SCRIPTA SCORE Scientific Medical Journal Vol. 5 No. 2 (2023) 139-47

talenta PUBLISHER

SCRIPTA SCORE Scientific Medical Journal
Journal homepage: https://talenta.usu.ac.id/scripta

Effectiveness and Safety of Bovine Human Pentavalent Rotavirus Vaccine (BRV-PV) in Preventing Severe Acute Rotavirus Gastroenteritis (SRVGE): A systematic review of the experience in developing countries

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ARTICLE INFO

Article history:
Received 28 December 2023
Revised 26 February 2024
Accepted 28 February 2024
Available online 29 February 2024

E-ISSN: 2686-0864
P-ISSN: 2088-8686

How to cite:
Zefianto, Ansyori AR, Sarah. Effectiveness and Safety of Bovine Human Pentavalent Rotavirus Vaccine (BRV-PV) in Preventing Severe Acute Rotavirus Gastroenteritis (SRVGE): A systematic review of the experience in developing countries. SCRIPTA SCORE Sci Med J. 2024 Feb 29;5(2):139-47

https://doi.org/10.32734/scripta.v5i2.15201

ABSTRACT

Background: Severe acute rotavirus gastroenteritis (SRVGE) is the world's highest cause of children mortality, with symptoms of severe dehydrating diarrhea due to rotavirus (RV) infection. SRVGE provides a high economic burden, mostly in developing countries. Currently, three RV vaccines (Rotarix, RotaTeq, Rotavac) are licensed internationally by the World Health Organization (WHO) and are not yet applicable in developing countries. Hence, research shows the potential of BRV-PV in preventing RV infection in pediatrics, especially in developing countries. **Objective:** This review aims to analyze the effectiveness and safety of BRV-PV in developing countries. **Methods:** This systematic review includes studies from the ScienceDirect, PubMed, Elsevier, and Cochrane databases that met the inclusion and exclusion criteria. The search method uses the Boolean operator with the articles from the last ten years. Eight articles with a total of 9088 children were reviewed to analyze the effectiveness and safety of BRV-PV. **Result and Discussion:** Of all the studies involved, BRV-PV has effectively reduced the incidence of hospitalization and emergency cases due to SRVGE. Furthermore, BRV-PV is also safe for children in developing countries, proven by increased anti-RV IgA concentrations and minimal side effects. **Conclusion:** BRV-PV is more effective, safe, heat-stable, and affordable than the previous three RV vaccines in developing countries
Keyword: BRV-PV, Gastroenteritis, Rotavirus, Rotavirus Vaccine

ABSTRAK

Latar Belakang: Severe acute rotavirus gastroenteritis (SRVGE) merupakan penyebab kematian anak tertinggi di dunia dengan gejala diare dehidrasi parah akibat infeksi rotavirus (RV). SRVGE memberikan beban ekonomi yang tinggi, terutama di negara-negara berkembang. Saat ini, tiga vaksin RV (Rotarix, RotaTeq, Rotavac) dilisensikan secara internasional oleh World Health Organization (WHO) dan belum dapat diterapkan di negara-negara berkembang. Oleh karena itu, penelitian menunjukkan potensi BRV-PV dalam mencegah infeksi RV pada anak-anak, khususnya di negara berkembang. **Tujuan:** Ulasan ini bertujuan untuk menganalisis efektivitas dan keamanan BRV-PV dalam mencegah SRVGE. **Metode:** Tinjauan sistematis ini mencakup studi dari database ScienceDirect, PubMed, Elsevier, dan Cochrane yang memenuhi kriteria inklusi dan eksklusi. Metode pencariannya menggunakan operator boolean dengan artikel sepuluh tahun terakhir. Delapan artikel dengan total 9088 pediatri ditinjau untuk menganalisis efektivitas dan keamanan BRV-PV. **Hasil dan Pembahasan:** Dari semua penelitian yang terlibat, BRV-PV telah secara efektif mengurangi kejadian rawat inap dan kasus darurat akibat SRVGE. Selain itu, BRV-PV juga aman untuk anak-anak di negara berkembang, terbukti dengan peningkatan konsentrasi IgA anti-RV dan efek samping yang minimal. **Kesimpulan:** BRV-PV lebih efektif, aman, tahan panas, dan terjangkau dibandingkan tiga vaksin RV sebelumnya di negara berkembang..
Kata Kunci: BRV-PV, Gastroenteritis, Rotavirus, Vaksin Rotavirus

1. Introduction

Rotavirus (RV) is the most common cause of severe acute gastroenteritis in young children worldwide.[1] RV infections are a significant public health problem in developing countries because three-quarters of children get their first RV before 12 months, and many are infected more than once.[2] The diagnosis of SRVGE can be detected in stool specimens of children with gastroenteritis through antigen detection tests including enzyme-linked immunosorbent tests (ELISA) and commercially available immunochromatography tests in widespread use. Most of these tests have high sensitivity and specificity (90–95%).[2,3] Severe acute rotavirus gastroenteritis (SRVGE) is an important cause of death due to severe dehydrating diarrhea in children under five years, with an estimated more than 500,000 deaths annually or 29% of all deaths due to diarrhea.[3] SRVGE has been reported in 2 million hospitalizations and 25 million visits to the emergency department annually, most of which were in Asia and Africa.[4] In addition, SRVGE has also imposed a high economic burden in Asia, estimated to account for $2926,4 per year.[5]

Rehydration and food supply are the only supportive therapy for treating diarrhea as a clinical manifestation of SRVGE.[6] However, these supportive therapies are ineffective because they require high costs, high repetition rates, and cannot treat intestinal mucosal damage due to RV infection.[6] Therefore, RV vaccines have been introduced in the national immunization program; it would be a cost-effective measure to reduce morbidity and mortality due to SRVGE.[7,8]

Currently, three RV vaccines (Rotarix, RotaTeq, Rotavac) are licensed internationally by the World Health Organization (WHO).[7] However, their price remains a constraint for developing countries, and their availability is uncertain globally.[7] Although the WHO recommends universal immunization with RV vaccines, only 17% of young children in developing countries receive it.[8] In addition, the three RV vaccines have complicated storage operations and are prone to damage in developing countries due to the hot temperatures.[9] Therefore, it is necessary to establish alternative RV vaccines that are more cost-effective, applicable, and adaptive for developing countries that need them the most.

A new RV vaccine made by bovine-human reassortant technology (BRV-PV) has been developed and tested in developing countries.[10] BRV-PV is a live attenuated pentavalent RV vaccine containing five strains that cause 90% of cases of SRVGE worldwide.[10] This vaccine was found safe, heat-stable, cost-effective, immunogenic, and efficacious in clinical studies.[9,10] Although the BRV-PV has proven well-controlled clinical trials against SRVGE and reduced hospitalizations in developing countries, its effectiveness and safety data generated in a randomized controlled trial were not available publicly.

Here we report the effectiveness and safety of BRV-PV against SRVGE in developing countries. The primary objective was to evaluate the vaccine effectiveness of BRV-PV to reduce hospitalizations for severe dehydrating diarrhea due to SRVGE, and to increase the concentration of anti-RV immunoglobulin A (IgA) in serum blood at least 14 days following the third dose. The key secondary objective was the safety of BRV-PV for all adverse events (AEs) within 30 days after each dose.

2. Method

2.1 Study Design and Data Sources

This systematic review was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The following PICO criteria were used for selecting relevant studies: population (P), children who are susceptible to RV infection in developing countries; intervention (I), children receiving BRV-PV; comparison (C), children receiving RV vaccines other than BRV-PV (Rotavac, Rotarix, and Rotateq), and outcome (O), effectiveness and safety of BRV-PV against SRVGE in developing countries. All randomized controlled trial (RCT) studies were eligible for inclusion over 2013 until 2023. ScienceDirect, Pubmed, Elsevier, and Cochrane were used as search engine databases. Paid articles, publications in languages other than Indonesian and English, and research objects other than humans were excluded. The search keywords used were rotavirus AND BRV-PV AND rotavirus vaccine AND gastroenteritis.

2.2 Study Selection

Preliminary searches yielded 542 distinct references from ScienceDirect, 398 references from PubMed, 147 references from Elsevier, and 46 references from Cochrane. 656 articles were screened after the removal of duplicates. Those that did not match the inclusion criteria were excluded (Figure. 1). Subsequently, the full-text review of 25 articles was performed. Of these, 17 articles were further excluded on the basis of the exclusion criteria, leaving eight articles that met eligibility for the analysis (Figure. 1).

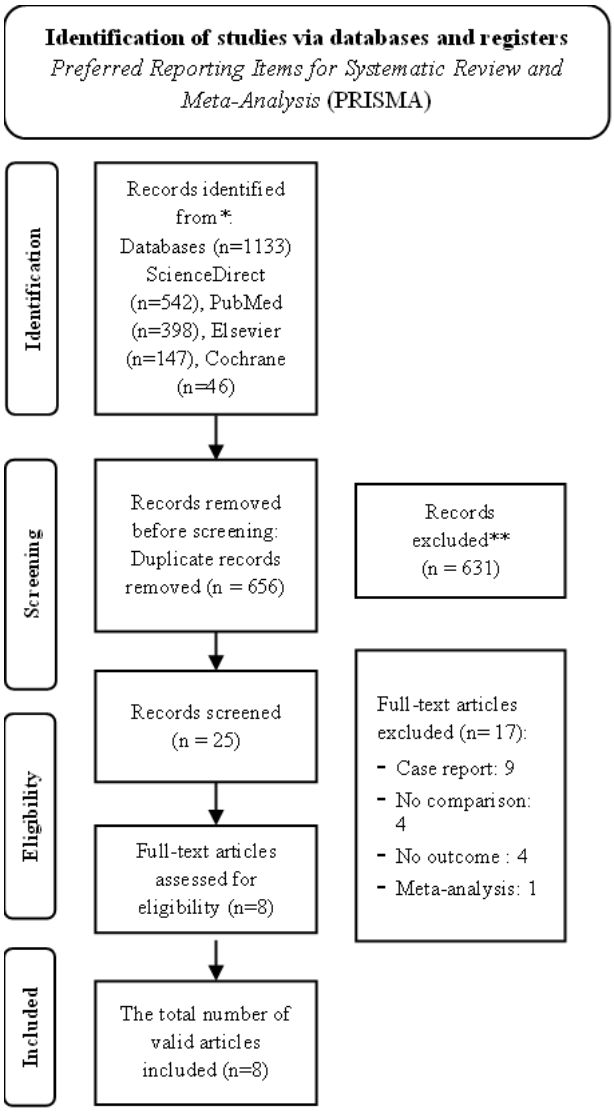

Figure1. PRISMA Flow Diagram of the Selection of Eligible Studies

2.3 Data Extraction

Pre-defined tables for data extraction were developed and piloted with eight articles. The information extracted included author, publication year, country, study design, age range, sexuality, RV vaccine type, and number of samples. To assess effectiveness and safety of BRV-PV, we extracted the number of children who vaccinated with RV vaccines (BRV-PV vs. placebo) each study. We reviewed comprehensive studies about the effectiveness and safety of BRV-PV against SRVGE hospitalization and AEs. All the study estimates represent a complete vaccine series (one to three doses of BRV-PV). We used Microsoft Excel and Microsoft Word Software 2017 to write this systematic review.

3. Result and Discussion

3.1 Pathophysiology of Diarrhea due to SRVGE

RV is a non-enveloped double-stranded RNA (dsRNA) virus that have three concentric capsids that surround a genome of 11 segments of dsRNA.[11] The RNA segments encode six structural viral proteins (VP1, VP2, VP3, VP4, VP6 and VP7) and six non-structural proteins (NSP1, NSP2, NSP3, NSP4, NSP5 and NSP6).[11] Ten different RV species (A–J) have been classified on the basis of sequence and antigenic differences of VP6.[12] Species A rotaviruses (A-RV), which are the most common cause of infections in children.[12] Six strains of species A-RV generally account for >90% of globally circulating species A-RV: G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12P[8].[13]

RV infects and replicates in the mature, non-dividing enterocytes in the middle and tip of the villi and in enteroendocrine cells in the small intestine.[11] RV infections cause SRVGE and are associated with non-bloody diarrhea that lasts for a relatively short duration.[11,14] Thus, RV-induced diarrhea is considered non-inflammatory and has two proposed mechanisms: osmotic diarrhea due to malabsorption (secondary to

enterocyte damage or death, or to decreased epithelial absorptive function) and secretory diarrhea due to the effects of non-structural protein-4 (NSP4) and activation of the enteric nervous system.[13, 14] In addition, RV infection-mediated secretion of serotonin can activate signalling pathways that can induce diarrhea and vomiting.[13]

RV infection in the duodenal mucosa has been shown to disrupt normal cellular homeostasis.[11,15] It results in villous atrophy, loss of microvilli, infiltration of mononuclear cells, distended endoplasmic reticulum, and swelling of the mitochondria in enterocytes.[15] Mechanisms underlying the reduction of epithelial absorptive function that contributes to RV-induced diarrhea include the loss of infected enterocytes and NSP4-mediated impairment of sodium-coupled solute symporters involved in the reabsorption large volumes of water under physiological conditions.[11,14,15]

NSP4 secreted from cells infected with RV binds to intestinal epithelial cells and signals through phospholipase-C to increase cytoplasmic calcium levels, which activates calcium-dependent chloride channels.[13] It causes excessive secretion of chloride ions into the intestinal lumen, creating an osmotic gradient that facilitates water transport into the lumen, leading to secretory diarrhea.[13,14] RV infection and NSP4-mediated increase in intracellular calcium levels can induce secretion of serotonin from enteroendocrine cells in humans, which can activate enteric nerves that innervate the small intestine and ultimately lead to increased intestinal motility.[13]

3.2 ***Problems of Three Licensed RV Vaccines (Rotateq, Rotarix, Rotavac) in Developing Countries***

Since 2006, two live oral RV vaccines have been prequalified by WHO licensed in >100 countries, namely RotaTeq and Rotarix. RotaTeq (Merck and Co) is a three-dose pentavalent bovine-human reassortant RV vaccine distributed in a single 2mL dose vial.[16] Rotarix (GSK Biologics) is a two-dose monovalent human G1P[8] RV vaccine distributed in one 1.5mL vial (Table. 1). In 2017, Rotavac (Bharat Biotech) and BRV-PV (Serum Institute of India) were seeking prequalified as a live oral rotavirus vaccine by WHO (Table. 1). Rotavac is a three-dose monovalent human-bovine G9P[11] vaccine and BRV-PV is a three-dose pentavalent bovine-human reassortant RV vaccine.[16]

Table 1. Types of Rotavirus Vaccines (Rotarix, RotaTeq, BRV-PV, and Rotavac)

	Rotarix	**RotaTeq**	**BRV-PV**	**RotaVac**
Organization	GSK Biologics	Merck and Co	Serum Institue of India	Bharat Biotech
Composition	Live human-attenuated rotavirus strain, G1P	Live attenuated bovine-human reassortant strains G1, G2, G3, G4, P1	Bovine-Human Reassortant Rotavirus Vaccine [G1, G2, G3, G4, G9	Live attenuated neonatal rotavirus strain, G9P[11] (aka 116E)
Doses	2	3	3	3
Advantages	More effective in developed countries (>90%) but in developing countries (50%)	More effective in developed countries (>90%) but in developing countries (64%)	More effective in developing countries, heat stable for six months at 40°C, well distributed in developing countries due to its low price and minimal side effects	More effective in developed countries (>90%) but in developing countries (54%)
Disadvantages	Difficult to distribute in developing countries due to its expensive, not heat stable, and having more side effects (case of intussusception)	Difficult to distribute in developing countries due to its expensive, not heat stable, and having more side effects (case of intussusception)	NI	Difficult to distribute in developing countries due to its expensive, not heat stable, and having more side effects (case of intussusception)
Price/dose	$2.50	$3.20	$2.00	$2.50
References	[7,16,17,18]	[7,16,17,18]	[7,9,16,19,20]	[7,16,17,18]

Clinical trials of RV vaccine efficacy and post-licensure effectiveness evaluations of RotaTeq, Rotarix, and Rotavac in developed countries demonstrated that the vaccines were >90% effective in preventing SRVGE (Table. 1). However, clinical trials in developing countries with higher child mortality due to SRVGE found that RotaTeq, Rotarix, and Rotavac were less efficient in these settings, with published effectiveness estimates ranging from 30–48% (Table. 1). Dissimilar to the results from their clinical trials, effectiveness of the BRV-PV in developing countries against hospitalization for diarrhea due to SRVGE was 70-75% in a clinical trial in India and 67% in niger.[8,9,19]

BRV-PV promises improvement on certain programmatic aspects of RotaTeq, Rotarix, and Rotavac.[16] For example, BRV-PV is expected to cost USD$2.00, compared to approximately USD$3.20 for RotaTeq, USD$2.50 for Rotarix, and USD$2.50 for Rotavac through UNICEF's supply division (Table. 1). BRV-PV is a lyophilized RV vaccine that is heat-stable for six months at 40°C (Table. 1). The clinical trial for BRV-PV in Niger found the vaccine was efficacious after storage at up to 25°C in the distribution facility and the ambient temperature once distributed to the vaccination centres.[9] BRV-PV, as a heat-stable vaccine, could reduce the burden on the cold chain and the financial costs and forecasting challenges associated with vaccine wastage due to temperature excursions.[9,16,20]

3.3 Characteristics of Included Articles

Of the eight articles that evaluated the vaccine effectiveness and safety of BRV-PV using randomized controlled trial methods, five were undertaken in India, one in Niger, one in South Africa, and one from China (Table. 2). Four articles met the inclusion criteria without including duration, and the article with the most prolonged duration was done by Desai et al. (11 months). All articles are multicenter except for the studies of Isanaka et al., Paul et al., and Barakat et al. The total sample of 8 included articles that received BRV-PV vaccination was 9088 under five years of age (Table. 2). From the total sample, more boys received BRV-PV vaccination (6606) than girls (Table. 2). All samples in the BRV-PV group received three doses of vaccine, except for Barakat et al. and Paul et al., who used a single dose.

Table 2. Characteristics of the Studies Included in this Systematic Review

No.	Study	Study design	Year	Duration (month)	Country	Center	Sample (n)				Ref.
							Treatment of choice	Sample (n)	Sample age mean (SD)	Sexuality (M/F)	
1.	Desai, et al.	RCT	2018	11	India	Multi	BRV-PV	375	NI	NI	[23]
							Rotarix	375			
2.	Kulkarni, et al.	RCT	2014	NI	India	Multi	BRV-PV	3749	48.3 days (4.05)	1858/3749	[22]
							Placebo	3751	48.2 days (4.11)	1923/3751	
3.	Rathi, et al.	RCT	2018	NI	India	Multi	BRV-PV	225	6.74 months (0.56)	585/540	[8]
							Rotarix	225	6.78 months (0.57)	206/169	
4.	Isanaka, et al.	RCT	2022	5	Nigeria	Single	BRV-PV	2044	6.8 months (0.7)	1030/1014	[9]
							Placebo	2047	6.8 months (0.7)	1004/1043	
5.	Paul, et al.	RCT	2014	1	India	Single	BRV-PV	15	34.4 month (21-56)	15/0	[19]
							Placebo	5	34.4 month (21-56)	5/0	
6.	Barakat, et al.	RCT	2016	NI	South Africa	Single	BRV-PV	70	11.00 months (9.00–15.00)	46/34	[20]
							Placebo	70	12.00 months (9.00–15.00)	37/43	
7.	Saluja, et al.	RCT	2017	4	India	Multi	BRV-PV	590	6.36 months (0.523)	312/278	[24]
							RotaTeq	592	6.33 months (0.526)	303/289	
8.	Mo, et al.	RCT	2017	NI	China	Multi	BRV-PV	2020	59.6 month (10.3)	1029/991	[21]
							Placebo	2020	59.4 month (10.1)	1062/958	

3.4 Effectiveness of BRV-PV Against SRVGE in Developing Countries

All studies suggest that BRV-PV significantly reduces the incidence of severe diarrhea associated with SRVGE in the study population (Table. 3). Mo et al.'s study reported the highest percentage of effectiveness of the BRV-PV vaccine, which was 79.1%, reducing the number of emergency cases and hospitalizations in China.[21] The effectiveness of BRV-PV is different for each country, even though the percentage tends to be good; for example, the vaccine's effectiveness in Niger is 66.67%, in China is 79.1%, and in India, it is more than 70% (Table. 3). These differences are associated with several factors, such as host characteristics, epidemiology, and the period of vaccine administration.[8,9,20,21]

A study by Kulkarni et al., who conducted a clinical assessment of the effectiveness of the BRV-VP vaccine in preventing severe rotavirus gastroenteritis (SRVGE) in India, concluded that BRV-PV vaccination prevented SRVGE more than 50%.[22]This finding is similar to Rathi et al.'s study, which reported that the BRV-PV reduced the incidence of hospitalizations for diarrhea due to RV infection to 75% after the third phase of vaccination among children in India.[8] In addition, the BRV-PV vaccine is relatively affordable in India and heat-stable in the global strategy for preventing diarrhea due to SRVGE.[8,19,22,23,24]

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Table 3. Summary of Studies on the Effectiveness and Safety of BRV-PV

No.	Study	Doses	Outcome of effectiveness	Reactogenicity and safety	Ref.
1.	Desai, et al.	3 doses of 2 ml vaccine at 6,10,14 weeks	- BRV-PV has significant efficacy to prevent infants diarrhea gastroenteritis case at India. - BRV-PV has potential effect on the immunogenicity of concomitantly administered EPI vaccine in infants.	BRV-PV does not interfere with the immunogenicity of concomitantly administered routine infants vaccines.	[23]
2.	Kulkarni, et al.	3 doses of 2 ml vaccine at 6,10,14 weeks	- BRV-PV prevented more than 50% of very severe rotavirus infections in India. - There is no data available regarding IgA concentrations after vaccination.	No significant AEs of vaccination (P>0.05).	[22]
3.	Rathi, et al.	3 doses of 2,5 ml vaccine	- BRV-PV prevent up to 75% incidence of hospitalization related to diarrhea due to rotavirus infection. - BRV-PV have IgA seropositive rate around 47% in India.	No significant side effects were correlated with the administration of BRV-PV, except for two cases of gastroenteritis (P>0.05).	[8]
4.	Isanaka, et al.	3 doses of 2 ml vaccine at 6,10,14 weeks	- BRV-PV had an efficacy of 66,67% against severe rotavirus gastroenteritis among infants in Niger. - There is no data available regarding IgA concentrations after vaccination.	No confirmed cases of intussusception were observed, a finding that was consistent with the results of other trials of oral rotavirus vaccine in the region.	[9]
5..	Paul, et al.	1 doses of 0,5 ml vaccine preceded by 2,0 ml antacid	- BRV-PV prevents more than 70% of cases of severe diarrhea due to rotavirus infection in India. - BRV-PV make greater fold rise in 46,6% of the volunteers rotavirus specific IgA Antibody post vaccination.	BRV-PV vaccine recipients reported no symptoms (solicited, unsolicited or serious adverse events) in both arms during and after ten days of vaccination.	[19]
6.	Barakat, et al.	1 doses of BRV-PV	- BRV-PV could be used as adjuvant therapy as it reduces both the frequency and the duration of diarrhea. - There is no data available regarding IgA concentrations after vaccination.	No confirmed cases of side effect in intervention group.	[20]
7.	Saluja, et al.	3 doses of 2 ml vaccine with interval between each dose is 28 days	- BRV-PV had an acceptable safety profile in infants. - BRV-PV was immunogenic regarding the serum IgA response.	Confirmed 10 cases of side effects in intervention group, but not correlate with vaccine administration.	[24]
8.	Mo, et al.	3 doses of 2 ml oral vaccine with interval between each dose is 28 days	- BRV-PV significantly increased the effectiveness in reducing the incidence of severe diarrhea related to rotavirus infection, reaching 79,1%. - There is no data available regarding IgA concentrations after vaccination.	There was no statistical difference between the BRV-PV and placebo groups concerning the incidences of fever, vomiting, and diarrhea.	[21]

The IgA seropositivity rate among children who received BRV-PV was about 47% or 16% lower compared to the second phase update in India.[8] However, the IgA seropositivity rate after four weeks of the third dose of the BRV-PV vaccine was 34% higher than the group that received the Rotarix in India.[8] This finding is inline to Saluja et al.'s study, which reported that BRV-PV was immunogenic regarding the serum IgA response.[24] Although BRV-PV appears to be more immunogenic than Rotarix, the differences observed could be due to several factors, such as the antigen used in IgA and the time of sampling.[8,24]

A study in Niger, West Africa, by Isanaka et al. conducted a double-blind, suspended placebo, randomized, phase 3, event-based trial to assess the effectiveness and safety of BRV-PV against SVRGE.[9] The direct result was that BRV-PV vaccination was 66.7% more effective at treating SRVGE than placebo in the Nigerian infant population (95% confidence interval [CI], 49.9 to 77.9).[9] This finding is similar to Barakat et al.'s study, which reported that BRV-PV is more effective in treating acute diarrhea and could be used as the first-choice adjuvant therapy for the prevention of RV infection in the African region.[20]

The vesikari score among children in South Africa who received BRV-PV was significantly lower than in the placebo group (p=0.00005).[20] This finding is similar to Isidore Bonkoungou et al.'s study, which reported that diarrhea hospitalizations due to SRVGE decreased from 46 to 23 percent in the second post-BRV-PV year in children under five.[25] The cases of diarrhea due to RV infection fell from 49 to 20 percent after one year of BRV-PV introduction among infants under 1 in South Africa.[20,25]

The study of Mo et al. reported that BRV-PV provided an effective percentage of 79.1% (95% CI: 44.2, 93.8) or an increase of 12.3% over the first dose vaccine period in reducing the incidence of SRVGE hospitalization in a population of healthy infants aged 6–12 weeks in China.[21] BRV-PV is efficacious for at least 14 days after the third vaccination against SRVGE caused by G1, G9, or P1A[8].[21] The effectiveness of BRV-PV against SRVGE caused by other serotypes did not show statistical significance, which is likely due to insufficient SRVGE cases.[21] In addition, the population in Mo et al.'s study located in Guangxi Zhuang is a relatively underdeveloped autonomous region in China, so the results in the study apply to most regions in China whose socioeconomic status is still below average.[21]

3.5 Safety of BRV-PV in Developing Countries

According to all included studies, children in developing countries who received BRV-PV vaccination did not experience any severe side effects (Table. 3). Some symptoms, such as fever, decreased appetite, nausea, vomiting, and diarrhea, occurred in the BRV-PV or placebo groups (Table. 3). A study by Saluja et al. proves that no side effects arise 30 minutes after administering the BRV-PV.[24] Isanaka, et al. also examined the safeness of BRV-PV; medical investigators determined that no serious AEs were related to the trial intervention.[9] There were no confirmed cases of intussusception, but immediate AEs (all grade 1 or 2 fever or vomiting) were reported in 3 infants in the BRV-PV group and 1 in the placebo group (P=0.37).[9] Analyses of the AEs showed a similar frequency of all events in the two groups (P>0.15).[9] The finding is similar to the safety analysis of BRV-PV conducted by Desai et al. and Barakat et al., which gets similar results (Table. 3). The study by Mo et al. reported that in the BRV-PV group, only ten children encountered side effects, but these conditions did not correlate with BRV-PV.[21]

A study by Paul et al. reported that children who received BRV-PV vaccination did not experience AEs in both arms during and after vaccination.[19] The administration of the BRV-PV or placebo did not result in a significant difference in the laboratory parameters between baseline and ten days after vaccination.[19] In some instances, systemic side effects occur due to respiratory infections and genetic diseases unrelated to BRV-PV.[19] BRV-PV is generally safe to use unless the patient has a history of comorbidities.[19]

The BRV-PV was well tolerated when given together with DTP-HB-Hib and oral polio vaccines.[22] Gastroenteritis was the only AEs reported by Kulkarni et al. that occurred within seven days after BRV-PV vaccination.[22] Of the 12 cases of gastroenteritis, seven were in the BRV-PV group, and five were in the placebo group.[22] However, only one tested positive for RV antigen in the stool, while 11 tested negatives.[22] Thus, gastroenteritis is unlikely to be caused by BRV-PV.[22]

The study by Rathi et al. reported that 11 children from the BRV-PV group experienced mild vomiting within five minutes after vaccination.[8] After seven days of the BRV-PV vaccine, 940 children from the BRV-PV group (83.70%) and 314 (83.96%) from the placebo group experienced mild to moderate AEs, and most resolved within two days.[8] Fever, decreased appetite, and vomiting were the most common AEs in the BRV-PV (73.37%) and Rotarix (72.99%) groups.[8] However, there was no significant difference in AEs levels (p>0.05) between the BRV-PV and placebo groups because all samples in the study had received the reactogenic RV vaccine (BRV-PV or Rotarix).[8] In addition, BRV-PV was well tolerated due to the very low incidence of vomiting compared to the Rotarix group.[8]

Safety of BRV-PV also examined by Saluja et al., which reported that there were no immediate solicited or unsolicited AEs or adverse reactions within 30 min of vaccination in either group.[24] The percentages of solicited and unsolicited AEs reported throughout the trial were similar for both groups.[24] In conclusion of their study, oral doses of the BRV-PV had an acceptable safety profile in infants (Table. 3).

3.6 Effect of Dosage on the Effectiveness of BRV-PV

The dose of BRV-PV will affect the vaccine's effectiveness in activating the anti-RV IgA immune response. Study Mo et al. reported that three doses of BRV-PV were 96% more effective in activating the IgA immune response than single or multiple doses.[21] These findings are simillar to the study of Saluja et al., who reported that the geometric mean anti-RV IgA serum concentration on day 28 after the third dose of BRV-PV was higher than other competing rotavirus vaccines (Rotarix, RotaTeq, and Rotavac).[24] Paul's study et al. support this statement and suggest that the effective dose of BRV-PV in vaccination for the prevention of diarrhea associated with SRVGE is three doses of 2.0 ml with an interval between doses of 28 days.[19] No further explanation has been found regarding the differences in the effectiveness of each dose of BRV-PV in activating the IgA immune response.

4. Conclusion

Severe acute rotavirus gastroenteritis (SRVGE) is the world's highest cause of children mortality, with symptoms of severe dehydrating diarrhea due to rotavirus (RV) infection. Currently there are several vaccines used to prevent SRVGE, one of which is BRV-PV. BRV-PV effectively prevents the severe clinical manifestations of RV infection and has minimal side effects. This vaccine is more effective and efficient in developing countries because it stable to heat and significantly increase the concentration of anti-RV IgA at a relatively low cost. Furthermore, BRV-PV was well tolerated when given together with DTP-HB-Hib and oral polio vaccines. The limitations of this systematic review are the limited sample size from Asian populations and the lack of studies on effective doses of the BRV-PV vaccine in various countries.

5. Recommendations

Further research is needed regarding the effectiveness, safety, and reference dose of BRV-PV in populations of Asia and other developing countries, especially Indonesia.

6. Conflict of Interest

Author declared that there are no conflict of interest in this article.

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