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Associations of Host Characteristics, Immunisation History and Rash Onset with Measles-Rubella Specific Immunoglobulin M (IgM) Status in South Sulawesi

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Abstract

Measles and rubella are viral diseases that are transmitted through the air by droplets, and are one of the most common and highly contagious diseases. Measles and rubella infections have similar symptoms when viewed from the symptoms that appear in patients where fever and maculopapular rash as the main symptoms. The aim of the study was to determine the relationship of host characteristics, measles-rubella immunisation history and specimen collection time to immunoglobulin M (IgM) infection markers in suspected measles-rubella patients in South Sulawesi Province. Observational research with a *Cross Sectional Study* design using secondary data from the *Case Based Measles Surveillance (CBMS)* programme of the South Sulawesi Provincial Health Office in 2019-2023 (June). A total of 675 suspected measles-rubella cases had specimens collected for IgM confirmation. The results were 25.2% (n = 170/675) positive and 74.8% (n = 505/675) negative. In terms of gender, there was no significant difference between males (23.1%; n = 78/337) and females (27.2%; n = 92/338) who were IgM positive. As for the age group variable, the highest positive IgM was in the age group of 2-5 years, 35.6% (n = 48/135) and the lowest in the age group of >30 years, only 5.6% (n = 3/54). Measles-rubella IgM positive immunised 60.4% (n = 408/675), never/unknown immunisation status 39.6% (n = 267/675). Sampling time variable 0-3 days was 56.0% (n = 378/675) and 4-28 days was 44.0% (n = 297/675). The results of this study reported positive measles-rubella IgM serological test results were not associated with age, gender and time of specimen collection. However, statistically (*p value* = 0.000) there was an association between MR immunisation status and positive measles-rubella IgM status in South Sulawesi in 2019-June 2023.

Keywords: measles, rubella, CBMS, specimen collection time

Full length article **Corresponding Author*, e-mail: ibaskaminah@gmail.com Doi # https://doi.org/10.62877/49-IJCBS-24-25-19-49

1. Introduction

Measles and rubella are viral diseases transmitted through the air by droplets, and remain one of the most common and highly contagious diseases. Although these diseases can infect all people regardless of age, the highest frequency of cases occurs in children under the age of five [1]. Measles and rubella infections have similar symptoms when viewed from the symptoms that appear in patients where fever and maculopapular rash are the main symptoms [2]. Measles is a highly contagious disease characterised by acute symptoms such as high fever, conjunctivitis, coryza, cough and maculopapular rash [3]. These symptoms can cause serious illness if accompanied by severe complications, such as pneumonia, encephalitis and death [4]. In contrast to measles, rubella also known as "German measles", is generally a mild disease for children but can have serious complicating consequences for pregnant women [5]. Rubella is a mild disease in children, but can have adverse effects if it occurs in first trimester pregnant women, namely miscarriage or disability in infants often called *Congenital Rubella Syndrom* (CRS) such as heart and eye abnormalities, deafness and delays in child development [6]. The CBMS programme means that every clinical measles case is individually recorded *(case line listed)* and laboratory confirmed by serological/Imunoglobulin M testing [7]. In 2022, South Sulawesi became the 15th province in Indonesia with 290 suspected cases and the proportion of measles

suspected cases that were immunised, 68.6%. There were seven laboratory-confirmed measles cases (measles IR: 0.77 per 100,000 population) and 16 positive rubella cases (Rubella IR: 1.76 per 100,000 population). In the same year, South Sulawesi reported two suspected measles outbreaks, one in Maros District with 12 suspected cases and one *confirmed rubella* outbreak in Tana Toraja District with five suspected cases with serological examination results of three rubella positive IgM cases and two negative cases.

2. Materials and Methods

2.1. Data collection and serological testing

We used secondary data from *case-based measles surveillance (CBMS)* in South Sulawesi with a population of 9,022,276 people and consisting of 24 districts and cities. The population in this study was all suspected measles cases from districts and cities that had serum specimens taken and tested for Immunoglobulin M (IgM). One copy of the measles-rubella suspected case investigation form (MR-01) was attached when sending serum specimens to the measles-rubella national/sub-national reference laboratory. Samples sent to the national/sub-national measles reference laboratory are tested for immunoglobulin M (IgM) by *Enzyme Link Immunosorbant Assay (ELISA)* technique using *EUROIMMUN ELISAs Reagent* and a commercial kit, *Humareader HS, Germany*. Patients with measles IgM-positive serum samples were classified as laboratory confirmed measles cases and patients with rubella IgM-positive serum samples were classified as confirmed rubella cases. Due to limited resources, all samples with measles IgM-positive results were not followed up with rubella serological testing.

2.2. Data Analysis

We conducted a cross-sectional study of the provincial *Case Based Measles Surveillance (CBMS)* programme for the period 2019-2023 (June) in South Sulawesi, Indonesia. Data were analysed using the statistical programme *Stata 14 (Stata Corp. College Station, USA)* and *Quantum Geographic Information System version 3.26.2*.

3. Results and discussion

A total of 675 suspected measles-rubella cases had specimens collected for confirmation of immunoglobulin M (IgM) infection markers at the measles-rubella reference laboratory. 25.2% (n = 170/675) were positive for measles-rubella IgM and 74.8% (n = 505/675) were negative/discarded. In the gender variable, there was no significant difference between males (23.1%; n = 78/337) and females (27.2%; n = 92/338) detected positive measles-rubella IgM which can be seen in table 1. As for the age group variable, measles-rubella IgM positivity was highest in the 2-5 years age group with 35.6% (n = 48/135) while the lowest in the >30 years age group with only 5.6% (n = 3/54). The results of hypothesis testing showed that the variables statistically associated with measles-rubella IgM status of measles suspected patients in South Sulawesi were MR immunisation history variables (IDL and booster) while age, sex and time of specimen collection had no association with the incidence of measles-rubella immunoglobulin M (IgM) positive disease in South Sulawesi (table 2). Only 60.4% (n = 408/675) of measles-rubella IgM positive cases were immunised, 39.6% (n = 267/675) were never immunised, which can be seen in table 3. Only 19.7% (n = 133/675) had received the first dose of MR immunisation, 18.7% (n = 126/675) including two children aged 0-17 months (table 4), too young to complete the recommended booster immunisation schedule, and six children (4.8%) aged 18-23 months. Those who received two or more booster doses were 22.1% (n = 149/675). Table 3 above shows that the sampling time of 0-3 days was 56.0% (n = 378/675) and the specimen collection time of 4-28 days was 44.0% (n = 297/675). Figure 1 shows the distribution of the number of positive IgM measles cases in 2019-2023 (June) where the number of measles cases in 2023 increased significantly compared to the previous year and the distribution was almost in all districts/cities. While the number of positive IgM rubella cases tends to decrease, this is due to the examination mechanism at the measles-rubella referral laboratory not continuing the rubella serological examination if it has found positive IgM measles and this is a weakness in this study. Figure 2 shows the distribution of measles-rubella IgM positive cases in 2019-2023 (June). The highest distribution of positive IgM measles cases was reported from three districts in South Sulawesi, while positive IgM rubella cases were almost evenly distributed in each district/city. The data of this study were taken from the *Cased Based Mealses Surveillance (CBMS)* report of South Sulawesi Province for the period of 2019-June 2023. It was found that the number of suspects who took specimens for specimen examination at the national/sub-national measles-rubella referral laboratory was 675 suspected measles cases with positive measles-rubella IgM laboratory examination results as many as 170 samples, and as many as 505 samples showed negative results of measles and rubella IgM. The results of this study showed that the age variable had no association with the incidence of measles-rubella IgM positive *(p-value = 0.317)*. Whereas the results of a study in Uganda reported an association between the age variable and measles-rubella IgM positivity before the immunisation campaign and after the MR immunisation campaign *(p-value = 0.001)* [1]. A study conducted in Taiwan comparing measles-rubella cases between 2011-2020 showed no significant difference between genders. Specifically, gender was not a risk factor for measles and rubella; however, the rate was slightly higher in males (57.8% for measles cases and 64.4% for rubella cases) than females [8]. In line with this study, the gender variable did not have an association with the incidence of measles-rubella IgM positivity in males 23.1% (n = 78/337) and females 27.2% (n = 92/338). This study reported that MR immunisation status was associated with positive measles-rubella IgM serology laboratory results. A study of measles infection after the COVID-19 pandemic in the United States showed that a decrease in vaccination rates had a highly non-linear effect on the number of measles cases, with a 5% decrease in vaccination rates resulting in a doubling of measles cases when the decrease in vaccination rates was concentrated in low-income households [10]. This result is not in line with a *case-control* study using CBMS data conducted in Kediri (*p-value* = 0.161; 95% CI = 0.849-5.315) [9].

Table 1. Laboratory-confirmed measles suspected cases by sex and age group, 2019-2023 (June)

Description	n	Laboratory Examination Results	
		Measles-rubella IgM (+)	Negative (Discarded)
MR suspects with specimen, n (%)	675 (100)	170 (25.2)	505 (74.8)
Gender, n (%)			
Male	337 (49.9)	78 (23.1)	259 (76.9)
Women	338 (50.1)	92 (27.2)	246 (72.8)
Age group, n (%)			
<24 months	112 (16.6)	33 (29.46)	79 (70.5)
2-5 years	135 (20.0)	48 (35.6)	87 (64.4)
6-10 years	173 (25.6)	47 (27.2)	126 (72.8)
11-20 years	145 (21.5)	25 (17.2)	120 (82.8)
21-30 years	56 (8.3)	14 (25.0)	42 (75.0)
>30 years	54 (8.0)	3 (5.6)	51 (94.4)

Source: MR02 South Sulawesi Provincial Health Office

Table 2. Significance based on the variables studied

Research Variables	*P-Value*
Age	0.317
Gender	0.223
MR immunisation history (IDL and booster)	0.000
Specimen collection time	0.353

Table 3. Measles suspected cases with laboratory testing by immunisation status and time of specimen collection, 2019-2023 (June)

MR suspects with specimen, n (%)	Laboratory confirmed cases	Laboratory Examination Results			
		IgM Positive		IgM Negative	
		n	%	n	%
Immunisation Status	675 (100)	170	25.19	505	74.81
Not immunised/don't know	267 (39.6)	88	32.96	179	67.04
Immunised	408 (60.4)	82	20.09	326	79.90
Dose 1 (IDL)	133 (19.7)	36	27.07	97	72.93
Booster 1	126 (18.7)	22	17.46	104	82.54
Booster 2+	149 (22.1)	24	16.11	125	83.89
Specimen collection time					
0-3 days	378 (56.0)	90	23.81	288	76.19
4-28 days	297 (44.0)	80	26.94	217	73.06

Source: MR02 South Sulawesi Provincial Health Office

Table 4. Measles suspected cases by immunisation status and age group, 2019 - 2023 (June)

MR suspects with specimen, n (%)	Laboratory confirmed cases	Age Group						
		0-17 months	**18-23 months**	**2-5 years**	**6-10 years**	**11-20 years**	**21-30 years**	**>30 years**
Immunisation Status	675	85 (12.6)	27 (4.0)	135 (20.0)	173 (25.6)	145 (21.5)	56 (8.3)	54 (8.0)
Not immunised/don't know	267 (39.6)	66 (24.72)	7 (2.6)	60 (22.5)	46 (17.2)	34 (12.7)	17 (6.4)	37 (13.9)
Immunised	408 (60.4)	19	20	75	127	111	39	17
Dose 1 (IDL)	133 (19.7)	17 (12.8)	14 (10.5)	32 (24.1)	29 (21.8)	24 (18.1)	11 (8.3)	6 (4.51)
Booster 1	126 (18.7)	2 (1.6)	6 (4.8)	27 (21.4)	33 (26.2)	36 (28.6)	18 (14.3)	4 (3.2)
Booster 2+	149 (22.1)	0	0	16 (10.7)	65 (43.6)	51 (34.2)	10 (6.7)	7 (4.7)

Source: MR02 South Sulawesi Provincial Health Office

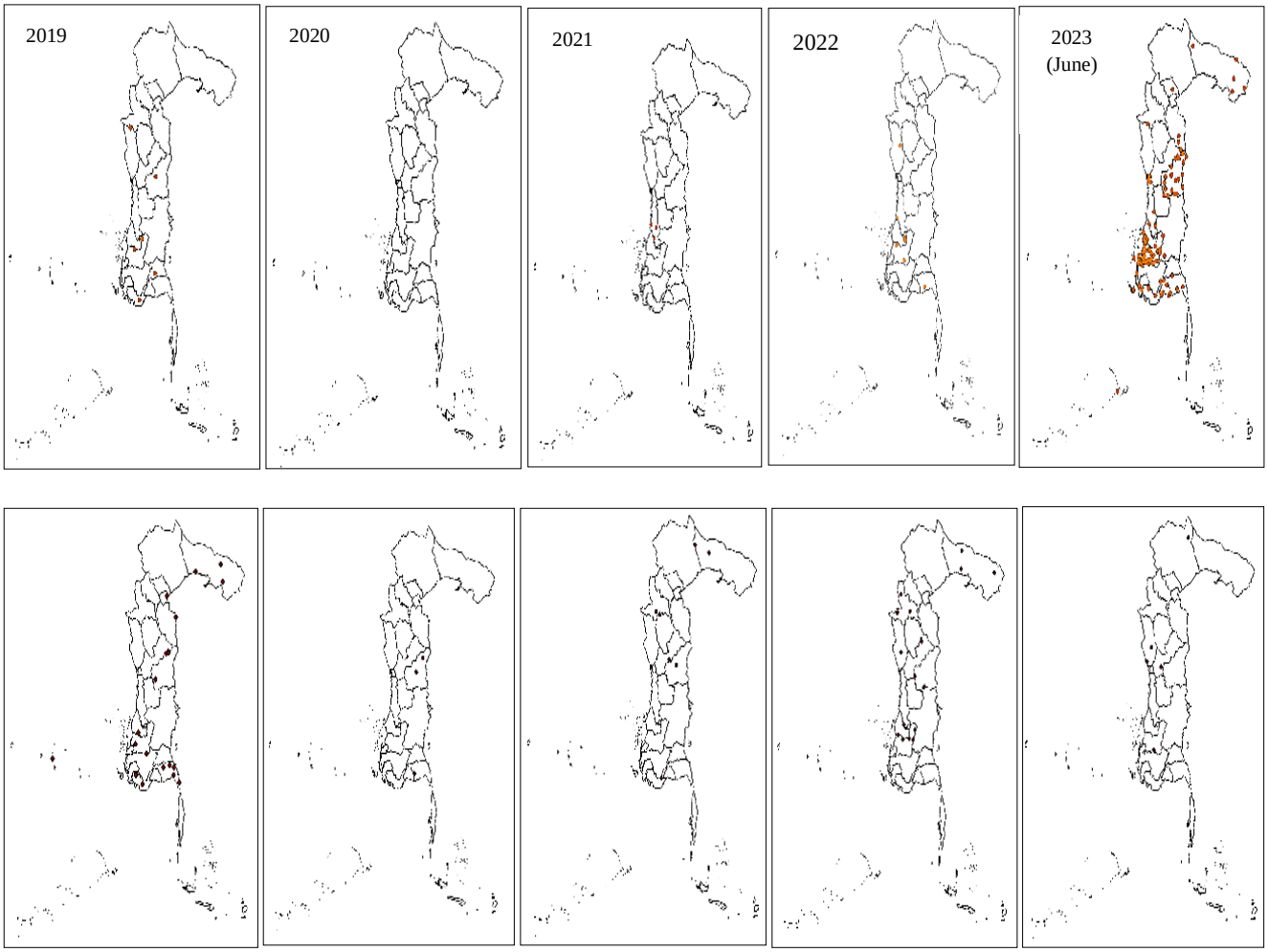

Figure 1. District Distribution of Measles-rubella incident over time in South Sulawesi-Indonesia, 2019 - 2023 (June)

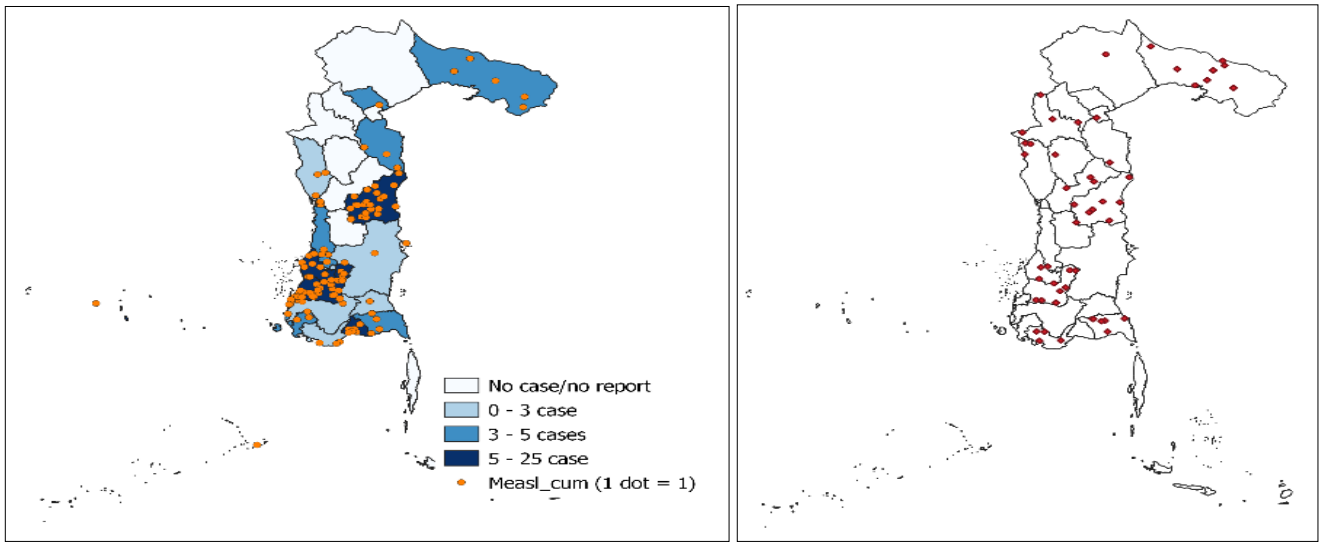

Figure 2. District Distribution of Measles-rubella cumulative incidence over time in South Sulawesi-Indonesia, 2019 - 2023 (June)

In measles-rubella surveillance, ELISA for measles-rubella specific IgM is considered the *gold standard* for laboratory screening of measles cases. However, the IgM ELISA is found to be most sensitive between day 4 to day 28 after the rash [11]. Up to 30% of measles sera in the first 3 days after the rash are found to be negative for measles-specific IgM, which can lead to false-negative results [12]. This study reported no association between the time of specimen collection and the incidence of measles-rubella IgM positivity. This is in contrast to a previous study conducted by [13]. The results showed that specimen collection more than three days after the appearance of rash symptoms affected the confirmation of measles IgM positivity by 1.5 times compared to specimens taken less than three days. Further research conducted in China by *Cui et al., 2018* with the title *"Importance of real-time RT-PCR to supplement the laboratory diagnosis in the measles elimination programme in China"* suggested that if only measles-specific IgM ELISA is used, many IgM-negative measles cases will be missed in measles surveillance. Given the high transmission of measles-rubella virus, such missed measles cases will lead to the spread of measles-rubella virus and pose a great challenge for measles-rubella eradication. Therefore, detection of viral nucleic acid by Real Time-PCR is essential for confirmation of measles cases in the measles pre-elimination phase, especially for measles cases with a history of MR immunisation, no rash symptoms, and specimen collection time of 0-3 days after onset. Site-based epidemiological analysis (Figure 2) of IgM-positive measles-rubella cases in South Sulawesi from 2019 to June 2023 shows that measles-rubella infection is widespread in many districts/cities. This is certainly a problem in areas with high population density. These areas become vulnerable to measles-rubella transmission if the number of vulnerable populations is large enough [14]. This study is consistent with previous studies showing that measles-rubella infection is widespread in several countries. Research in Ethiopia data from 2011 to 2015, approximately 2,295 laboratory-confirmed rubella cases were identified from 11 regions and two administrative cities in Ethiopia. Among these cases, 92% of rubella infections occurred in children aged <15 years revealing that the infection is prevalent in school children [15].

4. Conclusions

The results of this study can conclude that positive measles-rubella IgM serological test results are not associated with age, gender and time of specimen collection. However, there is a statistical association between MR immunisation status (IDL and Booster) and positive measles-rubella IgM status in South Sulawesi during 2019-June 2023.

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