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Review Article

Efficacy of rotavirus vaccines in Indonesia: A review of genotype distribution and impact

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Abstract

Rotavirus remains the leading cause of diarrhea among children under five years of age, with an incidence of 31.1–90.9% in Indonesia. Initially, a rotavirus vaccination program was introduced in several provinces of Indonesia in 2022, which would be conducted nationally. This review provides information on the rotavirus genotype distribution in Indonesia, efficacy and effectiveness data of the rotavirus vaccine, and an update on the status of rotavirus vaccine implementation worldwide. The results show a varied distribution of G and P genotypes from 1978 to 2018, with G1–G3, G9, P[4], P[6], and P[8] as the prevalent genotypes, followed by a small proportion of G4, P[9], P[10], and P[11]. Three rotavirus vaccines, which are prequalified by the World Health Organization (WHO) and available in Indonesia, showed an efficacy of 17.6–76.9% in high-mortality countries. The Indonesian government procured ROTAVAC with a G9P[11] genotype for the national immunization program, which showed 31.3–69.1% protective efficacy against severe gastroenteritis caused by other strains. This review suggested that the decision to choose the rotavirus vaccine for the national program should take into account the country's prevalent circulating genotype and the vaccine's efficacy against severe diarrhea. The use of a pentavalent rotavirus vaccine with high efficacy in high-mortality countries can be regarded as the prime choice for the program. Another alternative is the rotavirus vaccine, which showed efficacy data in multiple high-mortality countries. In addition, regular surveillance of the rotavirus genotypes and the clinical manifestations of diarrhea are necessary to design vaccination strategies in Indonesia.

Keywords: Review, rotavirus, vaccine, vaccination, Indonesia

Introduction

Diarrheal disease ranked as the third leading cause of sepsis-related mortality in children under five years old in 2017, underscoring its critical impact on child health globally [1]. Among the pathogens contributing to diarrheal disease, rotavirus remains a predominant etiological agent in early childhood, particularly affecting children in this vulnerable age group [2]. Data from a five-year national study conducted in Australia (1998–2003) highlighted the significant burden of rotavirus, with over 10,000 hospitalizations, 22,000 emergency department visits, and 115,000 consultations with general practitioners annually among children under five years [3]. The global burden is similarly substantial. In 2016, rotavirus caused approximately 4.9 million and 29 million diarrheal cases in Western Europe and Southeast Asia, respectively, with an estimated 129,000 deaths globally among children under five, representing a small but significant fraction of the 258 million cases recorded that year [4]. Notably, rotavirus infections persist even in

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Received: November 4, 2024 - Accepted: January 21, 2025 - Published online: February 10, 2025

developed nations with advanced sanitation systems, illustrating the virus's resilience and widespread nature.

In developing regions, particularly in Asia and Africa, the burden of rotavirus-related gastroenteritis is markedly higher due to limited access to healthcare infrastructure and high population densities of young children [5]. Indonesia, home to approximately 22 million children under five (around 8% of its total population), faces a considerable public health challenge due to rotavirus [6]. Diarrhea remains the leading cause of death in this demographic, accounting for 10.3% of mortality in children under five [7]. A surveillance study conducted in 2015 across one rural and two urban hospitals in Indonesia reported that 54.93% of 406 hospitalizations for acute gastroenteritis were attributable to rotavirus infection [8]. Additionally, a review consisting of 33 studies spanning 1972–2018 indicated that the rotavirus positivity rate among children with acute gastroenteritis ranged from 31.1% to 90.9%, with clinical manifestations predominantly including diarrhea, vomiting, fever, and dehydration [9]. Severe dehydration was a common complication, particularly among hospitalized cases, with rates ranging from 60% to 100% [9].

To combat the high disease burden, the World Health Organization (WHO) recommended the inclusion of rotavirus vaccines in national immunization programs (NIPs) in 2009 [10]. By March 2024, 126 countries had adopted rotavirus vaccines into their immunization schedules [11]. In Indonesia, the phased introduction of the rotavirus vaccine began in 2022, targeting 21 high-risk districts across 18 provinces, with a three-dose schedule starting at 2–6 months of age and a minimum four-week interval between doses [12,13]. By August 2023, the Ministry of Health expanded the program to the national level, marking a significant public health milestone [14].

The effectiveness of rotavirus vaccination depends not only on coverage rates but also on the circulating rotavirus genotypes within a population [15]. Globally, the predominant genotypes include G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8], with emerging genotypes such as G12P[6] and G12P[8] being reported [16]. In Indonesia, studies have identified both prevalent and uncommon genotypes, including non-typeable and mixed strains, highlighting considerable regional variability [8,17-33]. This genetic diversity underscores the importance of understanding rotavirus strain distribution before and during vaccine implementation [34]. Given the critical need for robust data on efficacy, safety, and genotype distribution, the aim of this review was to provide comprehensive insights into the circulating rotavirus genotypes in Indonesia, the characteristics of available vaccines, and updates on the global progress of rotavirus vaccine introduction.

Rotavirus genotype distribution in Indonesia

The distribution of rotavirus genotypes across several provinces in Indonesia, derived from 15 studies spanning 1978 and 2018, is illustrated in **Figure 1A** and **Figure 1B**. During 1978–1979, the only rotavirus study ever conducted was only typed the G genotype [17]. During the initial study period (1978–1979), only the G genotype was typed, with G3 identified as the predominant strain, accounting for 52.5% of G genotypes. In contrast, G4 (35.6%), G2 (8.5%), and G1 (1.7%) were detected at lower frequencies [17].

Two decades later, between 2004 and 2009, G1 emerged as the dominant genotype in Yogyakarta (55.0%) and West Papua (75.0%) [18-22]. Simultaneously, G9 was the most prevalent genotype in South Sumatra (62.5%) [22]. P[6] was commonly detected in South Sumatra, Jakarta, and West Papua, while P[8] predominated in Yogyakarta, representing 69.6% of the total P genotypes [19].

From 2010 to 2018, G3 was again the most frequently identified genotype in West Java (50.0%), Yogyakarta (98.3%), and East Java (35.0%) [23-25,35,36]. G1 dominated in West Nusa Tenggara (82.0%), while G2 was exclusive to East Nusa Tenggara (100%) [26, 27, 37]. Equine-like G3 was first detected during this period, notably in South Sumatra (50.0%) and West Papua (100%), alongside equine-like P[6] in the same regions, accounting for South Sumatera (50.0%) and West Papua (91.3%) [37]. P[8] remained prevalent in four provinces, including West Java (80.0%) and Yogyakarta (93.8%), whereas P[4] was most common in Riau (31.8%) and East Nusa Tenggara (100%) [23-28,35-37].

Aman et al. Narra J 2025; 5 (1): e1681 - http://doi.org/10.52225/narra.v5i1.1681

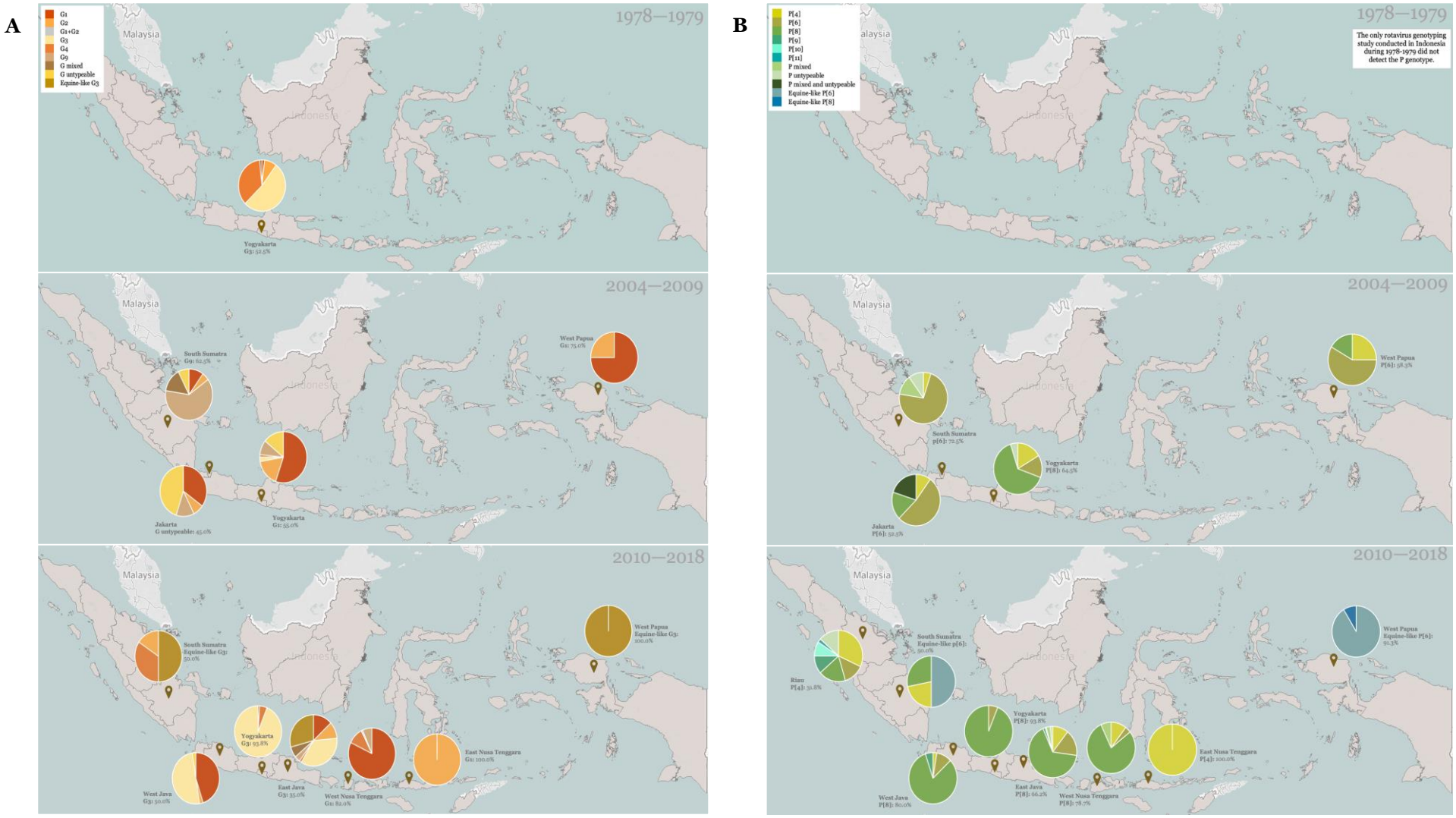

Figure 1. Distribution of rotavirus G (A) and P (B) genotypes between 1978 and 2018 in Indonesia [17-28,35-37].

Pooled data from six multicenter studies across seven provinces (South Sumatra, Jakarta, West Java, Yogyakarta, Bali, West Nusa Tenggara, and South Sulawesi) revealed the prevalence of G1 (18.79%), G2 (15.69%), G9 (14.78%), and mixed G genotypes (28.92%) between 2004 and 2009 [8,29-33]. The P genotypes identified included P[4] (15.35%), P[6] (19.99%), P[8] (23.56%), and untypeable or negative strains (36.53%) [8,29-33]. Between 2010 and 2018, G1 (60.58%), G3 (24.25%), and P[8] (79.44%) became the dominant genotypes (**Figure 2A** and **Figure 2B**) [8,29-33]. Reverse transcriptase polymerase chain reaction (RT-PCR) was implemented to detect the G and P genotypes, however particular samples yielded the mixed type of genotypes, the untypeable genotypes, or negative results for both G and P genotypes [8,29-33].

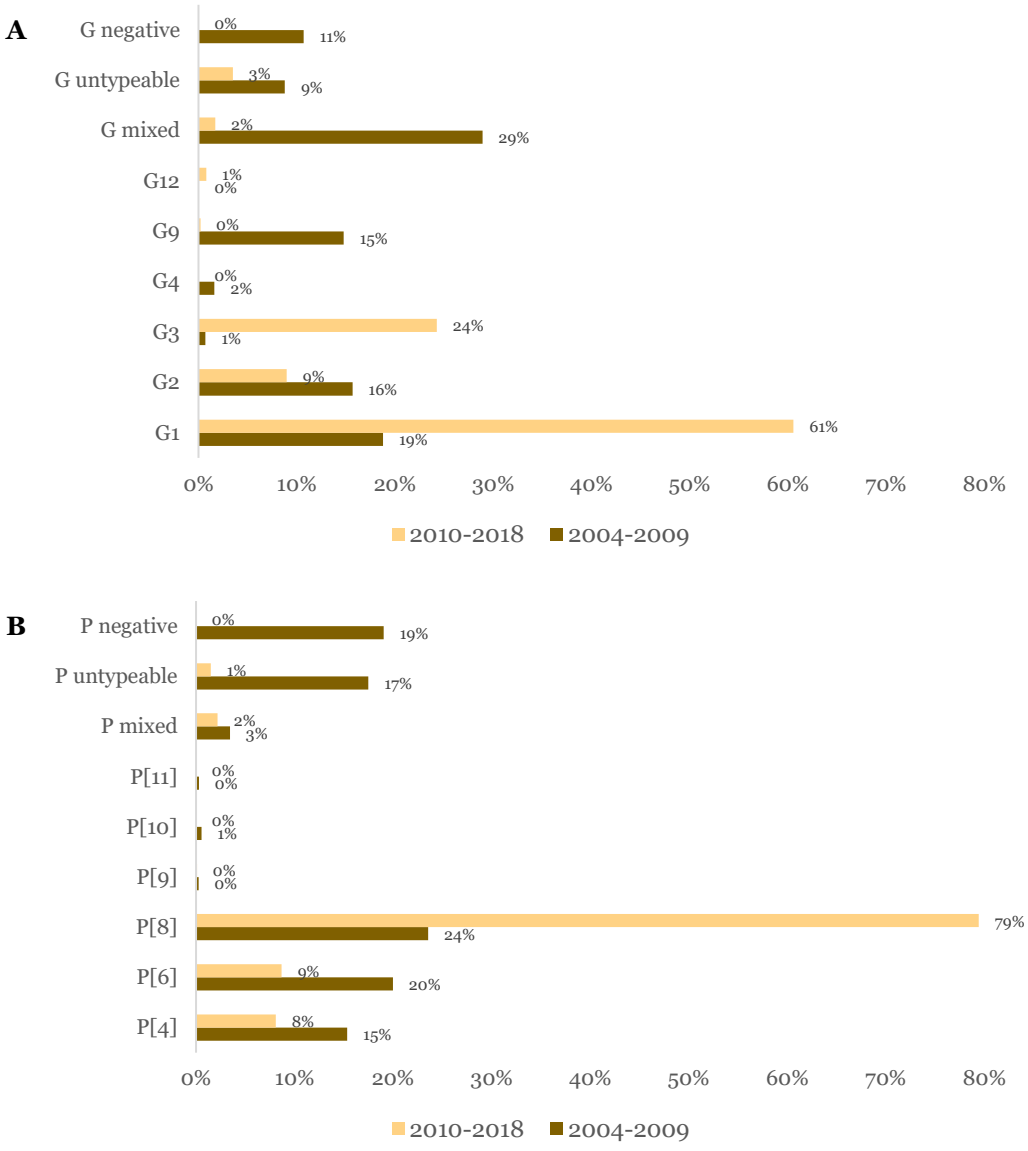

Figure 2. Distribution of G genotypes (A) and P genotypes (B) of rotavirus in Indonesia based on pooled data from six multicenter studies between 2004 and 2018 [8,29-33]. The G and P negative results were detected by RT-PCR [33].

A comprehensive review of 21 genotyping studies highlighted that the predominant G genotypes throughout 1978–2018 were G1, G2, G3, and G9, with G4 detected at lower frequencies [9]. P[4], P[6], and P[8] were the most frequently identified P genotypes, while P[9], P[10], and P[11] appeared infrequently [9]. Throughout 2004–2018, the G1, G2, and P[8] genotypes were the prevalent genotypes [9]. However, G3 became the predominant strain in 1978–1979 and reemerged in 2010–2018 [9]. Notably, G3, which was dominant in 1978–1979, reemerged during 2010–2018 alongside the sustained circulation of P[4]. During 2004–2009, G1, G2, G9, and P[6] were prevalent, with P[8] maintaining dominance [9]. The dynamic shifts in genotype distribution underscored the emergence of new strains over time.

Ongoing rotavirus surveillance is needed for monitoring the prevalence and antigenic variability of emerging genotypes circulating worldwide to develop novel vaccines in the future [16]. The observed shifts in genotype distribution may be influenced by the population's acquired immunity to circulating strains [33,38]. Comprehensive surveillance should routinely include clinical data on diarrhea and genotypic analyses to monitor rotavirus dynamics in Indonesia [39]. Surveillance conducted before and after vaccination can provide valuable insights for optimizing vaccine strategies and detecting atypical strains responsible for diarrhea [39].

Rotavirus vaccines

Currently, six rotavirus vaccines are licensed globally, as presented in **Table 1**, comprising live-attenuated strains of human and/or animal sources, and are administered orally [40]. Four of these rotavirus vaccines, including RotaTeq (Merck Sharp & Dohme, Kenilworth, USA), ROTASIIL (Serum Institute of India, Pune, India), ROTARIX (GlaxoSmithKline Biologicals SA, Wavre, Belgium), and ROTAVAC (Bharat Biotech International Limited, Hyderabad, India) are available worldwide and prequalified by the WHO [41]. A WHO-prequalified vaccine indicates that it meets stringent standards for quality, safety, and efficacy, as validated by the WHO Expert Committee on Biological Standardization [42]. Furthermore, these vaccines fulfill the United Nations operational procurement criteria, ensuring their appropriateness for the target populations [42]. In addition, two rotavirus vaccines, Lanzhou Lamb Rotavirus (LLR) from the Lanzhou Institute of Biological Products (Lanzhou, China) and Rotavin-M1 from POLYVAC (Hanoi, Vietnam), are licensed for local use within China and Vietnam, respectively [43]. These vaccines are not available globally. The Gavi Vaccine Alliance has supported the procurement of ROTASIIL (Pune, India), ROTAVAC (Hyderabad, India), and ROTARIX (Wavre, Belgium) for use in low-income countries, enhancing access to these life-saving vaccines [44].

Efficacy and effectiveness data for rotavirus vaccines have been analyzed within the context of country stratification by the United Nations Children's Fund (UNICEF) based on child mortality levels [45]. Countries are classified into low-, medium-, and high-mortality categories based on the mortality rate of children under five years: low-mortality countries have fewer than 6.7 deaths per 1,000 children, medium-mortality countries report between 6.7 to 15.9 deaths per 1,000 and high-mortality countries have 15.9 or more deaths per 1,000 children [45,46]. Indonesia is classified as a high-mortality country with 24.6 fatalities per 1,000 children under the age of five [45]. Taiwan and Hong Kong are categorized as regions with low child mortality rates, further indicating the diversity in vaccine implementation and effectiveness across different global regions [47].

World Health Organization (WHO)-prequalified rotavirus vaccines

RotaTeq is a pentavalent human–bovine (WC3-G6P7[5]) reassortant vaccine, produced in Vero cells, offering broad cross-protection [48,49]. It consists of five human strain reassortants, incorporating outer capsid proteins VP4 (P1[8]) and VP7 (G1, G2, G3, and G4) that are critical for neutralization. The vaccine's inclusion of the P1[8] reassortant, which is prevalent in strains G1, G3, G4, and G9, enhances its efficacy across various rotavirus strains [49]. Efficacy trials have demonstrated that RotaTeq reduces severe rotavirus diarrhea by 96%, 79%, and 44% in low-, medium-, and high-mortality settings, respectively [46]. Among children under 12 months, the vaccine's effectiveness against laboratory-confirmed rotavirus was 86% in low-mortality countries and 66% in high-mortality countries [50]. Additionally, RotaTeq provides cross-genotype protection against G12P[8] strains, with a vaccine efficacy of 83% (95% confidence interval (CI): 57–93) [51]. Safety data from 82,502 participants across 14 global trials confirmed that RotaTeq did not increase the incidence of serious adverse events or intussusception, and it did not affect all-cause mortality significantly (RR: 0.97; 95%CI: 0.74–1.26) [46].

Table 1. Characteristics of currently licensed rotavirus vaccines

Vaccine trade name	Manufacturer	Strains	Doses	VVM	Storage and shelf life	Price in USD	Licensure (year)	References
Globally Licensed								
RotaTeq	Merck Sharp & Dohme (MSD), USA	Pentavalent human-bovine consist of G1, G2, G3, G4, and P1A[8] reassortant rotavirus vaccine	3	-	2°C–8°C for 24 months	3.20^	WHO prequalified (2008) Approved by FDA (2006), EMA (2006), and BPOM (2020)	[41,44]
ROTASIIL	Serum Institute of India, India	Pentavalent human-bovine consist of G1, G2, G3, G4, and G9 reassortant rotavirus vaccine	3	30	Vaccine: 2°C–8°C for 30 months, diluent: 2°C–8°C for 60 months, reconstituted vaccine: 2°C–8°C for up to 6 hours	0.95^ 0.95–1.55*	WHO prequalified (2018)	[41,44]
ROTASIIL-Liquid				7	2°C–8°C for 24 months	0.8–2.5^ 0.8–1.05*	WHO prequalified (2021)	[41,44]
ROTASIIL Thermo				250	25°C for 30 months	1.25–1.85*	WHO prequalified (2020)	[41,44]
ROTARIX	GlaxoSmithKline Biologicals SA, Belgium	Monovalent human rotavirus strain G1P[8]	2	14,17	2°C–8°C for 24 months	2.24–6.46^ 2.06–2.36*	WHO prequalified (2009) Approved by FDA (2008), EMA (2006), and BPOM (2017)	[41,44]
ROTAVAC	Bharat Biotech International Limited, India	Monovalent neonatal rotavirus strain G9P[11]	3	2,7	-20°C or below until the expiry date. 2°C–8°C for up to 6 months	0.6–2.0^ 0.6–0.85*	WHO prequalified (2018) Approved by BPOM (2023)	[41,44]
ROTAVAC 5D					2°C–8°C for 24 months	1.15–1.35^ 1.15*		[41,44]
Nationally Licensed								
Lanzhou Lamb Rotavirus (LLR)	Lanzhou Institute of Biomedical Products, China	Monovalent lamb rotavirus strain G10P[12]	5	-	-	-	China (2000)	[56]
Rotavin-M1	POLYVAC, Vietnam	Monovalent human rotavirus strain G1P[8]	2	-	-25°C to -15°C for 24 months and at 2°C–8°C for 2 months	-	Vietnam (2012)	[57]

-: Not applicable; BPOM: the Indonesian Food and Drug Authority (Badan Pengawas Obat dan Makanan); EMA: European Medicines Agency; FDA: US Food and Drug Administration; UNICEF: United Nations Children's Fund; VVM: Vaccine vial monitor; WHO: World Health Organization
^price per dose per product per supplier per calendar year, based on supply agreement; data was obtained from UNICEF, last updated on 22 February 2024
*2024 price per dose; data was obtained from Detailed Product Profiles for WHO prequalified vaccines Gavi The Vaccine Alliance 2024 price

ROTASIIL, another pentavalent rotavirus vaccine, also uses human–bovine reassortants and is administered orally in a three-dose regimen [52]. The vaccine contains five rotavirus reassortants, with the G6P[5] bovine strain serving as the backbone. This reassortant incorporates human strain genes G1, G2, G3, G4, and G9 [52]. Initially lyophilized to maintain stability in acidic gastric conditions, ROTASIIL is now available in lyophilized, thermostable, and liquid formulations [44,52,53]. Efficacy trials in high-mortality countries showed variable results: a trial in Niger (2014) demonstrated a 66.7% efficacy against severe rotavirus gastroenteritis, while another trial in India reported a 36% efficacy [54,55]. Safety analyses indicated that ROTASIIL had minimal to no impact on all-cause mortality, intussusception, or serious adverse events, demonstrating a generally favorable safety profile [54,55].

ROTARIX, a live-attenuated rotavirus vaccine, is derived from a human G1P[8] strain isolated from an infant with gastroenteritis [40]. The strain is propagated in Vero cells and is formulated as an oral suspension available in various delivery forms, including powder with solvent, prefilled applicator, squeezable tube, and multi-monodose squeezable tube [40,44,58,59]. Clinical trials demonstrated its efficacy against severe rotavirus diarrhea across varying mortality settings: 90% in low-mortality countries, 78% in medium-mortality, and 35% in high-mortality countries after two years of follow-up [46]. Real-world effectiveness was highest in low-mortality countries (86% in children aged 12–23 months), compared to 54% and 58% in medium- and high-mortality settings, respectively [50]. A United States-based study further showed ROTARIX's effectiveness at 74% (95%CI: 40–89) against G3P[8] [51]. Despite its efficacy, a systematic review found no significant difference between ROTARIX and placebo in all-cause mortality, risk of serious adverse events, or intussusception [46].

ROTAVAC, another WHO-prequalified vaccine, is a monovalent vaccine developed from the human neonatal G9P[11] strain (116E) identified during outbreaks of asymptomatic neonatal infection in India [60]. The G9P[11] strain contains a combination of bovine (1) and human (10) rotavirus genes, enhancing its adaptation to the intestinal environment [44]. Available in frozen and liquid (ROTAVAC 5D) formulations, the frozen version requires storage below -20°C but remains stable at 2°C–8°C for up to six months [44]. The liquid formulation can be stored at 2°C–8°C for up to 24 months but should not be frozen [61]. In a clinical trial conducted in India, ROTAVAC showed a vaccine efficacy of 53.6% against severe rotavirus gastroenteritis in infants by the age of one year, with efficacy ranging from 31.3% to 69.9% against various rotavirus genotypes [62]. A study in India showed that ROTAVAC and ROTASIIL can be used interchangeably for routine immunization and resulted in a non-inferior seroresponse compared with a single vaccine regimen (ROTAVAC only or ROTASIIL only) [63]. The safety data from ROTAVAC trials in India showed no significant difference in the number of serious adverse events (RR: 0.93; 95%CI: 0.85–1.02) and deaths (RR: 0.88; 95%CI: 0.50–1.56) [46]. In addition, between 2005 and 2015, intussusception rates were documented as 0.13% in the vaccine group and 0.11% in the placebo group [46].

Locally licensed vaccines

The LLR is an oral monovalent rotavirus vaccine which only available in China [64]. It is a live-attenuated lamb rotavirus strain G10P[15], which is produced in neonatal calf kidney cells [64]. Despite its widespread use, no efficacy data are available since placebo-controlled phase III trials were never conducted [46]. However, case-control studies in Chinese children under five estimated vaccine effectiveness against rotavirus diarrhea to range from 35% to 77% [65-68]. Notably, enhanced protection was observed against moderate diarrhea caused by the G3 serotype [65].

In Vietnam, a locally available monovalent rotavirus vaccine (Rotavin-M1) was formulated using strain G1P[8] and licensed since 2012 [69]. It is derived from a live-attenuated G1P[8] strain first isolated from children with acute gastroenteritis in Vietnam and cultivated in Vero cells [70]. Although the master seed for this vaccine was detected to be free from porcine circovirus DNA, the pilot vaccine lot was not tested for porcine circovirus [71]. An observational and case-control study from 2016 to 2021 showed that this vaccine could prevent 57% of moderate-to-severe rotavirus hospitalizations among children aged 6–23 months in Vietnam [72]. Additionally, a 2009–2010 study confirmed its immunogenicity and safety, showing no

significant differences in fever, diarrhea, vomiting, or irritability compared with ROTARIX, another monovalent vaccine containing the same strain [71]. The immunogenicity data showed that the rates of IgA seroconversion after a two-dose schedule of Rotavin-M1 vaccination in low- and high-titer groups were 61% (95%CI: 45–76) and 73% (95%CI: 58–88), respectively [71]. Similarly, the ROTARIX group showed an IgA seroconversion rate of 58% (95%CI: 42–73) [71]. Furthermore, 65% of ROTARIX recipients exhibited virus shedding after the first dose, compared to 44%–48% among Rotavin-M1 recipients ($p<0.05$) [71].

Efficacy and effectiveness data for rotavirus vaccines are summarized in **Table 2** and **Table 3**. The high incidence of rotavirus infection is associated with a foreseeable reduction in vaccine efficacy estimates [73]. Unvaccinated children may acquire natural immunity; therefore, this phenomenon should be taken into account when comparing efficacy estimates across settings [73]. In low-mortality countries, pentavalent and monovalent vaccines showed comparable effectiveness, exhibiting significant protection against medically attended rotavirus infections [51,74,75]. In Taiwan, from 2014 to 2017, pentavalent (RotaTeq) and monovalent (ROTARIX) vaccines demonstrated over 80% effectiveness in children under 36 months, though effectiveness declined by 1.2%–32.6% in older children [76]. Similarly, a review of six rotavirus studies in Indonesia revealed that rotavirus infection peaks between 6 and 23 months of age, which then declines and is occasionally detected up to five years of age [21,22,29,77-79].

Upcoming rotavirus vaccines

Aside from the currently available rotavirus vaccines, novel vaccines have been developed, including RV3-BB and P2-VP8 [80]. The RV3-BB (human neonatal strain, G3P6) vaccine, derived from a human neonatal strain (G3P[6]), represents the first rotavirus vaccine developed by Bio Farma in Indonesia. It recently completed a phase IIb trial, demonstrating significant immunogenicity [81]. Endorsed by the Indonesian government, RV3-BB is a monovalent, live-attenuated oral vaccine, with support stemming from its demonstrated ability to reduce gastroenteritis cases among neonates and infants in Yogyakarta and southern Central Java [81]. A trial indicated high vaccine response rates, with seroresponse achieved in 94% of neonates and 99% of infants; however, vaccine efficacy was notably lower, at 75% in neonates and 51% in infants [81]. Vaccine response was assessed via seroresponse, defined as a threefold increase in IgA or neutralizing antibody titers four weeks post-vaccination, and detection of vaccine strain shedding in stool samples collected on days 3–7 post-vaccination using RT-PCR and sequencing techniques [81]. Adverse events occurred at similar rates across all study groups, and no cases of intussusception were observed within the 21-day risk window [81]. Another trial also reported that the three doses of RV3-BB were immunogenic in neonates and well tolerated among adults, children, and neonates [82].

The P2-VP8 vaccine is a trivalent subunit protein vaccine targeting P[4], P[6], and P[8] genotypes, developed by the Program for Appropriate Technology in Health (PATH) [80]. Unlike traditional oral vaccines, P2-VP8 is a parenteral, nonreplicating vaccine designed to address the limited efficacy of oral vaccines in low- and middle-income countries (LMICs) [80,83]. A clinical trial in South Africa demonstrated a promising anti-P2-VP8 IgG and neutralizing antibody response among the three P types [84]. The reduced efficacy of oral rotavirus vaccines in LMICs is attributed to several factors, including maternal antibody interference, micronutrient deficiencies, gut dysbiosis, co-infections, enteric dysfunction, and genetic variability [85, 86]. Notably, integrating P2-VP8 administration into existing childhood immunization programs, such as those delivering the Diphtheria-Tetanus-Pertussis (DTP) pentavalent vaccine, could enhance coverage and reduce immunization delivery costs [87]. This approach can potentially reduce the delivery cost of the immunization program [87].

Table 2. Efficacy of licensed rotavirus vaccines

Vaccine trade name	Country mortality rate^	Country	Percentage of efficacy (95%CI) *	Follow-up period	Reference
Globally licensed					
RotaTeq	High-mortality	Bangladesh	42.7 (10.4–63.9)	up to 2 years	[88]
		Vietnam	63.9 (7.6–90.9)		[88]
		Ghana	55.5 (28.0–73.1)	up to 21 months	[88]
		Kenya	63.9 (-5.9–89.8)		[88]
		Mali	17.6 (-22.9–45.0)		[88]
	Medium-mortality	China	78.9 (59.1–90.1)	2 years	[89]
	Low-mortality	Finland, the U.S	100 (13.0–100)	1 year	[90]
		The U.S	100 (43.5–100)	1 year	[91]
		Finland	98.3 (90.2–100)	up to 2 years	[92]
		Japan	100 (55.4–100)	25 months	[93]
	High-, medium-, low-mortality	Belgium, Costa Rica, Finland, Germany, Guatemala, Italy, Jamaica, Mexico, Puerto Rico, Sweden, Taiwan, the US	98.0 (88.3–100)	2 years	[94]
ROTASIIL	High-mortality	Niger	66.7 (49.9–77.9)	2 years	[54]
		India	34.6 (9.6–52.7)	2 years	[55]
ROTARIX	High-mortality	South Africa	76.9 (56.0–88.4)	1st year of life	[95]
		Malawi	48.4 (19.2–68.3)	1st year of life	[95]
	Medium-mortality	China	72 (54.1–83.6)	2 years	[96]
	Low-mortality	Hong Kong, Singapore, Taiwan	96.1 (85.1–99.5)	2 years of age	[97]
		Hong Kong	95.6 (73.1–99.9)	2 years of age	[98]
		Japan	91.6 (62.4–99.1)	2 years of age	[99]
ROTAVAC	High-mortality	India	53.6 (35.0–66.9)	2 years of age	[62]
Locally licensed					
Lanzhou Lamb Rotavirus (LLR)	-	-	-	-	-
Rotavin-M1	-	-	-	-	-

-: Not applicable
^Categorization was based on mortality rate for children younger than 5 years from the UNICEF on “levels and trends in child mortality”
*% of rotavirus efficacy for severe rotavirus gastroenteritis

Table 3. Effectiveness of licensed rotavirus vaccines

Vaccine trade name	Country mortality rate^	Country	Percentage of vaccine effectiveness (95%CI)	Study endpoints	Reference
Globally licensed					
RotaTeq	High-mortality	Burkina Faso, Nicaragua, Rwanda	66 (51–76)	Children <12 months Laboratory-confirmed rotavirus	[50]
	Medium-mortality	China	85 (50–95)*	3 doses Any severity of rotavirus gastroenteritis	[100]
	Low-mortality	Finland	92.1 (50.0–98.7)**	3 doses	[101]
		Australia, Israel, the US	86 (76–92)	Hospitalized rotavirus gastroenteritis Children <12 months Laboratory-confirmed rotavirus	[50]
ROTASIIL	-	-	-	-	-
ROTARIX	High-mortality	Bolivia, Botswana, Ghana, Kenya, Malawi, Philippines, South Africa, Tanzania, Zimbabwe	63 (54–70)	Children <12 months Laboratory-confirmed rotavirus	[50]
	Medium-mortality	Armenia, Brazil, Colombia, El Salvador, Moldova	77 (66–85)	Children <12 months Laboratory-confirmed rotavirus	[50]
	Low-mortality	Australia, Belgium, the US, the UK	86 (81–90)	Children <12 months Laboratory-confirmed rotavirus	[50]
ROTAVAC	-	-	-	-	-
Locally licensed					
Lanzhou Lamb Rotavirus (LLR)	Medium-mortality	China	34.9 (5.3–55.3)*	1 dose All gastroenteritis cases	[102]
Rotavin-M1	High-mortality	Vietnam	57 (39–70)*	2 doses Moderate-to-severe diarrhea	[72]

-: Not applicable
^Categorization was based on mortality rate for children younger than 5 years from the UNICEF on “levels and trends in child mortality”
*Adjusted vaccine effectiveness
**Crude vaccine effectiveness

Update on the status of rotavirus vaccination worldwide

With no specific antiviral treatment available for rotavirus gastroenteritis, vaccination remains the most effective preventive measure [103]. Although vaccine effectiveness is lower in developing countries, the potential impact is substantial due to the high disease burden and mortality rates in these regions [104]. Routine rotavirus immunization programs have had a profound impact on more than 100 countries [56]. According to the WHO's Global Rotavirus Surveillance Network (GRSN), data from 69 countries show a nearly 40% reduction in hospitalized rotavirus cases following vaccine introduction [105].

Currently, more than 66 million (51%) children in 126 countries have received rotavirus vaccines as part of their national/subnational immunization programs (**Figure 3**) [11]. Seventeen additional countries plan to introduce the vaccine, while 50 remain undecided [11]. In Venezuela, the rotavirus vaccination program has been suspended since 2018 [106, 107]. Globally, four rotavirus vaccines, including ROTARIX, RotaTeq, ROTAVAC, and ROTASIIL, are widely used or planned for use in 194 countries [107]. ROTARIX was the most used or planned to-be-used rotavirus vaccine in 87 countries [107]. Moreover, 76 countries procured ROTARIX as the only vaccine, whereas 11 countries used it interchangeably with RotaTeq [107]. Furthermore, RotaTeq was used or planned to be used in 24 countries [107]. Meanwhile, 11 countries used ROTAVAC, six countries used ROTASIIL, and one country (India) used ROTAVAC and ROTASIIL interchangeably in their vaccination programs [107]. The Indonesian government procured ROTAVAC containing the G9P[11] strain for their rotavirus immunization program [12].

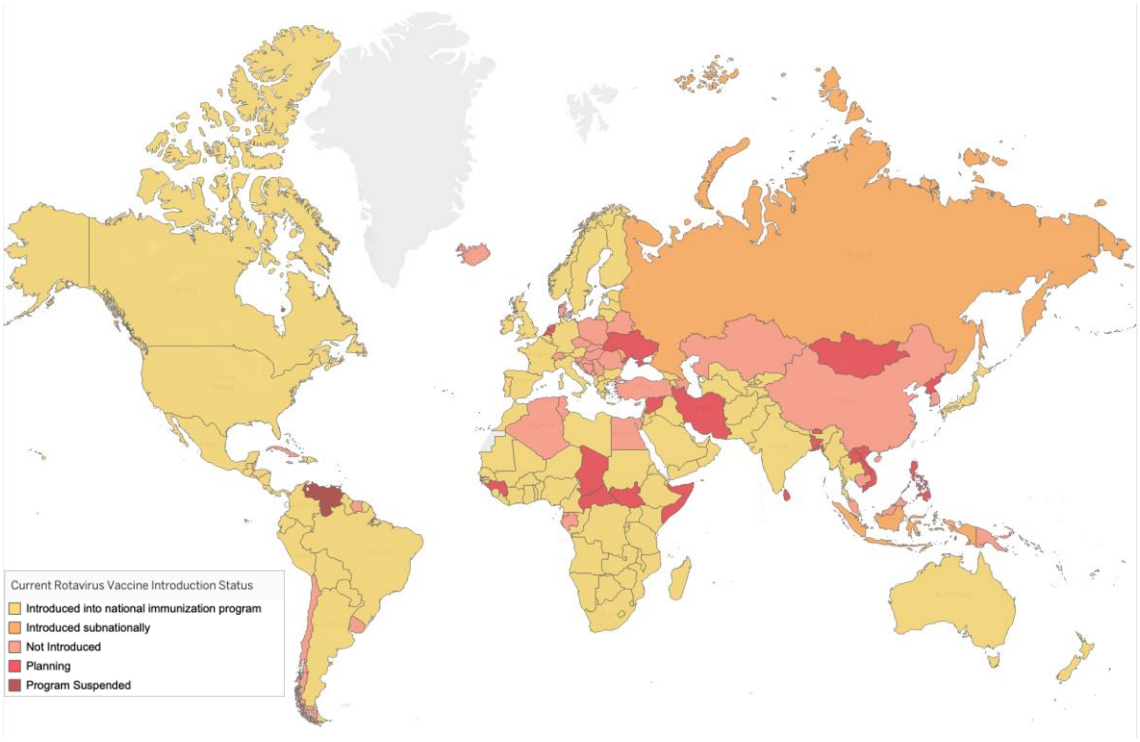

Figure 3. Global update of rotavirus vaccine introduction to the national immunization program (NIP) by 2024.

Aside from Indonesia, ROTAVAC is being used in Benin, Gambia, Ghana, India, Kenya, Nigeria, Senegal, Tanzania, Timor-Leste, Zambia, and Zimbabwe [107]. In Indonesia, a review revealed a varied distribution of G and P genotypes within the period of 1978–2018 with G1–G3, G9, P[4], P[6], and P[8] as the prevalent genotypes, followed by a small proportion of G4, P[9], P[10], and P[11] [9]. G9 is one of the most common rotavirus strains circulating in Indonesia that was initially detected in 2004 and occasionally occurred until 2015 [9]. Meanwhile, P[11] was identified as a less frequent genotype [9]. The efficacy data of ROTAVAC, including its cross-protective efficacy toward other strains, were only available among Indian children [62]. In addition to the context of genotype distribution, the predominant genotypes circulating in Indonesia and Ghana differed from those in India. In India, the predominant G and P genotypes

from 2012 to 2020 in the pre and postvaccine period were G1, G2, G3, G9, P[4], P[6], and P[8] [108]. In Ghana, G1, G2, G3, P[6], and P[8] were identified as the prevalent VP7 and VP4 genotypes in the prevaccine period between 2009 and 2012 [109]. These differences highlight the need for tailored vaccine selection in the NIP. A multivalent vaccine offering broad genotype coverage and high efficacy in high-mortality regions is preferable. Where procurement of multivalent vaccines is not feasible, alternatives should demonstrate efficacy in multiple high-mortality settings.

Conclusion

More than 100 countries worldwide have introduced rotavirus vaccines into their NIP. Vaccination can effectively prevent and control rotavirus gastroenteritis in many countries, which accounted for an approximately 40% relative reduction of hospitalized rotavirus cases following the introduction of vaccines. Four of the six available vaccines have been prequalified by the WHO, whereas the other two are locally available in China and Vietnam. Although RotaTeq, ROTARIX, and ROTAVAC are available in Indonesia, ROTAVAC has been used in the NIP since 2022. We need to bring this into concern because ROTAVAC was developed from genotype P[11], a less frequent genotype from 1978–2018 in Indonesia. Meanwhile, RotaTeq and ROTARIX contain strains that closely mimic the typical circulating rotavirus genotypes in Indonesia. Considering the shift of circulating rotavirus strains over the years, available vaccines should have cross-protective efficacy toward other strains. Moreover, a comprehensive rotavirus surveillance program should be implemented to monitor the dynamics of circulating rotavirus strains in Indonesia.

Ethics approval

Not required. However, this review obtained ethical clearance from the Medical and Health Research Ethics Committee Universitas Gadjah Mada (KE/FK/0170/EC/2024).

Acknowledgments

We express our gratitude to the Research Directorate of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, for providing language editing services.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This study received no external funding.

Underlying data

All data are available as part of the article.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilized at any stage of this study, including during data collection, analysis, visualization, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

How to cite

Aman AT, Patriani A, Mawarti Y. Efficacy of rotavirus vaccines in Indonesia: A review of genotype distribution and impact. Narra J 2025; 5 (1): e1681 - http://doi.org/10.52225/narra.v5i1.1681.

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