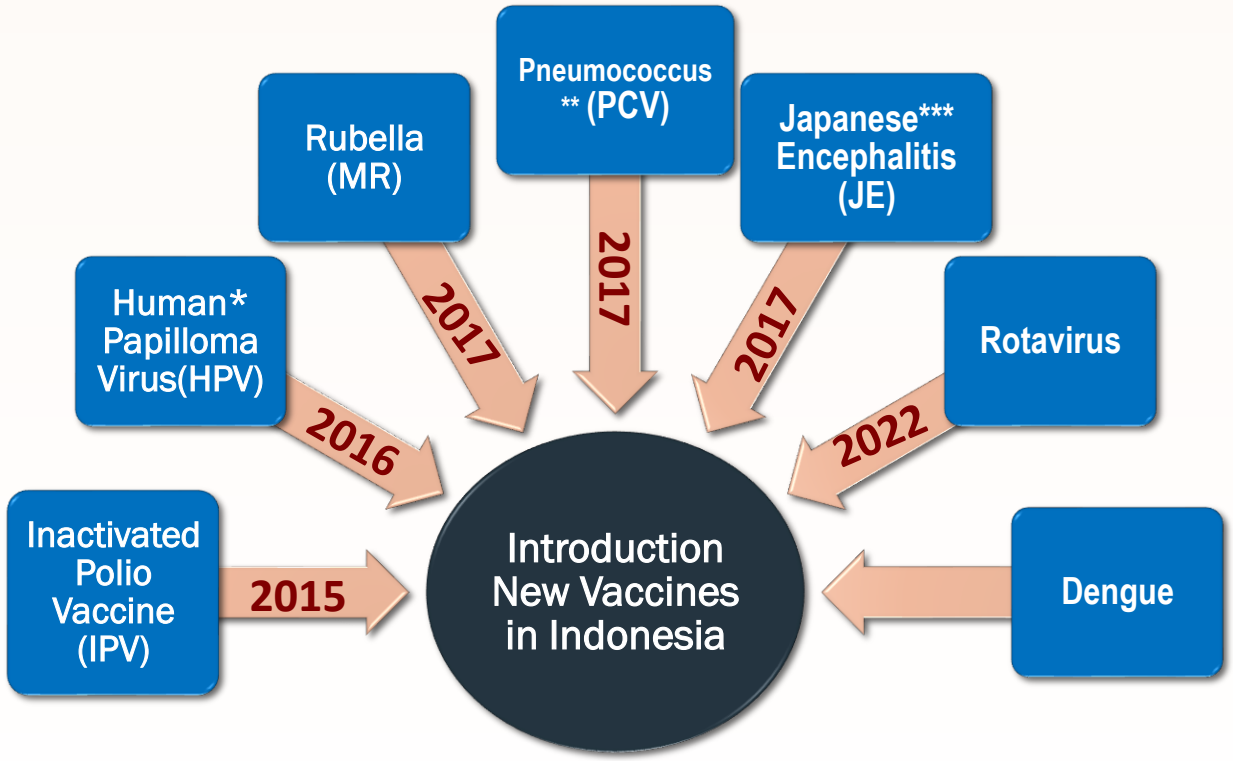
JARIR AT THOBARI

FACULTY OF MEDICINE, PUBLIC HEALTH & NURSING
UNIVERSITAS GADJAH MADA (UGM)
YOGYAKARTA - INDONESIA

Introduction of New Vaccine in Indonesia

The Indonesian Technical Advisory Group on Immunization" (ITAGI) was established in 2007 to advice to MoH, relating to introduction new vaccines, evidence-based recommendations are needed. ITAGI consists of recognized experts in the fields of pediatrics, infectious diseases, immunology, medical microbiology, internal medicine, Health Economics, and Epidemiology





Evidences recommendation are needed for introduction of new vaccines

RVV Program Examined in the CEA Study

The major component of the vaccine program option analysed is the live oral BioFarma RVV which is in clinical development

Administered as a 3-dose schedule at 1-week, 2-months and 3-months of age (Bio Farma) or 2, 3 and 4 months of age (Imported)

Assumption: BioFarma RVV will be licensed and available from 2023

RVV PROGRAM

	BioFarma	Imported
2022-2023	0%	4%
2023-2024	12%	4%
2024-2025	50%	4%
2025 -2031	100%	0%

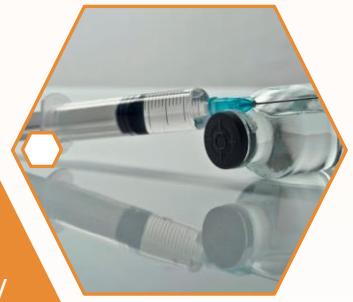
Percentage from the targeted population (newborn cohort in Indonesia)

Cost-effectiveness study of rotavirus vaccine in Indonesia: UNIVAC Modeling

RVGE incidence under-five years old, age-specific incidence, severity, mortality, hospitalisation, non-hospitalisation, LOS, healthy time loss

Vaccine schedule & coverage, timeliness, wastage

Program costs (Training, Cold Chain)



Vaccine efficacy, safety vaccine price

Epidemiology Data

Health Care Costs

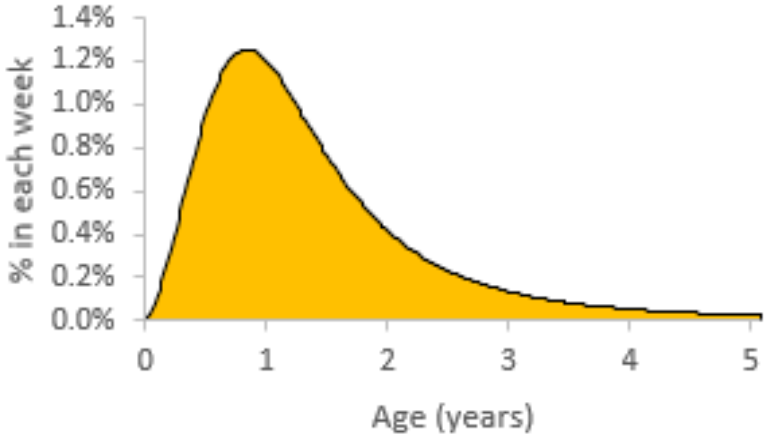
Health System Costs

Direct and indirect cost of illness (hospitalization costs, outpatient costs, household costs)

ICER per DALY averted,

Input parameters:

Epidemiological data RV cases



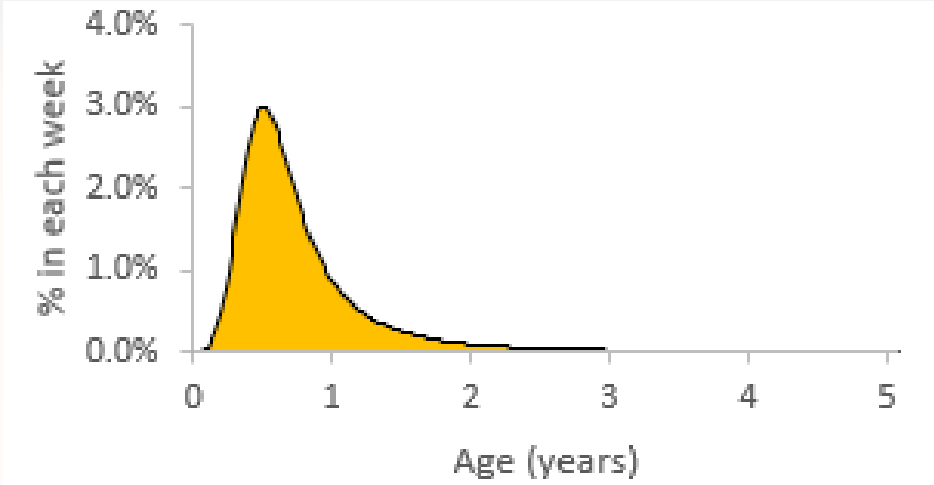
	BASE CASE	LOW	HIGH	SOURCE
Annual incidence rate/100,000 children <5yrs				
Overall RVGE cases	10,000	7,000	14,000	Bilcke et al., 2009
Overall RVGE outpatient visits	8,000	5,600	11,200	DHS, 2017, seeking rates of 80% for diarrhea in children
Severe RVGE cases	1,600	1,175	3,526	5.6% attack rate in placebo group of RV3 phase IIb trial by scaling using the age distribution curve to estimate cases occurring beyond the 18 months of age and converting to an annual incidence
Hospitalised RVGE cases	602	418	1135	Base case and high: BPJS 2015-2018 data sample (1%), (unpublished), extrapolated for the whole population & assuming rotavirus positivity rate from Indonesian Rotavirus surveillance ; High is estimated from unpublished RV3 phase IIb trial data (incidence of hospitalised RVGE was 71% of the incidence of severe RVGE)
RVGE deaths	19.52	9.02	33.21	Global burden disease (Indonesia)

RVGE cases age distribution : <1mo (0%), <2mo (1%), <3mo (2%), <6mo (11%), <1y (42%), <2y (82%), <3y (94%), <4y (98%) and <5y (100%) (Hasso-Agopsowicz et al, 2019)

Bilcke J, Van Damme P, Van Ranst M, Hens N, Aerts M, Beutels P. Estimating the incidence of symptomatic rotavirus infections: a systematic review and meta-analysis. PLoS One. 2009;4(6):e6060; National Population and Family Planning Board (BKKBN) SIB, Ministry of Health (Kemenkes), and ICF. Jakarta, Indonesia. Indonesia Demographic and Health Survey 2017. 2018; Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719-30.; Debellut F, Clark A, Pecenka C, Tate J, Baral R, Sanderson C, et al. Re-evaluating the potential impact and cost-effectiveness of rotavirus vaccination in 73 Gavi countries: a modelling study. The Lancet Global Health. 2019;7(12); Walker CLF, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. The Lancet. 2013;381(9875):1405-16; Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22; GBD Results Tool | GHDx (healthdata.org); Hasso-Agopsowicz M, Ladva CN, Lopman B, Sanderson C, Cohen AL, Tate JE, et al. Global Review of the Age Distribution of Rotavirus Disease in Children Aged <5 Years Before the Introduction of Rotavirus Vaccination. Clin Infect Dis. 2019;69(6):1071-8

Input parameters:

Intussusception disease burden



	BASE CASE	LOW	HIGH	SOURCE
Annual incidence rate/100,000 children <5yrs				
Overall Intussusception cases	19.16	4.44	63.15	Estimated by scaling hospitalised cases for DTP1 coverage as a proxy for access to hospital care
Hospitalised Intussusception cases	18.51	4.29	61.00	Clark AD, et al., 2019
Intussusception deaths	0.64	0.14	3.45	Clark AD, et al., 2019

Intussusception cases age distribution*	Base case
<1 month	0%
<2 months	0%
<3 months	3%
<6 months	31%
<1 year	80%
<2 years	96%
<3 years	99%
<4 years	100%
<5 years	100%

*Clark AD, Hasso-Agopsowicz M, Kraus MW, Stockdale LK, Sanderson CFB, Parashar UD, et al. Update on the global epidemiology of intussusception: a systematic review of incidence rates, age distributions and case-fatality ratios among children aged <5 years, before the introduction of rotavirus vaccination. Int J Epidemiol. 2019;48(4):1316-26

Input parameters:

Disability weights & illness duration

	BASE CASE	LOW	HIGH	SOURCE
Disability weights (% healthy time lost) & disease duration				
Non-severe RVGE	18.8%	12.5%	26.4%	Salomon et al., 2015
Severe RVGE	24.7%	16.4%	34.8%	Salomon et al., 2015
Intussusception	32.4%	22%	44.2%	Salomon et al., 2015
Duration of severe RVGE (days)	5.31	2.61	8.01	Base case: Posthoc analysis of data from phase IIb trial. Low and high are +/- 1 SD
Duration of non-severe RVGE (days)	3.06	1.46	4.65	Base case: Posthoc analysis of data from phase IIb trial. Low and high are +/- 1 SD
Duration of Intussusception (days)	1.8	0.4	9.9	Jehangir et al., 2014

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. The Lancet Global Health. 2015;3(11):e712-e23.
Jehangir S, John J, Rajkumar S, Mani B, Srinivasan R, Kang G. Intussusception in southern India: comparison of retrospective analysis and active surveillance. Vaccine. 2014;32 Suppl 1:A99-103.

Input parameters:

Vaccine Safety

	Base case	Low	High	Source
Vaccine Safety				
Relative risk of IS in the 1–7-day risk period following RVV vaccination				
Dose 1	6.26	4.25	9.22	Clark A, et al., 2019
Dose 2	1.82	1.41	2.34	
Dose 3	1	1	1	
Relative risk of IS in the 8–21-day risk period following RVV vaccination				
Dose 1	1.69	1.05	2.72	Clark A, et al., 2019
Dose 2	1.37	1.03	1.84	
Dose 3	1	1	1	

Clark A, Tate J, Parashar U, Jit M, Hasso-Agopsowicz M, Henschke N, et al. Mortality reduction benefits and intussusception risks of rotavirus vaccination in 135 low-income and middle-income countries: a modelling analysis of current and alternative schedules. The Lancet Global Health. 2019;7(11):e1541-e52

Input parameters: *Vaccine Coverage*

	Base case	Source
OPV1 as proxy for BioFarma RVV dose 1	90.8%	(DHS, 2017)
DTP1 as proxy for BioFarma RVV dose 2 and for Imported RVV dose 1	88.9%	(DHS, 2017)
DTP2 as proxy for BioFarma RVV dose 3 and for Imported RVV dose 2	84.2%	(DHS, 2017)
DTP3 as proxy for Imported RVV dose 3	76.7%	(DHS, 2017)

National Population and Family Planning Board (BKKBN) SIB, Ministry of Health (Kemenkes), and ICF. Jakarta, Indonesia. Indonesia Demographic and Health Survey 2017. 2018

Input parameters: *Vaccine Timelines*

For the primary analysis, vaccines were assumed to be delivered ‘on-time’ at the target age as follows:

- BioFarma RVV dose 1: 1 week of age; dose 2: 2 months of age; dose 3: 3 months of age;
- Imported RVV dose 1: 2 months of age; dose 2: 3 months of age; dose 3: 4 months of age.

Sensitivity Analysis: For a secondary analysis, realistic delays (vaccine timeliness) were estimated from unpublished DHS2017 data, with some imputation for missing data.

For the probabilistic sensitivity analyses, vaccines were assumed to be delivered at the target ages without delays.

Sanderson, unpublished analysis, LSHTM

Input parameters: *Vaccine Efficacy (Biofarma)*

	Base case	Low	High	Source
Vaccine efficacy against severe RVGE				
Dose 1 BioFarma RVV efficacy				
2 weeks after vaccination	49.9%	38.2%	65.3%	Clark A., et al. 2019 (meta-analysis efficacy for high mortality setting & RV3 neonatal schedule waning)
6 months after vaccination	40.9%	27.9%	58.8%	
12 months after vaccination	16.5%	8.0%	33.1%	
Dose 2 BioFarma RVV efficacy				
2 weeks after vaccination	100%	100%	100%	Clark A., et al. 2019 (RV3 neonatal schedule waning)
6 months after vaccination	82%	73.1%	90.0%	
12 months after vaccination	33.1%	20.9%	50.7%	
Dose 3 BioFarma RVV efficacy				
2 weeks after vaccination	100%	100%	100%	Clark A., et al. 2019 (RV3 neonatal schedule waning)
6 months after vaccination	82%	73.1%	90.0%	
12 months after vaccination	33.1%	20.9%	50.7%	

Clark A, van Zandvoort K, Flasche S, Sanderson C, Bines J, Tate J, et al. Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomised controlled trials. The Lancet Infectious Diseases. 2019;19(7):717-27

Input parameters: *Vaccine Efficacy (Imported)*

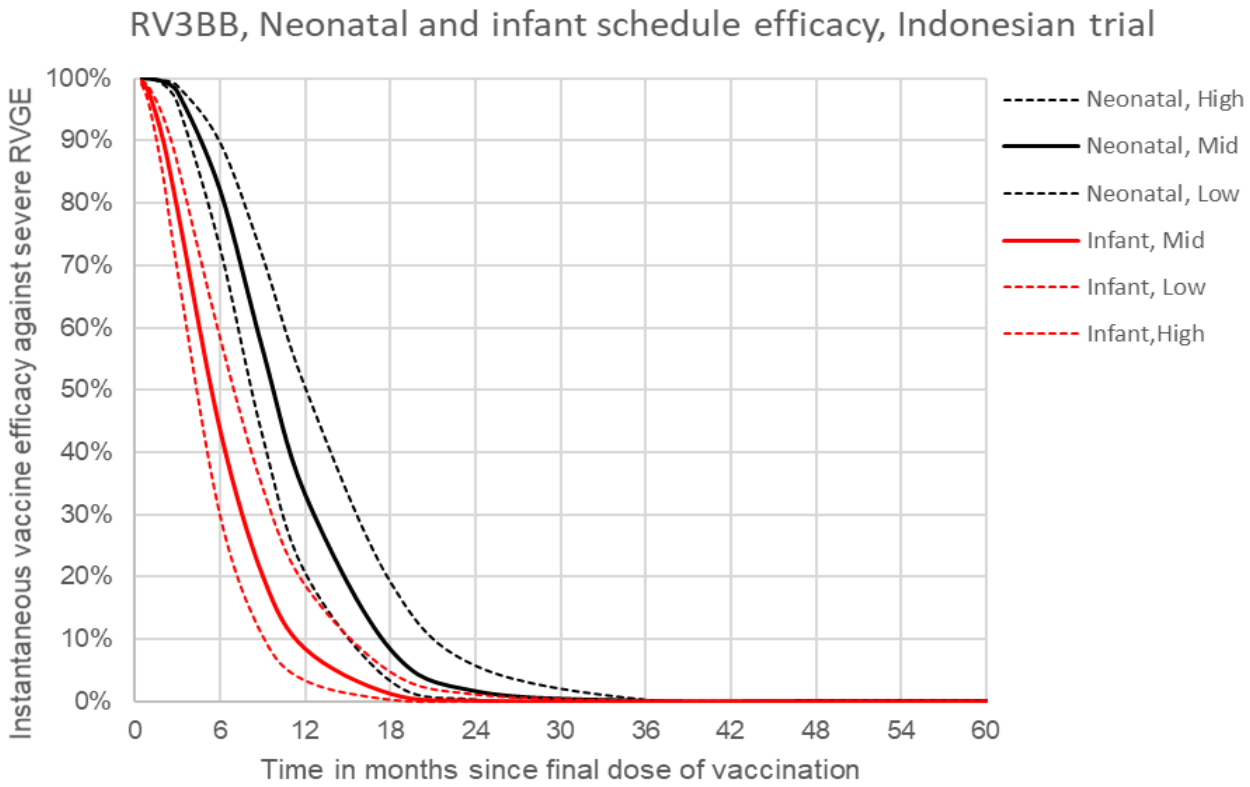
	Base case	Low	High	Source
Vaccine efficacy against severe RVGE				
Dose 1 Imported RVV efficacy				
2 weeks after vaccination	49.9%	38.2%	65.3%	Clark A., et al. 2019 (Meta-analysis efficacy for high mortality setting & RV3 infant schedule waning)
6 months after vaccination	21.8%	11.6%	38.4%	
12 months after vaccination	4.2%	1.3%	12.2%	
Dose 2 Imported RVV efficacy				
2 weeks after vaccination	99.5%	99.2%	99.7%	Clark A., et al. 2019 (RV3 infant schedule waning)
6 months after vaccination	43.5%	30.2%	58.7%	
12 months after vaccination	8.5%	3.4%	18.7%	
Dose 3 Imported RVV efficacy				
2 weeks after vaccination	99.5%	99.2%	99.7%	Clark A., et al. 2019 (RV3 infant schedule waning)
6 months after vaccination	43.5%	30.2%	58.7%	
12 months after vaccination	8.5%	3.4%	18.7%	
Efficacy against non-severe RVGE				
As proportion of efficacy against severe RVGE	0.84	0.84	0.85	Bines J, et al., 2018; Rogawski ET, et al., 2018

Clark A, van Zandvoort K, Flasche S, Sanderson C, Bines J, Tate J, et al. Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomised controlled trials. The Lancet Infectious Diseases. 2019;19(7):717-27; Bines JE, At Thobari J, Satria CD, Handley A, Watts E, Cowley D, et al. Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth. N Engl J Med. 2018;378(8):719-30

Rogawski ET, Platts-Mills JA, Colgate ER, Haque R, Zaman K, Petri WA, et al. Quantifying the Impact of Natural Immunity on Rotavirus Vaccine Efficacy Estimates: A Clinical Trial in Dhaka, Bangladesh (PROVIDE) and a Simulation Study. J Infect Dis. 2018;217(6):861-8

Input parameters:

Vaccine Efficacy (RV3 neonatal schedule efficacy and waning)



Indonesian phase IIb efficacy trial of RV3-BB demonstrated 94% efficacy against severe RVGE to 12 months follow-up for the neonatal schedule (assume similar with BioFarma RVV)

The initial efficacy, duration of protection and waning rate of the neonatal schedule presented in a pooled-analysis of rotavirus vaccine efficacy trials

The base case initial efficacy, duration of protection and waning rate for imported RVV is assumed as equivalent to the infant arm of the RV3 Phase IIb trial in Indonesia.

Clark A, van Zandvoort K, Flasche S, Sanderson C, Bines J, Tate J, et al. Efficacy of live oral rotavirus vaccines by duration of follow-up: a meta-regression of randomised controlled trials. The Lancet Infectious Diseases. 2019;19(7):717-27

Input parameters:

Vaccine prices (vaccine only),wastage rates, Health system costs per dose, health care costs

	Base case	Low	High	Source
Vaccine price per dose				
BioFarma RVV, including delivery to provinces (7%)	$2.14			BioFarma - informed estimate
Imported RVV (incl. Int. handling and delivery) and delivery to provinces (7%)	$1.75			GAVI informed estimates
Wastage (single dose presentation)	4%	1%	10%	GAVI indicative wastage and expert opinion
Health system costs per dose	$1.32	$1.02	$3.77	Portnoy A. et al., 2020 (2019 USD)
Healthcare costs				
Cost per hospitalised RVGE case (health sector perspective)	$98.80	$43	$156.60	At Thobari et al 2021
Household cost per hospitalised RVGE case	$14.80			At Thobari et al 2021
Cost per RVGE outpatient visit (health sector perspective)	$7.60	$3.3	$11.90	At Thobari et al 2021
Cost per hospitalised intussusception case	$584			BPJS tariff

There is uncertainty in the future purchase price of the vaccines. In order to explore the potential impact of different prices, we ran two scenarios for each of higher pricing for each vaccine: $5 per dose and $10 per dose. PAHO have purchased rotavirus vaccines for USD6.50 per dose (excluding international handling and delivery), which broadly informed the selection of prices for the scenario analysis.

https://www.gavi.org/sites/default/files/2021-03/Gavi-Rotavirus-vaccines-profiles-March-2021.pdf

Portnoy A, Vaughan K, Clarke-Deelder E, Suharlim C, Resch SC, Brenzel L, et al. Producing Standardized Country-Level Immunization Delivery Unit Cost Estimates. Pharmacoeconomics. 2020;38(9):995-1005

Cost Effectiveness Threshold

- An explicit CE threshold in not available for Indonesia
- WHO 2003: interventions that avert one DALY
  - less than one time GDP/capita income is very cost–effective
  - less than three times GDP per capita is cost–effective;
- For this analysis, ICERs are compared with
  - 0.25xGDP per capita, 0.5xGDP/capita, and 1.0xGDP/capita.
  - The GDP per capita for Indonesia 2020 is USD 3870

Potential Impact of Implementation RVV in Indonesia

	No vaccination	RVV Program	Difference
Cases (in thousands)	22,917	15,600	7,317
Non-severe RVGE	19,213	13,249	5,964
Severe RVGE	3,660	2,307	1,352
Intussusceptions	44	44	0
Visits (in thousands)	18,298	12,445	5,853
Non-severe RVGE	15,371	10,600	4,771
Severe RVGE	2,928	1,846	1,082
Hospitalizations (in thousands)	1,419	910	509
Severe RVGE	1,377	868	509
Intussusception	42	42	0
Deaths (in thousands)	46	29	17
Severe RVGE	45	28	17
Intussusception	2	2	0
DALY (in thousands)	1,208	786	422

Results - Potential Impact of Implementation RVV in Indonesia on Heath Care Costs

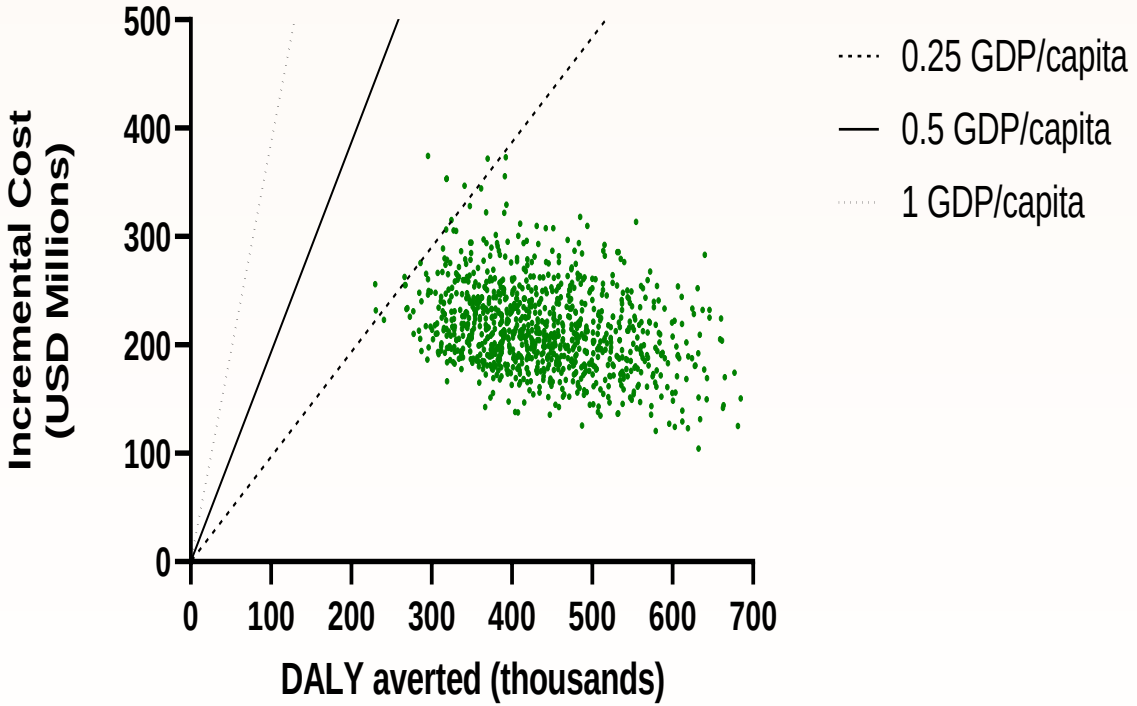
	No vaccination	RVV Program	Difference
Societal perspective	276	190	86
Visits	119	82	37
Hospitalization	157	108	49
Healthcare sector perspective	259	179	80
Visits	119	82	37
Hospitalization	140	97	43
Vaccine program costs	0	282.6	-283

Costs are in USD million

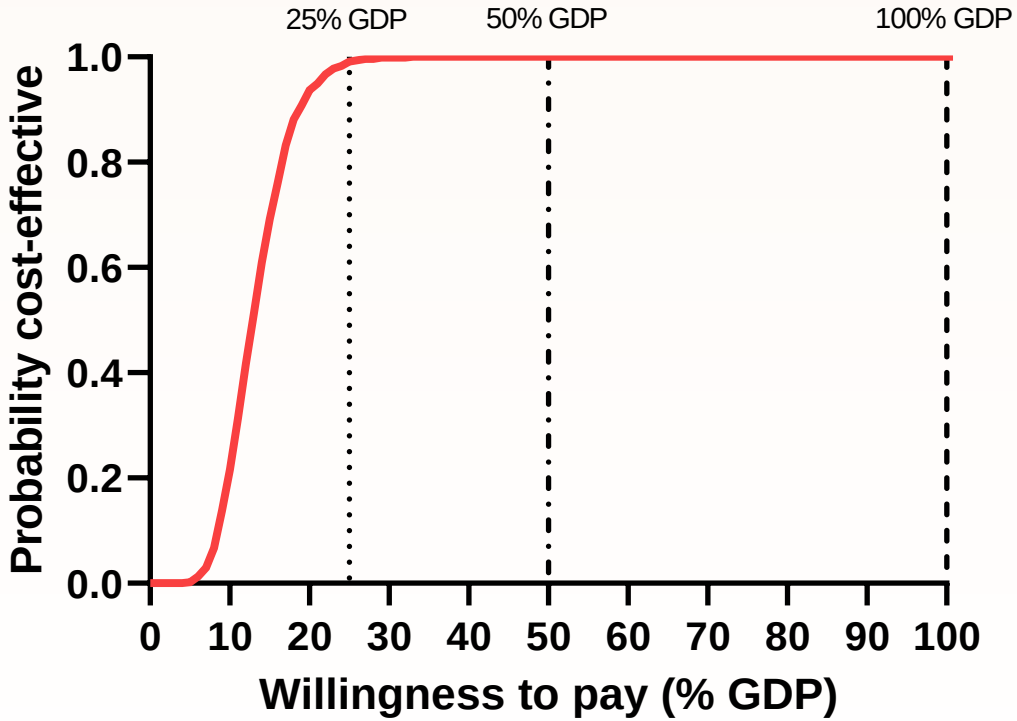
ICER of RVV in Indonesia

	No vaccination	RVV Program	Difference
Societal Perspective (USD million)			
Vaccine program costs	0	283	283
Health care costs	276	190	86
Incremental costs			196
Healthcare perspective (USD million)			
Vaccine program costs	0	283	283
Health care costs	259	179	80
Incremental costs			202
DALY (in thousands)	1,208	786	422
		ICER (Costs per DALY, in USD)	% of GDP
Societal Perspective (USD)		464	12%
Healthcare perspective (USD)		479	13%

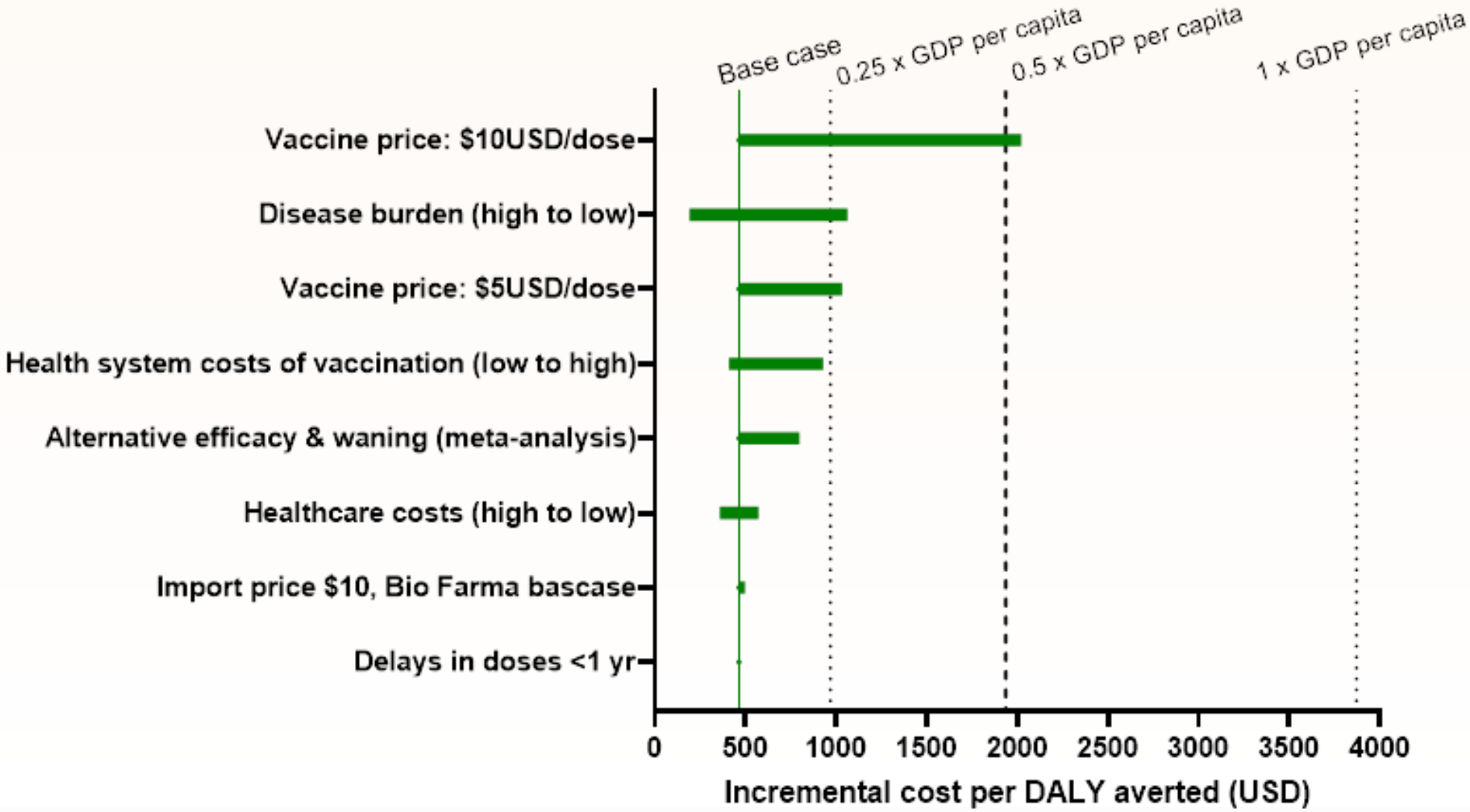
CEA Plane of RVV program compared to no vaccination (societal perspective).



Probability RVV program is cost-effective compared to no vaccination



Sensitivity Analysis of RVV Program vs. No Vaccination



Conclusion

We estimated that RVV may lead to a reduction of clinic visits (32%), hospitalization (36%) and death (36%) due to RVGE in children under five years of age in Indonesia.

Compared to no vaccination, introduction of RVV into the NIP across neonates and infants in Indonesia is likely to be highly cost-effective (below 0.25 of GDP per capita of Indonesia) from both a societal and health sector perspective

Collaborators

- Center for Child Health, Pediatric Research Office, Faculty of Medicine, Public Health and Nursing, UGM, Yogyakarta, Indonesia
  - Yati Soenarto, Jonathan Hasian Haposan, Asal Wahyuni
- Murdoch Children's Research Institute (MCRI) & Department of Paediatrics, University of Melbourne, Australia
  - Julie Bines, Emma Watts
- School of Population and Global Health, University of Melbourne, Parkville, Australia
  - Natalie Carvalho
- PATH Center for Vaccine Innovation and Access, Geneva, Switzerland
  - Frederic Debellut
- Department of Health Services Research and Policy, Faculty of Public Health and Policy, London School of Hygiene & Tropical Medicine, London, UK
  - Andrew Clark
- ITAGI Ministry of Health Indonesia
  - Sri Redzeki Hadinegoro, Julita Sari, Mardiati Nadjib

Terima Kasih

"Children are our greatest treasure, they are our future" – Nelson Mandela

Thank you very much for your kind attention