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Implementation of Universal Rotavirus Vaccination in Indonesia: Review Article

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ABSTRACT

Background: Rotavirus is a leading cause of severe diarrhea in children under five years of age worldwide, with significant morbidity and mortality, particularly in low- and middle-income countries like Indonesia. Diarrhea in Indonesia is the second leading cause of death after pneumonia. Rotavirus is the main cause of severe diarrhea in children under five years of age (41%-58%). Because of this, in 2022 Indonesia launched a high-risk Rotavirus vaccine in 21 districts. ***Objective:*** This study aims to determine the universal use of the rotavirus vaccine in Indonesia and the impact of the rotavirus vaccine on the community. ***Method:*** Information on Implementation of Universal Rotavirus Vaccination in Indonesia: Review Article was gathered using NCBI, PubMed, Google Scholar, WHO, and the Ministry of Health. The types of data obtained in this literature review are articles, journals, and books accessed through online searches. Online search. The keywords used were 'Rotavirus', 'Rotavirus Vaccine', 'Rotavirus Diarrhea', and 'Vaccine Distribution'. ***Result:*** The Rotavirus vaccine reduces the incidence of rotavirus diarrhea in children and currently the government has made rotavirus vaccine free in Indonesia.

Keywords: rotavirus vaccination; rotavirus diarrhea; rotavirus; vaccine distribution.

INTRODUCTION

Diarrhea is one of the highest-incidence diseases and is the second leading cause of death in children under five years of age [1], causing the death of approximately 1.7 million children worldwide and 10,000 children annually in Indonesia [2,3]. The most common cause of diarrhea in children under five years of age is viral and the most common is Rotavirus, which is 40% worldwide [4]. From this incidence, several factors cause Rotavirus diarrhea, which is related to the human host in general (e.g. malnutrition, blood histo-group antigens, co-administration of ORV with polio vaccine, and maternal factors), the agent (e.g. genetic diversity, infectious strength, and maternal factors), and the virus in particular: genetic diversity, the strength of infection and co-infection), and environment (enteropathy or gut microorganisms, genetic diversity, strength of infection and co-infection) have been suggested as possible etiologies driving differences in vaccine-evoked protective immunity between two socioeconomic settings [5].

Rotavirus is a major pathogen of death from diarrheal disease [6]. Rotaviruses are double-stranded RNA viruses with segmented genomes and are classified in the family Reoviridae [7]. Rotaviruses in the world were discovered in 1970 and Rotavirus was first identified as a cause of diarrhea in 1973 [8]. In 2016, rotavirus diarrhea caused more than 258,000,000 infections and nearly 129,000 deaths in children under 5 years of age globally. In children under five years of age In Indonesia, Rotavirus is found in 47.5% of hospitalized diarrhea cases with a mortality rate of 19.5 per 100,000 children under 5 years of age [9].

This article discusses the implementation of rotavirus vaccination programs in the world and Indonesia, assessing their successes, challenges, and impact on public health. It also discusses strategies implemented to overcome barriers to vaccine access and uptake, such as public education campaigns and improved healthcare systems.

By analyzing recent data and experiences from vaccination efforts in Indonesia, this article aims to provide insights into program effectiveness as well as lessons learned in combating rotavirus-related morbidity and mortality in Indonesia.

METHOD

The method in this study uses database sources from journal publications in NCBI, PubMed, Google Scholar, WHO, and the Ministry of Health. The types of data obtained in this literature review are articles, journals, and books accessed through online searches. Online search. The keywords used were ", 'Rotavirus', 'Rotavirus Vaccine', 'Rotavirus Diarrhea' and 'Vaccine Distribution'". This literature can be accessed in the form of full text in PDF format and peer-reviewed journals. The data collection strategy used was to collect several journals from the internet and highlight a few sentences from each journal found. From the highlights, we organized them into points.

RESULT AND DISCUSSION

Rotavirus is the most common causative agent of severe acute gastroenteritis worldwide. Rotavirus is primarily transmitted via the fecal-oral route but also through food, water, fecal-contaminated hands and surfaces, and respiratory droplets [6]. The main symptoms of rotavirus infection of the small intestine are diarrhea and vomiting which can cause rapid dehydration that can lead to organ failure and death [10]. Obstacles experienced when there is an incidence of diarrhea are the unavailability of Rotavirus vaccines, and inaccessibility to the poor in high-risk communities, resulting in low demand and acceptance of vaccines in countries with more than 40% poor population [11].

As a result of the large number of Rotavirus deaths in toddlers, the World Health Organization (WHO) first recommended the inclusion of rotavirus vaccines in national immunization programs in Europe and the Americas in 2006 [6]. The result was that the disease had decreased significantly but Rotavirus outbreaks still occurred [12]. In 2009, it was recommended that the vaccine be extended to all regions around the world. [6] Then WHO advised all countries to include rotavirus vaccination in national immunization programs, especially vulnerable countries by 2017 [11]. Rotavirus vaccine was first discovered in 1998, namely Rota Shield in the United States [13]. Currently the global Rotavirus case the number of deaths in children under five has decreased to 128,500. Because the vaccine has been spread and recommended by WHO globally. The vaccines commonly used globally are the Rotateq and Rotarix vaccines. Rotateq itself is a live pentavalent oral vaccine containing 5 live rotaviruses consisting of Four reassortant rotaviruses expressing one of the outer capsid proteins (G1, G2, G3, or G4) The fifth reassortant virus expresses the attachment protein, P1A (genotype P[8]), which is hereinafter referred to as type P1A [14].

Then there is Sucrose, Sodium citrate, Sodium phosphate monobasic monohydrate, Sodium hydroxide, and Polysorbate 80 Rotateq itself has a way of working which first enters the digestive tract by infecting intestinal epithelial cells and then secondly recognizing by the immune system, namely dendrite cells in the intestine. The first is entering the gastrointestinal tract by infecting intestinal epithelial cells then the second is recognition by the immune system i.e. dendrite cells in the intestine recognize attenuated rotavirus antigens and continue to be presented to T and B lymphocytes in the intestinal lymphoid tissue third is antibody production i.e. activated B lymphocytes produce secretory IgA antibodies and systemic antibodies such as IgG are also formed providing long-term protection the last is immunological memory i.e. after the vaccine the body forms immune cells that allow a quick and effective response if the child is exposed to rotavirus in the future. Rotarix itself is also the same as an oral vaccine with type G1P containing sodium adipate, Dulbecco's Modified Eagle Medium (DMEM), sucrose, and sterile water [15].

The way it works itself is the same as Rotateq, which first enters the digestive tract by infecting intestinal epithelial cells then second recognition by the immune system, namely dendrite cells in the intestine recognize attenuated rotavirus antigens and proceed to be presented to T and B lymphocytes in the intestinal lymphoid tissue third antibody production, namely activated B lymphocytes produce secretory IgA antibodies and systemic antibodies such as IgG are also formed providing long-term protection, the last is immunological memory, namely after the vaccine the body forms immune cells that allow a quick and effective response if the child is exposed to rotavirus in the future[15].

Because rotavirus is a worldwide disease, Indonesia also experiences cases of Rotavirus diarrhea which has the Ministry of Health found that diarrhea is still a public health problem in Indonesia, with data from the Indonesian Health Profile in 2020 showing that diarrhea is the second leading cause of death in infants and toddlers. Rotavirus is the leading cause of severe diarrhea in under-fives, accounting for approximately 41%-58% of total hospitalized diarrhea cases. In addition to causing morbidity and mortality, diarrhea also inhibits child growth and can lead to stunting. Data from the Indonesian Nutrition Status Survey in 2021 showed that the prevalence of diarrhea in children under five reached 9.8% [15].

The 2020 Indonesian Health Profile revealed that diarrhea is the second cause of death after pneumonia, with as much as 9.8% of infants aged 29-11 months and 4.5% of infants aged 12-59 months of the total deaths. Data from the Indonesian Rotavirus Surveillance Network from 2001-2017 shows rotavirus to be the main cause of severe diarrhea at 41%- 58% in toddlers from the total cases of diarrhea treated in hospitals. Diarrhea can inhibit the growth and development of children to the extent of causing stunting due to repeated diarrhea infections so that micronutrients that play a role in the growth and development of children are lost [16]. Efforts have been made to overcome the problem of diarrhea,

namely improving environmental hygiene and sanitation, handling diarrhea with ORS and zinc, but have not provided optimal results. Diarrhea control is better accompanied by prevention with rotavirus immunization recommended by WHO and the National Immunization Expert Advisory Committee (ITAGI) [17].

Considering that Indonesia distributed the Rotavirus vaccine in 2022 in 21 districts with high intensity Rotavirus incidence, and expanded to 18 provinces in 2023. The vaccine is given in three doses from 2 months to 6 months of age. The active role of local governments, related sectors, health partners, and communities is key to the success of this program, in achieving high and equitable immunization coverage [18].

UNICEF and WHO fully support the expansion of rotavirus immunization in Indonesia which aims to protect 4.3 million children under one year of age from the dangers of severe diarrhea caused by rotavirus. The program is also driven by other prevention efforts such as exclusive breastfeeding support, healthy lifestyle, and early treatment. The following are the Rotavirus vaccine expansion sites in Indonesia [18]. Of the 21 districts, one of the pilot projects in Indonesia is in Pangkajene Kepulauan, August 15, 2023 – Pangkajen, Islands District (Pangkep) is one of the largest districts in South Sulawesi with an area of 12.362 km^2.

RV immunization in Indonesia is being carried out in stages, starting in 2022 in 21 high-risk districts/cities in 18 provinces, and will be expanded to all provinces and districts/cities this year. RV immunization is given in three doses starting at 2 months of age and a maximum at 6 months of age with a minimum gap of four weeks between doses. RV immunization should be given on time to provide the earliest possible protection to infants from the dangers of severe diarrhea due to rotavirus. In Indonesia, the vaccines commonly used are the Rotarix vaccine and the Rotateq Vaccine [19]. Different from the free Rotavirus vaccine program from the government which started on August 15, 2024, which is given is rotavac is a vaccine made in India [20].

Rotavac itself contains: Live Attenuated Human Rotavirus (Strain 116E), Sucrose, Monopotassium Glutamate, Potassium phosphate monobase, Dibasic potassium phosphate, Neomycin Sulfate, Kanamycin Sulfate, a Combination of Low Glucose DMEM with L-Glutamine, without sodium bicarbonate with sodium pyruvate, Water for Injection pH Range: 7.2 to 8.0 [21]. The mechanism of action of the rotava vaccine is the same as that of the retateq and rotarix vaccines, namely the first to enter the digestive tract by infecting intestinal epithelial cells, then the second to be recognized. The first enters the gastrointestinal tract by infecting intestinal epithelial cells then the second is recognition by the immune system, namely dendrite cells in the intestine recognize attenuated rotavirus antigens and continue to be presented to T and B lymphocytes in the intestinal lymphoid tissue third antibody production, namely activated B lymphocytes produce secretory IgA antibodies and systemic antibodies such as IgG are also formed providing long- term protection the last is immunological memory, namely after the vaccine the body forms immune cells that allow a quick and effective response if the child is exposed to rotavirus in the future [15].

Then there is the RV3 biofarma vaccine which is a domestically produced vaccine made by PT Biofarma in collaboration with researchers from various institutions, including from Gadjah Mada University, to provide a solution to the problem of diarrhea caused by rotavirus, especially in children, which was created and circulated in 2014 containing the rotavirus virus type G3P which is used for the prevention of rotavirus infection in infants aged 6 weeks to 24 months in accordance with the recommendations of health authorities [22].

The successful delivery of the new antigen immunization and other routine immunizations requires the active role of the Local Government, relevant cross-sectors, health development partners, and all levels of society. Together we support the acceleration of health transformation to achieve high and equitable immunization coverage to further strengthen the immunization program and the national health system [18].

WHO Indonesia appreciates and will continue to support the Indonesian government in its efforts to implement rotavirus immunization nationally. All WHO-prequalified vaccines, including those used in Indonesia's national immunization program, are safe and effective [18]. WHO Indonesia encourages According to a study conducted by Thobari, et al (2024), said hat Compared to not vaccinating, the implementation of rotavirus vaccination in Indonesia's national immunization program for newborns and toddlers was shown to provide significant cost benefits to society and the health sector. We estimate that rotavirus vaccination can reduce 32% of outpatient visits and 37% of hospitalizations and deaths due to RVGE in children under 5 years of age in Indonesia. These results are influenced by the important contribution of Bio Farma's RVV in supporting the integrated rotavirus vaccination initiative in Indonesia. Rotavirus vaccination coverage in Indonesia is as follows [23].

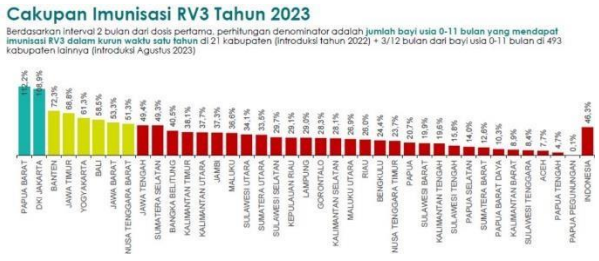

FIGURE 1: Rotavirus immunization coverage data in Indonesia in 2023 (Indonesian Ministry of Health, 2024).

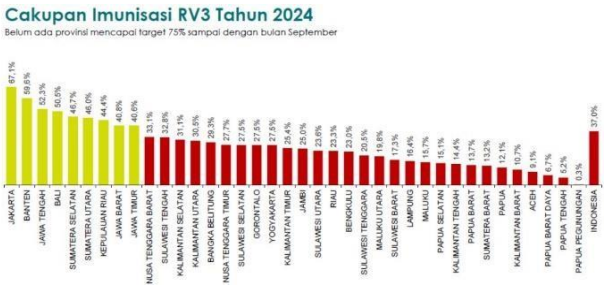

FIGURE 2: Rotavirus immunization coverage data in Indonesia in 2024 (Indonesian Ministry of Health, 2024).

The current rotavirus vaccines are live attenuated, orally administered vaccines derived from human and/or animal rotavirus strains that can multiply in the human gut to trigger an immune response. WHO guidelines also exist to ensure the quality, safety and effectiveness of these attenuated rotavirus vaccines. The first two rotavirus vaccines to be prequalified by WHO were RotaTeq in 2008 and Rotarix in 2009. In 2018, WHO also prequalified two additional vaccines, Rotavac and ROTASIIL. In addition, Rotavirus vaccines also have the efficacy, effectiveness and impact of [24].

Vaccine Efficacy

A recent Cochrane review of four rotavirus vaccines that have been qualified by WHO showed that vaccine efficacy in preventing severe RVGE is higher in countries with low mortality rates compared to countries with high mortality rates. Based on analysis of 11 randomized controlled trials (RCTs) for RotaTeq, 15 RCTs for Rotarix, 1 RCT for Rotavac, and 2 RCTs for ROTASIIL, this review found protection against severe RVGE after one or two years of follow-up, with moderate decline over the observation period. Vaccine efficacy ranged from 90%-95% in countries with low mortality rates, while in countries with high mortality rates, efficacy was only about 44%-70%. Sub-analyses in high-mortality countries in Africa and Asia showed that all vaccines had comparable efficacy in preventing severe RVGE, with efficacy ranging from 48% to 57% at one-year follow-up. In addition, RotaTeq was shown to be effective in preterm infants, although efficacy data in preterm infants for the other vaccines have not been reported [24].

Vaccine Effectiveness

The worldwide effectiveness of Rotarix and RotaTeq vaccines showed that vaccine effectiveness in preventing laboratory-confirmed severe RVGE was 86% in children less than 12 months in low mortality countries, 77% in moderate mortality countries, and 63% - 66% in high mortality countries. In children aged 12-23 months vaccine efficacy in low mortality countries was 84% - 86%, in moderate mortality countries (Rotarix only) 54% and in high mortality countries 58%. Rotarix and RotaTeq reduced the number of RVGE-related health facility visits in low mortality countries by 79 - 83%, medium mortality countries (Rotarix only) by 58% and high mortality countries (Rotarix only) by 48% - 69% [24].

Vaccine Impact

The global impact of the rotavirus vaccine is evident through a 40% reduction in rotavirus prevalence after vaccine administration, based on analysis of data from 69 countries in the Global Rotavirus Surveillance Network (GRSN). Other studies have also shown reductions in rotavirus hospitalizations, hospitalizations for acute gastroenteritis, and deaths from gastroenteritis across countries. In the GRSN analysis, the proportion of children who tested positive for rotavirus while hospitalized for acute gastroenteritis decreased from 38% to 23% after rotavirus vaccination was introduced, representing a 40% decrease in positivity. A recent systematic review of observational studies in 47 countries with varying child mortality rates reported an average reduction of 59% in rotavirus hospitalizations, 36% in acute gastroenteritis hospitalizations, and 36% in deaths from acute gastroenteritis in children under 5 years after the introduction of rotavirus vaccine. Similar to the GRSN analysis, the average percentage of children testing positive for rotavirus also decreased from approximately 40% to 20% after vaccination was introduced [24].

Bio Farma's RV3 neonatal rotavirus vaccine has been shown to be well tolerated in adults, children and neonates, and is immunogenic when administered according to the neonatal schedule in Indonesia. Three doses of vaccine given at 0-5 days, 8-10 weeks, and 12-14 weeks of age resulted in cumulative immune responses [25]. The vaccine showed similar immunogenicity to the WHO approved oral rotavirus vaccine, especially in areas with high rotavirus disease burden. However, in this study, no vaccine virus shedding from the feces of neonates was detected, in contrast to previous studies that showed virus shedding in most participants. This difference may be due to the different laboratory methods used to detect the virus. Overall, Bio Farma's RV3 vaccine is effective in stimulating immune responses in neonates and can be applied without the need for gastric acid pre- neutralization in neonate vaccination schedules in areas with high child mortality rates [26].

CONCLUSION

The success of rotavirus vaccination, first introduced by WHO in 2006 in Europe and the Americas, has shown a significant reduction in the incidence of severe rotavirus diarrhea. In 2009, WHO recommended that the vaccine be expanded worldwide, and in 2017, rotavirus vaccines were included in national immunization programs in many countries, including Indonesia. Indonesia began implementing rotavirus vaccination in 2022 in high-risk areas, and in 2023, the program was expanded to all provinces, with the aim of protecting millions of children from the dangers of severe diarrhea.

Rotavirus vaccines, both those produced by international companies such as Rotateq and Rotarix, as well as local vaccines such as Bio Farma's Rotavac and RV3, have been shown to be effective in reducing hospitalizations, health facility visits, and deaths from rotavirus diarrhea.

These vaccines work by triggering a strong immune response and providing long-term protection against rotavirus infection. Although vaccine effectiveness varies slightly in countries with high mortality rates, overall, these vaccines have had a major positive impact on reducing rotavirus prevalence.

The importance of collaboration between governments, the health sector, development partners and communities in supporting rotavirus immunization cannot be overlooked. Full support from UNICEF, WHO, and various related parties is key to achieving high and equitable vaccination coverage. This effort must be supported by increasing public awareness, strengthening health systems, and better access to vaccines in high-risk areas.

With rotavirus vaccination nationwide, Indonesia is expected to reduce mortality and morbidity from rotavirus diarrhea, as well as address other challenges such as stunting which is often associated with diarrheal infections. Therefore, the success of the rotavirus immunization program is an important part of achieving a better health transformation for future generations in Indonesia.

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