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Original Article

Factors Related to the Incidence of Congenital Rubella Syndrome (CRS) in Indonesia

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ABSTRACT

Congenital Rubella Syndrome (CRS) is a serious consequence in infants due to Rubella virus infection during early pregnancy which can cause several congenital abnormalities. In 2021, Indonesia became the country that reported the highest cases of CRS in the WHO Southeast Asia region with 229 cases out of a total of 402 cases (57%). There are various factors related to the incidence of CRS including vaccination, health facilities and mother and baby factors. Knowledge on these factors can be applied to improve efforts to prevent and control CRS cases. This study aims to determine the factors related to the incidence of CRS in Indonesia. This was a case-control study using secondary data derived from the 2020-2021 CRS sentinel surveillance reports of the Ministry of Health of the Republic of Indonesia. Based on the results of multivariate analysis using multiple logistic regression, it was revealed that there was one factor related to the incidence of CRS, namely the area of residence with an OR of 2.3 (95% CI: 1.49-3.42). The area of residence outside Java-Bali had a higher risk for the incidence of CRS by 2.3 times compared to the area of residence in Java-Bali. In contrast, other variables such as history of maternal vaccination, history of maternal Rubella infection, maternal age and the child gender were not found to be statistically related to the incidence of CRS. It can be concluded that the area of residence outside Java-Bali was a factor related to the incidence of CRS. Therefore, it is necessary to have an even distribution of Rubella vaccination coverage, strengthen the surveillance system and prepare equal distribution of health facilities to prevent the spread of Rubella cases.

Keywords : Rubella, Congenital Abnormalities, Congenital Defects, Sentinel Surveillance.

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INTRODUCTION

Congenital Rubella Syndrome (CRS) is a condition of various congenital abnormalities that occur in infants due to Rubella virus infection during pregnancy. Congenital abnormalities that usually occur include cataracts, congenital heart disease, hearing loss and developmental delays[1]. Congenital abnormalities due to the Rubella virus are most at risk in the first 12 weeks of pregnancy. Congenital abnormalities that occur in infants may cause serious consequences in the form of permanent disability, medical burden and financial burden since the treatment of infants with CRS is limited to treating symptoms that can last for years[3].

CRS cases still occur in countries with low vaccination coverage or with no implementation of Rubella vaccination. Indonesia is one of the countries that still reports CRS cases every year. In 2019

,Indonesia reported 211 cases of CRS, which decreased in 2020 by 122 cases and increased again in 2021 by 229 cases[4]. In 2021, Indonesia became the country that reported the highest cases of CRS in the WHO Southeast Asia region with 229 cases out of a total of 402 cases (57%). The increase in CRS cases in 2021 is in line with the decrease in Measles-Rubella vaccination coverage in 2020 - 2021 or since the COVID-19 pandemic took place. Decreased vaccination coverage during a pandemic could be due to delayed schedule of Community Health Care services and immunization logistics, parents were afraid of contracting COVID-19 when they came to health facilities, and COVID-195 virus exposure among healthcare workers, families and children[5].

Based on several studies, most cases of CRS occur in male children, with an age range of <1 – 5 months, and low birth weight babies. Most of clinical findings are heart defects, sight abnormalities and hearing loss that are permanent and occur in women who give birth with an age range between 14-30 years[6,7]. The results of a study on Rubella immunity seroprevalence in women showed that vaccination increases a person's antibodies thereby reducing the possibility of Rubella virus infection and giving birth to babies with CRS[8] [9]. Previous study on CRS in Indonesia observed CRS cases based on sentinel hospitals descriptively to determine the number of cases, clinical symptoms and the development of a surveillance system on CRS[10]. Another studies discussed the relationship between Rubella infection factors and the incidence of CRS through a spatiotemporal approach[11], and the relationship between vaccination factors and family awareness descriptively with the incidence of CRS[12,13]. Studies on CRS in Indonesia have mostly been conducted descriptively, but analytic studies and relationships between various factors have not been widely studied.

CRS is still a public health burden in several countries. Congenital abnormalities that occur in infants due to CRS can cause medical burdens as well as financial burdens for both the family and the country. Therefore, the main strategy that can be implemented to reduce the burden of CRS disease is through promotive and preventive efforts. In order to carry out effective prevention efforts in addressing the increase in CRS cases, it is necessary to have knowledge of the factors related to the incidence of CRS in Indonesia in order to determine the relationship and the size of effect of these factors on the incidence of CRS.

Based on the description above, the incidence of CRS still needs proper attention since it continues to occur every year and can cause various permanent congenital defects in infants. In addition, analytic studies regarding the factors of the incidence if CRS have not been widely conducted in Indonesia. This study aims to determine the factors related to the incidence of CRS in Indonesia.

METHOD

This was a case-control study which is defined as a study that traces back the causal factors that can lead to a health problem. The study was conducted in July – October 2022 using secondary data derived from the CRS Sentinel Surveillance Report of the Ministry of Health, Republic of Indonesia in 2020-2021. It was the result of investigation towards CRS cases from 18 sentinel hospitals in 15 provinces in Indonesia. The study population was all cases of suspected CRS recorded in the 2020-2021 CRS sentinel surveillance report, as many as 1,373 cases. Based on the two-proportion hypothesis test formula in a case-control study described, it was obtained a minimum sample size for each group of 180 samples. The sampling as conducted using cumulative sampling. The case group consisted of women with suspected CRS with the final classification of clinical CRS and laboratory confirmed CRS that met the inclusion and exclusion criteria, as many as 180 samples. Meanwhile, the control group consisted of women with suspected CRS with a final classification of non-CRS cases that met the inclusion and exclusion criteria, as many as 240 samples. The dependent variable of the current study was the incidence of CRS, while the independent variables included history of maternal rubella vaccination, history of maternal rubella infection, maternal age, child gender and area of residence.

Data were analyzed using the STATA application version 13.0 which consisted of bivariate analysis through the chi-square test for variables with 2 categories, the Fisher's exact test if there were cells with an expected frequency of <5, and the simple logistic regression test for variables with >2 categories. Meanwhile, multivariate analysis was conducted through multiple logistic regression

test to determine the relationship between independent variables and dependent variable as well as the most dominant variable in the relationship.

RESULTS

Bivariate analysis was conducted between two variables that were suspected to be related to each other, namely the independent variables and the dependent variable. If the results of statistical calculation obtained a p value of < α (0.05), then there is a significant relationship between the two variables. Table 1 presented that most of respondents in the case and control groups had no history of rubella vaccination (99.4% vs 99.2%) and had no history of rubella infection (99.4% vs 99.6%). Furthermore, most of respondents in both groups were 20-34 years of age (73.9% vs 66.7%), had male children (54.4% vs 53.8%) and lived the area of residence of Java-Bali

Table 1. Bivariate analysis on the Relationship between the Independent Variable and the Incidence of CRS.

Variable	Case n (%)	Control n (%)	Total n (%)	OR	p-value
History of Maternal Rubella Vaccination					
No	179 (99,4%)	238 (99.2%)	417 (99.3%)	1.00	0.607
Yes	1 (0.6%)	2 (0.8%)	3 (0.7%)	Reff	
History of Maternal Rubella Infection					
Yes	1 (0.6%)	1 (0.4%)	2 (0.5%)	1.00	
No	179 (99.4%)	239 (99.6%)	418 (99.5%)	Reff	0.647
Maternal Age					
14-19	5 (2.8%)	11 (4.6%)	16 (3.8%)	Reff	
20-34	133 (73.9%)	160 (66.7%)	293 (69.7%)	1.83	0.274
35-49	42 (23.3%)	69 (28.8%)	111 (26.3%)	1.33	0.611
Child Gender					
Male	98 (54.4%)	129 (53.8%)	227 (54%)	0.92	0.483
Female	82 (45.6%)	111 (46.3%)	193 (46%)	Reff	
Residence					
Outside Java-Bali	82 (45.6%)	65 (27.1%)	147 (35%)	2.25	0.0001
Java-Bali	98 (54.4%)	175 (72.3%)	273 (65%)	Reff	

The results of the bivariate analysis showed that there was one variable that had a significant relationship with the incidence of CRS, namely the area of residence (0.0001). In contrast, history of maternal Rubella vaccination (0.607), history of maternal Rubella infection (0.647), maternal age group of 20-34 years (0.274), maternal age group of 35-49 years (0.611) and child gender (0.483) variables were not statistically related to incidence of CRS (Table 1).

Analysis was continued with multivariate analysis through multiple logistic regression, namely by entering all the independent variables simultaneously into the model. Such analysis aims to assess the size of relationship of each independent variable after considering other independent variables and to find out the most dominant independent variable towards the dependent variable.

Based on the results of multivariate analysis, there was one variable that was statistically related to the incidence of CRS, namely the area of residence with OR = 2.3, 95% CI (1.49-3.42). The area of residence outside Java-Bali had a higher risk for the incidence of CRS by 2.3 times compared to the area of residence in Java-Bali. Other variables of maternal history of maternal Rubella vaccination (OR=2.8, 95% CI (0.25-31.4), history of maternal Rubella infection (OR=1.6, 95% CI (0.99-26.4), maternal age of 20-34 years (OR=1.5, 95% CI (0.50-4.53), and maternal age of 35-49 years (OR=1.1, 95% CI (0.36-3, 57) also had a risk for the incidence of CRS, but statistically had no significant correlation (p-value >0.05). On the other hand, the child gender variable was a variable that had no risk for the incidence of CRS (OR=1.0, 95% CI (0.66-1.47) and statistically had no significant correlation (Table 2).

Tabel 2. Multivariate Analysis of the Relationship between Independent Variable and the Incidence of CRS in Indonesia.

Variable	OR	95% CI		p-value
		Lower	Upper	
History of Maternal Rubella Vaccination				
No	2.8	0.25	31.40	0.410
Yes	Reff			
History of Maternal Rubella Infection				
Yes	1.6	0.99	26.41	0.735
No	Reff			
Maternal Age				
14-19	Reff			
20-34	1.5	0.50	4.53	0.464
35-49	1.14	0.36	3.57	0.821
Child Gender				
Male	1.0	0.66	1.47	0.949
Female	Reff			
Residence				
Outside Java-Bali	2.3	1.49	3.42	0.000
Java-Bali	Reff			

DISCUSSION

Area of residence outside Java-Bali had a highet risk for the incidence of CRS than area of residence in Java-Bali. The difference in the incidence of CRS between regions was closely related to the difference in Rubella vaccination coverage, the quality of CRS/Rubella surveillance and the difference in the quality of health services provided in the region[13]. Based on national vaccination coverage data for 2021, the lowest vaccination coverage was reported from provinces outside the Java-Bali region such as Aceh (40.9%), West Papua (56.9%) and Papua (54.6%). CRS sentinel surveillance performance in 2021 also revealed that areas outside Java-Bali (89%) were less likely to reach the target when compared to areas in Java-Bali (100%)[4]. In addition, the uneven availability of health facilities in Indonesia can lead to disparities in access to health services for women who plan for pregnancy, including in terms of vaccination and early detection of Rubella infection. Based on a study conducted by Misnaniarti (2017), the ratio of specialists tended to be lower in areas outside Java-Bali and most hospitals in Indonesia are located in the Java-Bali region (51.4%), most of which are type A hospitals (67.3%)[14]. Such differences in health infrastructure reflect that women living outside the Java-Bali region had fewer choices to obtain ideal quality maternal and fetal care compared to those living in the Java-Bali region[14,15].

The incidence of CRS in an area is also related to the incidence of Rubella cases. A study conducted by Sriwahyuni (2020) found that there was a spatio-temporal relationship between Rubella cases and the incidence of CRS, wherein CRS was detected 6-8 months after an increase in Rubella cases[11]. In 2020, there were 67 cases of Rubella and in 2021 there were 106 cases in areas outside Java-Bali with the majority of cases were among children who had not received vaccinations (55%)[16]. Such finding indicated that those areas are still vulnerable to Rubella and CRS. So, it is necessary to strengthen the surveillance system to prevent a wider spread of the disease.

Based on the study results, it was known that history of maternal vaccination was not related to the incidence of CRS, this is not in line with several studies which stated that history of maternal vaccination was proven to be effective in reducing Rubella cases and the incidence of CRS. The results of a study conducted in Yogyakarta found that there was a decrease in the number of CRS cases by 60.9% after 1 year since the measles-Rubella vaccination campaign was implemented[13]. Similar finding was also reported in Australia, which is one of the countries that have achieved Rubella elimination. Such study compared CRS case data in 2010 to the pre-vaccination era

(1960-1970). It was found that selective Rubella vaccination for school students could reduce CRS cases by 90%, while universal vaccination given to all children could reduce CRS cases more significantly (99%)[17].

A history of rubella infection during pregnancy was also statistically not related to the incidence of CRS. Such finding is not in line with the literature which stated that the incidence of CRS occurred due to rubella infection during pregnancy, especially in the first trimester[18]. CRS can occur because the Rubella virus is capable of infecting the placenta, spreading to the fetus and changing the function of several fetal systems by interfering with organ formation and causing systemic inflammation and further lead to various congenital abnormalities[19]. Based on the data source, the history of rubella infection in question was a history of maternal Rubella diagnosis during pregnancy based on laboratory confirmation. Out of the total sample, only 2 people (0.5%) had a history of Rubella infection with laboratory confirmation during pregnancy was found. This indicated that only a few mothers checked for symptoms of rubella infection during pregnancy at a health facility, which could be due to a lack of maternal knowledge about the symptoms of Rubella infection. They thought that infection only caused mild clinical symptoms or no symptoms so they didn't go to the hospital or health facilities or there was a lack of access to health services.

More than 50% of Rubella cases were asymptomatic and the clinical diagnosis of Rubella was unreliable because a similar rash can also occur due to other viral infections. Therefore, the diagnosis of Rubella infection among pregnant women requires standard laboratory test[20]. Rubella clinical manifestations are non-specific and very diverse, causing the identification of suspected CRS cases to be quite challenging[21], so that pregnant women's awareness to have examination is required. On addition, there should be accuracy of medical personnel and improvement of the quality of health services supported with screening and diagnostic equipment for other related cases, for example congenital heart defects using echocardiography and hearing defects using otoacoustic emission (OAE).

Maternal age is a factor that is not statistically related to the incidence of CRS. However, based on several studies, women of childbearing age are more susceptible to Rubella infection and are at risk of giving birth to babies with CRS compared to other age groups. A study conducted by Chandy (2011) found that women aged 24-34 years had a higher susceptibility to Rubella infection (14.5%) compared to the age group of 19-23 years (8%)[22], which could be due to a reduced immune response in such age group. Another study conducted by al Dossary (2022) revealed that susceptibility to Rubella increased in the age group of 29-34 years with an OR of 1.225 compared to other age groups. The higher the susceptibility of women of childbearing age to Rubella infection, the higher the risk for Rubella infection during pregnancy and giving birth to babies with CRS[23]. Therefore, it is important to ensure that women of childbearing age are aware of their Rubella immune status and if necessary they should get Rubella vaccination to increase immunity against Rubella infection[24].

The study results revealed that was no significant relationship between child gender and the incidence of CRS. This result is not in line with a study conducted by Tandililing (2016) and Singh (2013) which found that male babies had a higher risk for CRS than female babies. However, this study did not explain the reasons of it[25,26]. Previous study conducted by Mitchell revealed a different finding that women were more susceptible to Rubella and CRS since women have a slower onset of formation of E-specific IgG and IgM antibodies with a smaller proportion of total RV antibody responses indicating that there are hormonal and genetic influences on immune recognition of RV proteins. This is likely to be associated with an increase in the incidence of Rubella and CRS among women[27].

CONCLUSION

Area of residence outside Java-Bali was a factor related to the incidence of CRS in Indonesia. To support efforts to prevent and eliminate Rubella/CRS in 2026, it is necessary to increase and equalize the coverage of Rubella vaccination in all regions through cooperation with various related sectors. In addition, equal distribution of health facilities in Indonesia still needs to be considered so that mothers who have pregnancy plans in all regions can get quality health services to prevent CRS.

This study had several limitations, namely the samples who were selected from 18 CRS Sentinel Hospitals in 15 provinces. CRS Sentinel Hospital is a hospital owned by the central/regional government and private hospitals are not yet involved. So, it is possible that there were still many cases of CRS that had not been reported. Further study which involved more CRS case data from sentinel hospitals and more complete data is expected to provide more representative findings to describe the condition of CRS in Indonesia.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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