ORIGINAL RESEARCH ARTICLE

A Case-Control Study on Effect of Rotavirus Monovalent G9P[11] Vaccination on the Severity of Diarrhoea in Children Aged 2-24 Months in Indonesia

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ABSTRACT

Background: In Indonesia, rotavirus monovalent G9P[11] vaccine is the first rotavirus vaccine implemented through a government program and has never been evaluated. Makassar City is one of the 21 cities targeted for the introduction of rotavirus immunization in Indonesia. **Aims/Objectives:** To determine the association between rotavirus vaccination and the severity of diarrhoea in children aged 2-24 months.

Methodology: Facility-based Case-Control Study design was conducted at Daya and Paramount hospital in Makassar City in January-February 2024. A total of 180 respondents participated (90 cases and 90 controls). The sampling method used was non-probability sampling, specifically the consecutive sampling technique. Data were analysed using the logistic regression test in Stata version 14.

Results: Rotavirus vaccine status AOR = 4.25 (CI95% 1.82-9.90); *P* = 0.001. Not receiving the vaccine compared to receiving a partial dose of the vaccine COR = 4.03 (CI95% 1.79-9.16); *P* = 0.0002. Not receiving the vaccine compared to children receiving the full dose of the vaccine COR = 12.70 (CI95% 4.87-34.12); *P* = 0.0000. Duration of vaccine administration COR = 4.32 (CI95% 1.66-11.23); *P* = 0.0006.

Conclusions: The rotavirus vaccine status was significantly associated with the severity diarrhoea in children aged 2-24 months.

Keywords: Severe diarrhoea, Children, Vaccine, Rotavirus

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INTRODUCTION

The prevalence of diarrhoea in children under five is still high and remains a global health problem. According to WHO data, in 2019.[1] There were nearly 1.7 billion cases of diarrhoea disease in children each year worldwide. The estimated prevalence of acute diarrhoea is 10.4%, and chronic infections range from 12-35% in children in low-income countries.[2] Children in these countries suffer from prolonged acute diarrhoea illness, with 5-7% of cases lasting more than 14 days.[3]

Diarrhoea disease is one of the leading causes of death in children under five years of age worldwide. According to WHO 2022 data, diarrhoea disease is the leading cause of death among children under five, surpassing pneumonia, malaria, complications of premature birth, birth asphyxia, trauma, and congenital abnormalities.[4] UNICEF 2022 data reveals that diarrhoea is a significant cause of death in children, accounting for approximately 9% of all deaths among children under five globally in 2019. This means that more than 1,300 children under five die every day, or about 484,000 children per year, despite the availability of treatment solutions.[5]

Rotavirus diarrhoea is the leading cause of death in children under five.[6] More than 80% of rotavirus deaths occur in resource-poor countries in South Asia and Sub-Saharan Africa. Rotavirus-related deaths represent about 5% of all deaths of children under five worldwide.[7] The widespread nature of rotavirus infection, the easily progressive clinical nature of rotavirus disease, and the young age of infected infants make rotavirus particularly lethal. Rotavirus vaccination has been considered an important control strategy for the past 40 years.[8]

Makassar City is one of 21 cities targeted for the introduction of the first rotavirus immunization in Indonesia in November 2022. The target for rotavirus immunization starts as early as two months of age, with three doses given with a four-week gap between doses, and the last dose of rotavirus immunization is given until the baby is six months old. Based on the achievement of the initial dose of rotavirus vaccination in Makassar city, the target achievement of rotavirus vaccination services for infants aged 2-6 months in August 2023 in Makassar city is 51.6%.[9]

Rotavirus vaccines have been developed in other countries and have been evaluated, providing different magnitudes of protective effects in each country with different types of vaccines and doses. Indonesia is the first country to implement a rotavirus vaccine through a government program, and there has never been information on the protective effect on toddlers. The inclusion of rotavirus vaccine in the routine immunization program is expected to reduce the morbidity of rotavirus-induced diarrhoea. The absence of studies related to vaccines and the severity of diarrhoea in Indonesia, especially in Makassar City, has led researchers to have an interest in examining the relationship between rotavirus vaccination and the severity of diarrhoea in children aged 2-24 months in Makassar City, South Sulawesi, Indonesia.

This study aims to determine the association of rotavirus monovalent G9P[11] vaccination status with the severity of diarrhoea in children aged 2-24 months in Makassar City, South Sulawesi, Indonesia.

METHODOLOGY

Research Type and Design: This study is a facility-based case-control study conducted on information and data obtained from hospital medical records, vaccine card records, maternal and child health books, and interviews using questionnaire tools with parents of children, assisted by room nurses and hospital surveillance officers. This design is a convenient method because it is facility-based.[10]

Research Time and Location: This study was conducted from January to February 2024 at Daya and Paramount Hospitals in Makassar City, South Sulawesi, Indonesia.

Population and Sample:

The population in this study was diarrhoea patients aged 2-24 months who visited the hospital, totaling 286 children. The minimum sample size with a case-control design was calculated using Lemeshow's design[40] and resulted in a minimum of 90 case samples. The samples of the case group in this study were children aged 2-24 months who were hospitalized with the main diagnosis of moderate-to-severe dehydration diarrhoea, not dysentery, as evidenced by hospital medical records. There was a total of 90 children in this group. Samples in the control group were patients aged 2-24 months with a diagnosis of non-dehydration diarrhoea and other gastrointestinal diseases, as evidenced by hospital medical records. There were also 90 children in this group.

The inclusion criteria for sampling were children domiciled in Makassar City who received consent from parents and were willing to be studied until the end of this study. The exclusive criteria for sampling were children aged 2-24 months who lived outside the city of Makassar and did not have parental consent. The ratio of case and control samples was 1:1, with a total of 180 children aged 2-24 months who were considered eligible to be included in this study.

The measurement of the independent variable in this study was rotavirus vaccination status, with additional analysis of the number of vaccine doses received and the duration of vaccine administration. The control variables were the mother's occupation, mother's education level, mother's hand-washing habit, child's age, child's nutritional status, exclusive breastfeeding status, and child's vitamin A status, to control for confounding factors.

Research variables

Rotavirus vaccination status was determined if the child had received at least one dose of rotavirus vaccination as recorded in the vaccine book. For this study, a child was considered vaccinated if they had received at least one dose of vaccine 14 days before the onset of diarrhoea symptoms [10].

The number of rotavirus vaccine doses was determined based on the number of rotavirus vaccine doses the child had received recorded in the vaccine book, with the criteria being partial doses (1-2 doses) and complete doses (3 doses).

Duration of Rotavirus Vaccine was determined based on the time interval of vaccine administration calculated from the last dose received to the start date of treatment, with criteria of 2 weeks-12 months and more than 12 months.

Control Variables to control for confounding factors:

Maternal occupation is the occupational status of the mother of the patient with the criteria as a housewife and not a housewife.

The mother's education level is the last level of education of the mother of the patient with the criteria of high education (diploma, college) and low education (elementary, junior high, high school).

The mother's habit of washing hands before preparing food, feeding, and breastfeeding can be assessed with criteria of not being used to and used to.

The age of the child was calculated at the time of hospitalization and was categorized as 2-12 months and more than 12 months.

The nutritional status of the child can be assessed by the information recorded in the maternal and child health register book with the criteria of malnutrition (undernutrition and malnutrition), and normal (good nutrition).

The exclusive breastfeeding status of children can be assessed by information recorded in the maternal and child health registers with the criteria of not getting and getting.

Vitamin A status is the status of vitamin A supplementation in children recorded in the maternal and child health register book with the criteria of not getting and getting.

Data Collection: The sampling technique used was non-probability sampling, using consecutive sampling techniques. Researchers waited for patient visits that fit the sample criteria at the hospital until they met the total number of samples needed. This study used primary data obtained from in-depth interviews regarding appropriate data and information, using a structured questionnaire based on the rotavirus diarrhoea surveillance format [11]. Secondary data were obtained by searching medical records, vaccine cards, and maternal and child health registers. Secondary data in the form of vaccine status, nutritional status, and vitamin A status of children can be used if it is proven by vaccine cards and maternal and child health book records.

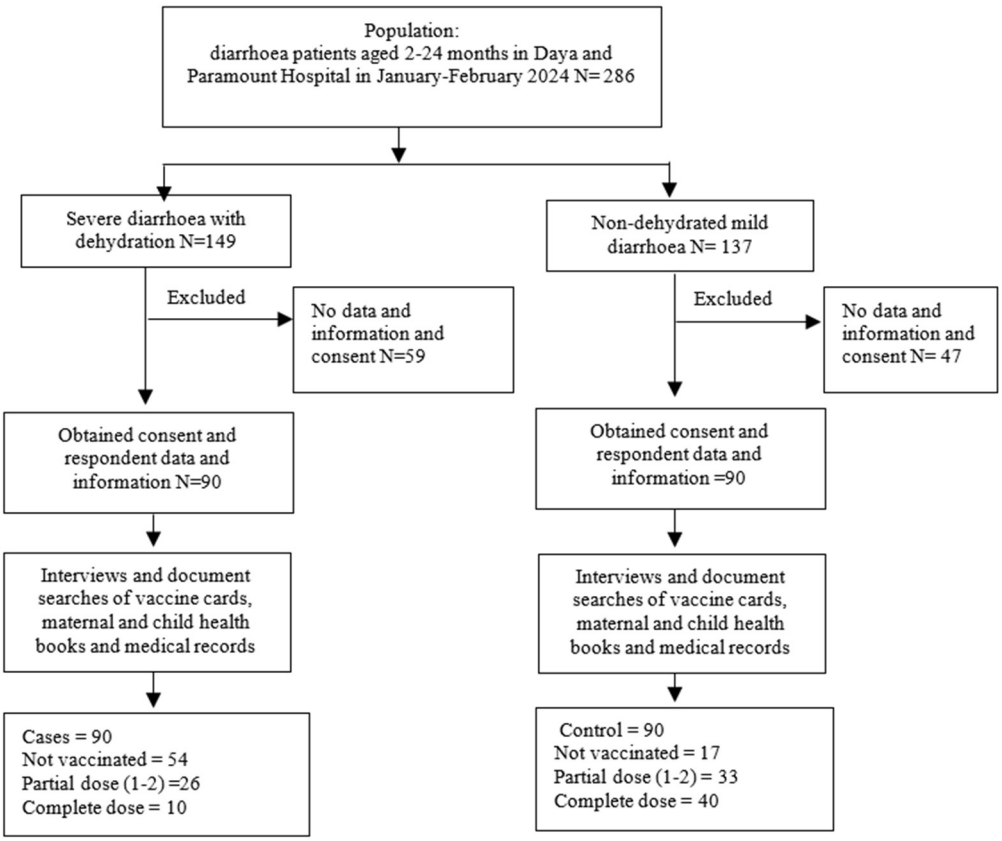

Figure 1: Research flow

Data Analysis: Data analysis was carried out using the STATA 14 application. The data were analyzed in three ways, namely univariate, bivariate and multivariate. Bivariate test analysis used the chi square test at the 95% confidence level (α = 5%) and multivariate used logistic regression test with a confidence level of 95% (α = 5%).

Ethical Approval: Research approval was granted by the research ethics committee of the Faculty of Public Health, Hasanuddin University Makassar, Indonesia, with a recommendation for ethical approval number 143/UN4.14.1/TP.01.02/2024. Approval is obtained from the respondent by having them sign the informed consent.

RESULTS

A total of 286 diarrhoea patients aged 2 to 24 months visited Daya and Paramount hospitals in Makassar City, Indonesia from January to February 2024. A total of 180 (62.6%) eligible children were included in this study (Figure 1).

Table 1 shows that children with severe diarrhoea were mostly female (51.11%). Based on the father's occupation, most children who suffered from severe diarrhoea had a father who was an employee (65.56%). Based on the age of the biological mother, most of the children with severe diarrhoea had mothers aged 25-30 years (57.7%).

Table 2 shows that most children with severe diarrhoea were not vaccinated against rotavirus G9P[11] (60%). The analysis results indicate a significant relationship between rotavirus G9P[11] vaccination status and the severity of diarrhoea in children aged 2-24 months, with a COR of 6.44 (95% CI 3.12-13.48); *P* = 0.0000.

Severe diarrhoea (Table 2) was mostly experienced by children who did not receive the vaccine compared to those who received partial doses (1-2 doses) at a rate of 67.50%. The analysis results of the number of vaccine doses show a significant relationship between the number of partial doses and the severity of diarrhoea in children aged 2-24 months, with a COR of 4.03 (CI95% 1.79-9.16); *P* = 0.0002. This suggests that children who did not receive the rotavirus G9P[11] vaccine had a 4.03 times higher risk of severe diarrhoea compared to those who received partial doses.

Similarly, most children with severe diarrhoea (Table 2) did not receive the vaccine compared to those who received the complete dose (3 doses) at a rate of 84.38%.

Table 1: Distribution of respondents based on characteristics

Characteristics Respondents	Severe diarrhoea (n=90) (%)	Mild diarrhoea (n=90) (%)	Total (n=180) (%)
Gender of the child			
Male	44 (48.8)	51 (56.7)	95 (52.8)
Female	46 (51.1)	39 (43.3)	85 (47.2)
Father's occupation			
Government employee/Army/Indonesian National Police	59 (65.5)	61 (67.8)	120 (66.7)
Self-employed	22 (24.4)	20 (22.2)	120 (66.7)
Farmers	2 (2.2)	2 (2.2)	4 (2.2)
Miscellaneous	7 (7.7)	7 (7.7)	13 (7.2)
Age of biological mother			
< 25 years	3 (3.3)	11 (12.2)	14 (7.7)
25 - 30 years	52 (57.7)	61 (67.7)	113 (62.8)
> 30 years	35 (38.8)	18 (20)	53 (29.4)

Table 2: Bivariate analysis Research variables

Variables	Severe diarrhoea (n=90) (%)	Non-dehydrated diarrhoea (n=90) (%)	Crude OR (95% CI)	*P*
Child receives at least 1 dose of rotavirus vaccine				
No	54 (60.0)	17 (18.9)	6.4 (3.1 -13.5)	0,000*
Yes	36 (40.0)	73 (81.1)		
The child received a partial dose of rotavirus vaccine				
No	54 (67.5)	17 (34.0)	4.03 (1.8 -9.2)	0,002**
Yes	26 (32.5)	33 (66.0)		
Child received the full dose of rotavirus vaccine (3 doses)				
No	54 (84.4)	17 (29.8)	12.7 (4.8 - 34.1)	0,000**
Yes	10 (15.6)	40 (70.2)		
Child received rotavirus vaccine with a duration of less than equal to 12 months				
No	19 (52.8)	15 (20.6)	4.32 (1.7 - 11.2)	0,006**
Yes	17 (47.2)	58 (79.5)		

*Significant level P<0,005 means a correlation with the dependent variable and is included in the multivariate analysis
**The variables were not included in the multivariate analysis due to differences in sample size with other candidate variables, but they were analysed as complementary variables of vaccination status

Table 3: Bivariate analysis of control variables

Variables	Severe diarrhoea (n=90) (%)	Non-dehydrated diarrhoea (n=90) (%)	Crude OR (95% CI)	*P*
Mother's occupation as a housewife				
No	47 (52.2)	25 (27.8)	2.84 (1.5 - 5.5)	0,008*
Yes	43 (47. 8)	65 (72.2)		
Mothers with a high level of education				
No	61 (67.8)	66 (73.3)	0.76 (0.3 - 1.5)	0,413
Yes	29 (32.2)	24 (26.7)		
Mom used to wash her hands				
No	16 (17.8)	6 (6.7)	3.02 (1.1 - 9.8)	0,020*
Yes	74 (82.2)	84 (93.3)		
Child age less than equal to 12 months				
No	66 (73.3)	33 (36.7)	4.75 (2.4 - 9.4)	0,000*
Yes	24 (26.7)	57 (63. 3)		
Well-nourished children				
No	9 (10.0)	6 (6.7)	1.55 (0.4 - 5.5)	0,418
Yes	81 (90.0)	84 (93.3)		
The child is exclusively breastfed				
No	51 (56.7)	25 (27.8)	3.4 (1.7 - 6.6)	0,001*
Yes	39 (43.3)	65 (72.2)		
Children get vitamin A supplements				
No	61 (67.8)	43 (47.8)	2.29 (1.2 - 4.4)	0,006*
Yes	29 (32.2)	47 (52.2)		

*Significant level P<0,005 means a correlation with the dependent variable and is included in the multivariate analysis

Table 4: Multivariate analysis (model 1)

Variables	Model 1				Model 2				Coef
	Crude OR (95% CI)	***P***	**Adjusted OR (95% CI)**	***P***	OR Customize (95% CI)	***P***	OR Customize (95% CI)	***P***	
Mother's occupation as a housewife	2.84 (1.46 - 5.54)	0.008	2.68 (1.29 - 5.59)	0.008*	2.68 (1.29 - 5.59)	0.008	2.74 (1.32 - 5.68)	0.007**	1.008
Mother's habit of not washing her hands	3.02 (1.05 - 9.85)	0.002	1.96 (0.61 - 6.24)	0.252					
Child is older than 12 months	4.75 (2.40 - 9.43)	0.000	2.91 (1.26 - 6.70)	0.012*	2.91 (1.26 - 6.70)	0.012	2.73 (1.19 - 6.24)	0. 017	1.004
Not exclusively breastfed	3.4 (1.74 - 6.65)	0.001	7.31 (2.25 - 23.71)	0.001*	7.31 (2.25 - 23.71)	0.001	4.85 (2.29 - 10.26)	0.000**	1.570
Not getting vitamin A	2.29 (1.20 - 4.41)	0.006	0.52 (0.16 - 1.63)	0.260					
Unvaccinated rotavirus vaccine	6.44 (3.12 -13.48)	0.000	4.32 (1.82 - 10.24)	0.001*	4.32 (1.82 - 10.24)	0.001	4.25 (1.82 - 9.90)	0.001**	1.44
-cons									-2.193

* Significant level P<0,005 means a correlation with the dependent variable and is included in the multivariate analysis model 2.
** Significant level P<0,005 means a correlation with the dependent variable

The analysis results of the number of vaccine doses show a significant relationship between the number of complete doses and the of severity diarrhoea in children aged 2-24 months, with a COR of 12.70 (CI95% 4.87-34.12); *P* = 0.0000. This indicates that children who did not receive the rotavirus G9P[11] vaccine had a 12.70 times higher risk of severe diarrhoea compared to those who received the complete dose.

Furthermore, most cases of severe diarrhoea (Table 2) occurred in children who had received the rotavirus vaccine for more than 12 months (52.78%). The analysis results of the duration time of administration of the rotavirus vaccine G9P[11] show a significant association with the severity of diarrhoea in children aged 2-24 months, with a COR of 4.32 (CI95% 1.66-11.23); *P* = 0.0006. Therefore, it can be concluded that children who received the last dose of the rotavirus G9P[11] vaccine more than 12 months ago are at a 4.32 times higher risk of suffering from diarrhoea compared to those who received the last dose less than or equal to 12 months ago.

The results of the bivariate analysis of control variables shown in Table 3 show that the variables of the biological mother's occupation, mother's habit of washing hands, child's age, exclusive breastfeeding status, and child's vitamin A status have a significant association (*P*<0.05) with the severity of diarrhoea. This indicates that the five variables are confounding factors that can affect the relationship between vaccination status and the severity of diarrhoea, so it is appropriate to include them in the multivariate analysis.

The multivariate analysis used was the multiple logistic regression test to see the relationship between several independent variables with one dependent variable through the predictive concept using the backward method. In this method, variables that can be analyzed multivariate are identified based on the results of bivariate analysis, namely *P* <0.25. Variables that were candidates for multivariate testing were the biological mother's occupation (p=0.0008), mother's hand-washing habit (P=0.02), child's age (p=0.0000), exclusive breastfeeding status (*P*=0.0001), and vitamin A status (*P*=0.006).

Multivariate analysis of model one (table 4) shows that four variables have a significant association with the severity of diarrhoea in children aged 2-24 in Makassar City. The four variables are the mother's occupation (*P*=0.008), child's age (*P*=0.12), exclusive breastfeeding status (*P*=0.001), and rotavirus vaccination status (*P*=0.001), which will then be included in the multivariate analysis model two

Table 5 is the last model of the multivariate analysis which resulted in the variable rotavirus vaccine status G9P[11] being significantly associated with the severity of diarrhoea aged 2-24 months in Makassar City AOR 4.25 (CI95% 1.82 - 9.90); *P* = 0.001. The results of this analysis can be concluded that children who do not receive the rotavirus G9P[11] vaccine have a risk of suffering severe diarrhoea 4.25 times compared to children who have received at least one dose of the rotavirus vaccine.

Discussion

This study found that most children with severe diarrhoea did not receive the rotavirus vaccine (60%). This is comparable to results from previous studies.[12-13] which found that the majority of children with diarrhoea who visited hospitals did not receive the rotavirus vaccine. This emphasizes the need to increase vaccination against diarrhoea diseases, although very few studies have directly compared the effectiveness of different types of vaccines.[14-15]

This study provides the results of a statistical analysis that shows a significant relationship between rotavirus vaccination status and the severity of diarrhoea (*P*=0.001). The analysis showed that children who did not receive the rotavirus G9P[11] vaccine were 4.32 times more likely to suffer from severe diarrhoea compared to children who received at least 1 dose of the vaccine.

Another study, which also examined the effectiveness of the rotavirus vaccine against severe diarrhoea, showed significant results in the group that received at least 1 dose of the rotavirus vaccine.[16] The study found that the rotavac vaccine, with the monovalent strain G9P[11], was significantly associated with diarrhoea in India. Evaluations of rotavirus vaccines have also shown that children who did not receive the rotavirus vaccine were 10.3 times more likely to develop rotavirus-induced diarrhoea compared to vaccinated children.[17] These vaccines have proven to be effective in reducing childhood diarrhoea morbidity in the region.[18] Similar results have shown a decrease in the prevalence of diarrhoea among vaccinated children[19], and the monovalent rotavirus vaccine has been effective in reducing the likelihood of hospitalization due to severe diarrhoea disease in children[20]. This suggests that the rotavirus vaccine plays an important role in addressing the high severity of diarrhoea and supports the government's vaccination program. Increasing rotavirus vaccination coverage to 90% could reduce global childhood diarrhoea mortality by 74.1%.[21]

Regardless of the type of rotavirus vaccine used, previous studies have shown that rotavirus vaccines protect against hospitalized acute diarrhoea in children.[22-26] However, this level of protection varies by country depending on the type of vaccine and dose used. The reasons for these differences are likely to be multifactorial due to differences in rotavirus epidemiology with high infectious strength, co-infection with other enteric pathogens, malnutrition, environmental enteropathy, impaired vaccine uptake by maternal antibodies, and concurrent administration of other vaccines.[8] Approaches to improve the evaluation of vaccine performance through integrated surveillance of rotavirus are taken into consideration in the selection of rotavirus vaccines.

An additional analysis model[27] matched by calculating the OR of each vaccine dose (unvaccinated to partially vaccinated, unvaccinated to fully vaccinated, and duration of vaccine administration) with the severity of diarrhoea found that most children with severe diarrhoea received the partial dose vaccine compared to children who received the full dose vaccine. This study also showed that children who did not receive the vaccine were at 4.03 times the risk compared to children who received the partial dose vaccine and 12,70 times the risk compared to children who received the complete dose (3 doses). This study showed an increased risk in the non-vaccinated group with each dose administered.

Several previous studies have also shown that the number of doses of rotavirus vaccine administration is associated with the severity of diarrhoea. Evaluation of the efficacy of three doses of rotavac G9P[11] after 14 days of the third dose until 2 years of age resulted in efficacy against severe diarrhoea; a secondary outcome was efficacy in preventing hospitalization.[28] The rotavirus vaccine provides a protective effect for the complete vaccine as a whole, with unvaccinated fully vaccinated children being more protected than partially vaccinated and unvaccinated children.[27] Similar results[13,29-30] showed that the number of doses was significantly associated with diarrhoea in hospitalized children.

This study showed an increased risk of diarrhoea with each dose administered when compared to the status of unvaccinated children. This shows the im-

portance of receiving a complete dose of the vaccine. Incomplete vaccines are more common in children[15], therefore health promotion efforts to increase parental awareness to participate in the fulfillment of the number of complete doses (dose 3) of the rotavirus vaccine, and the accuracy of the vaccine administration schedule, are some of the considerations to reduce the severity of diarrhoea in children.

This study showed that the majority of cases of severe diarrhoea were in children who had received the last dose of the vaccine for more than 12 months. The results of statistical analysis showed that the duration of vaccine administration had a significant association with the severity of diarrhoea. The OR value showed that children who received the last dose of the rotavirus vaccine for more than 12 months were more likely to suffer from severe diarrhoea compared to children who received the last dose of the rotavirus vaccine between 2 weeks and 12 months.

Previous studies have also shown an association between the duration of vaccine administration and the severity of diarrhoea. A meta-regression analysis[31] showed that the longer the duration of vaccine administration, the less the effect of the vaccine, leading to more children becoming infected at an older age and showed strong evidence of a higher vaccine effect after a 2-week-12-month administration period, with an initial peak starting at two weeks after vaccination and a decline after 12 months. The monovalent rotavac vaccine G9P[11] is one of the four WHO-prequalified rotavirus vaccine types that have vaccine efficacy against severe diarrhoea.[32] A subanalysis of high-mortality countries in Africa and Asia showed that rotavirus vaccines have vaccine efficacy against severe diarrhoea at 1 year of follow-up decreased after 1 and 2 years of administration.[33-34] Reasons for decreased vaccine efficacy based on the duration of administration have not been demonstrated, but hypotheses regarding lower immunogenicity include interference from maternal antibodies, interference from oral polio vaccine, neutralizing factors present in breast milk, malnutrition, and other enteric co-infections, rotavirus strain diversity, and HIV infection.[35] Nevertheless, the rotavirus vaccine still provides great benefits in reducing the severity of diarrhoea.[36] In addition to reduced vaccine-induced protection, program restrictions, including age limits on rotavirus vaccine administration, may limit the opportunity for childhood vaccine catch-up.[27]

Based on the results of this study and the support of previous studies that provide information, vaccine efficacy will decrease with the length of time of receiving doses and have the effect of more children being infected at an older age. Given that severe diarrhoea is likely to be experienced by children up to the age of five, the administration of additional doses of vaccine after the main vaccine dose of 3 doses (booster) is a consideration.

This study was not able to separate rotavirus and non-rotavirus diarrhoea groups, so we cannot explain the specific association of the rotavirus vaccine with the severity of rotavirus diarrhoea. However, overall, most children under five who are hospitalized for diarrhoea are rotavirus cases, and 92-94% occur in children less than 2 years[37,38,39], so we assume it is appropriate if the case group used is severe diarrhoea cases other than rotavirus diarrhoea.

Bias can occur due to the length of time the vaccine is administered on the effectiveness of the vaccine. To minimize bias, the researchers limited vaccination status to a child considered vaccinated at least 2 weeks after vaccine administration. The efficacy and safety of the rotavirus vaccine can be seen 14 days after vaccine administration.[28]

Conclusion

Monovalent rotavirus vaccine G9P[11] status was significantly have correlation with the severity of diarrhoea among children aged 2-24 months in Makassar City, South Sulawesi, Indonesia. Unvaccinated rotavirus vaccine G9P[11], Mother's occupation as a housewife, Child is older than 12 months, not exclusively breastfed are risk factors for severe diarrhoea in children aged 2-24 months.

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