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ORIGINAL ARTICLE

Hospital-based surveillance of congenital rubella syndrome in Indonesia

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Abstract Congenital rubella syndrome (CRS) has serious consequences, such as miscarriage, stillbirth, and severe birth defects in infants, resulting from rubella virus infection during pregnancy. However, rubella vaccine has not yet been implemented in Indonesia. This study aimed (1) to estimate the incidence of CRS in Indonesia, (2) describe the clinical features of CRS at our referral hospital, and (3) pilot a CRS surveillance system to be extended to other hospitals. We conducted a 4-month prospective surveillance study of infants aged <1 year with suspected CRS in 2013 at an Indonesian hospital. Infants with suspected CRS were examined for rubella-specific IgM antibody or rubella IgG antibody levels. Of 47 suspected cases of CRS, 11/47 (23.4%), 9/47 (19.1%), and 27/47 (57.5%) were diagnosed as laboratory-confirmed, clinically compatible, and discarded CRS, respectively. The most common defects among laboratory-confirmed CRS cases were hearing impairment (100%), congenital cataracts (72.7%), microcephaly (72.7%), and congenital heart defects (45.5%).

Conclusion: The number of laboratory-confirmed CRS cases among Indonesian infants is high. Furthermore, hearing impairment is the most common clinical feature of CRS in infants. Our findings indicate the importance of implementation of rubella vaccine in Indonesia. Conducting hospital-based surveillance of CRS in other hospitals in Indonesia may be appropriate.

What is Known:

- *Congenital rubella syndrome (CRS) has serious consequences in infants resulting from rubella virus infection during pregnancy.*
- *The incidence of CRS in most developed countries has greatly decreased since implementation of rubella vaccination.*
- *Rubella vaccine has not yet been implemented in many developing countries.*

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What is New:

- *The number of laboratory-confirmed CRS cases among Indonesian infants was high.*
- *Implementation of rubella vaccine into immunization programs in Indonesia is important because of the high number of CRS cases.*
- *Our study highlights the need for ongoing prospective surveillance of CRS in Indonesia.*

Keywords Congenital rubella syndrome · Hospital-based surveillance · Vaccine · Immunization · Indonesia

Abbreviations

ABR	Auditory brainstem response
ASD	Atrial septal defect
CRS	Congenital rubella syndrome
DORV	Double outlet right ventricle
F	Female
Ig	Immunoglobulin
LA	Left auditory
M	Male
Mo	Month
N/a	Not determined
PDA	Patent ductus arteriosus
PH	Pulmonary hypertension
RA	Right auditory
SNHL	Sensorineural hearing loss
TGA	Transposition of the great arteries
TI	Tricuspid insufficiency
VSD	Ventricular septal defect
Wnl	Within normal limits

Introduction

Rubella virus usually causes a mild self-limited fever and rash in children and adults. Congenital rubella syndrome (CRS) has serious consequences, such as miscarriage, stillbirth, and severe birth defects in infants, resulting from rubella virus infection during pregnancy, especially during the first trimester [20].

The main goal of rubella immunization is to prevent CRS [3, 20]. The incidence of CRS in most developed countries has greatly decreased since the implementation of rubella vaccination [2, 6, 9]. Effective rubella vaccination programs were implemented in the USA in the 1960s and resulted in the elimination of CRS in those countries since 2010 [10].

However, rubella vaccine has not yet been implemented in many developing countries [3]. Indonesia is among those countries that have not introduced a rubella vaccine into the national immunization program. Yogyakarta, a province of Indonesia with a population of 3.45 million [12], is an endemic area for rubella cases. Therefore, a large number of pregnant women are infected with rubella, and their children consequently suffer from CRS. In this study, we conducted a prospective surveillance study of infants aged <1 year with suspected CRS. This study aimed (1) to estimate the incidence of CRS in Indonesia, (2) describe the clinical features of CRS at our referral hospital, and (3) pilot a CRS surveillance system to be extended to other hospitals.

Materials and methods

This cross-sectional study was conducted between September and December 2013 to identify and describe CRS cases among infants aged <1 year who were hospitalized during those surveillance time at Dr. Sardjito Hospital, Yogyakarta. The Institutional Review Board for Human Research of the Faculty of Medicine, Universitas Gadjah Mada/Dr. Sardjito Hospital, approved this study (KE/FK/902/EC). Written informed consent was obtained from all parents for this study.

The infants were recruited from otolaryngology, neurology, cardiology, growth and development, and ophthalmology departments, private outpatient clinics, and pediatric wards. Classification of CRS cases in this study was based on the WHO case definition (Table 1) [21]. Definition of CRS cases included the following categories: suspected, laboratory confirmed, clinically compatible, and epidemiologically linked. The clinical criteria of CRS consisted of the presence of ≥two clinical features from group A, or one feature from group A and ≥one feature from group B in the following lists. Group A comprised sensorineural hearing impairment, congenital heart disease, pigmentary retinopathy, cataract(s), and congenital glaucoma. Group B comprised purpura, splenomegaly, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease, and jaundice with onset within 24 h of birth. Clinical examination of these cases was performed by a pediatric neurologist at the hospital. We also involved specialists from different units of the hospital, such as ophthalmologists, cardiologists, and otolaryngologists. Infants who presented with hearing impairment, congenital heart defects, congenital cataracts, or all of these defects were enrolled in the study. The exclusion criteria consisted of patients who presented with congenital defects that were not compatible with the definition of CRS.

Data were collected using a questionnaire that included patients' information, clinical characteristics, family history, and laboratory findings. Infants underwent an auditory brainstem response examination. Laboratory confirmation of CRS cases was based on the WHO case definition [21]. WHO laboratory criteria for confirmation of suspected CRS cases include the following: detection of rubella IgM antibody, or sustained rubella IgG antibody levels as determined on at least two occasions between 6 and 12 months of age in the absence of receipt of rubella vaccine; or detection of rubella virus (e.g.,

Table 1 CRS case definitions for surveillance purposes [21]

Case category	Definition
Suspected	Any infant aged <1 year with >1 clinical features from group A and no other obvious cause
All suspected cases have to be investigated and classified based on clinical, laboratory, and epidemiological data as one of the following:	
Laboratory confirmed	A suspected case which meets the laboratory criteria for CRS case confirmation
Clinically compatible	A suspected case which meets the clinical criteria for CRS and has not been adequately tested by laboratory
Epidemiologically linked	A suspected case which does not meet clinical criteria for CRS (i.e., has only one feature from group A), has not been adequately tested and has maternal history of laboratory-confirmed rubella during pregnancy
Discarded	A suspected case with negative results of adequate laboratory testing for evidence of rubella virus infection, or a suspected case which does not meet clinical criteria for CRS (i.e., has only one feature from group A), has not been adequately tested, and does not have maternal history of laboratory-confirmed rubella during pregnancy

nucleic acid detection by RT-PCR or isolation of rubella virus) in an appropriate clinical sample (best results are from throat swabs, but nasal swabs, blood, urine, or cerebrospinal fluid specimens are also acceptable) [21].

Investigation for specific IgM antibodies was conducted using Vidas® RUB IgM immunoassay test kits (bioMérieux Indonesia, Jakarta). Furthermore, infants aged ≥6 months were also tested for rubella IgG antibodies using Vidas® RUB IgG immunoassay test kits. Descriptive data, such as frequency, were analyzed using STATA 11 (StataCorp LP, College Station, TX, USA). Laboratory tests were performed in the same hospital.

Furthermore, we estimated the incidence of CRS by dividing the number of laboratory-confirmed CRS cases with the number of newborns in Yogyakarta Province from September to December 2013.

Results

In this study, we identified and described CRS cases among Indonesian infants. From September to December 2013, we evaluated 55 suspected cases of CRS in infants, of whom five participants were excluded for the following reasons: two cases of Down syndrome, one case of isolated patent ductus arteriosus, and two infants whose parents refused to participate in the study. Of 50 participants, 24, seven, three, one, one, seven, and eight infants were recruited from the departments of neurology, cardiology, growth and development, ophthalmology, and otolaryngology, private outpatient clinics, and pediatric wards, respectively. Three participants were excluded because of no serological test results. A total of 47 infants remained for further analysis.

The majority (89.4%) of infants were aged ≥1 month old, including 25 boys and 22 girls (Table 2). According to the WHO case definition, 11/47 (23.4%), 9/47 (19.1%), and 27/47 (57.5%) infants were classified as laboratory-confirmed, clinically compatible, and discarded CRS, respectively (Table 3).

Furthermore, 10/47 (21.3%) infants showed IgM-positive results for rubella and 1/47 (2.1%) had sustained rubella IgG antibody levels as determined on two occasions. Moreover, there were four IgM-negative (at birth) infants and five IgG-positive (at 6–11 months old) infants with suspected CRS who did not undergo a second test. Therefore, we further classified these infants as clinically compatible cases (Table 3). Most (63.6%)

Table 2 Characterization of congenital rubella syndrome cases in Yogyakarta, Indonesia

Characteristics	Suspected CRS (*n*, %)	Laboratory-confirmed CRS (*n*, %)
Age		
0–<1 month	5/47 (10.6)	1/11 (9.1)
1–5 months	21/47 (44.7)	7/11 (63.6)
6–11 months	21/47 (44.7)	3/11 (27.3)
Sex		
Male	25/47 (53.2)	3/11 (27.3)
Female	22/47 (46.8)	8/11 (72.3)
Clinical manifestations		
Hearing impairment		11/11 (100)
Congenital cataract		8/11 (72.7)
Microcephaly		8/11 (72.7)
Congenital heart disease		5/11 (45.5)
Hepatosplenomegaly		2/11 (18.2)
Global developmental delay		1/11 (9.1)

Table 3 Clinical and laboratory findings of Indonesian infants with congenital rubella syndrome

No	Identity	Sex	Age (mo)	Clinical manifestation	ABR test	Serology test		Final diagnosis
						IgM (index)	IgG (IU/mL)	
1.	HA	M	<1	Hearing impairment, microcephaly	LA: moderate SNHL RA: severe SNHL	0.22	–	Clinically compatible
2.	GA	F	6	Hearing impairment, macrocephaly	LA: severe SNHL RA: moderate SNHL	0.11	2	Discarded
3.	EA	M	11	Hearing impairment, microcephaly	LA: moderate SNHL RA: moderate SNHL	0.15	4	Discarded
4.	AR	M	6	Cataract, VSD, hearing impairment, microcephaly	LA and RA: profound SNHL	0.34	>400	Clinically compatible
5.	GR	F	<1	ASD, PDA, microcephaly	n/a	0.12	–	Clinically compatible
6.	KH	M	10	Hearing impairment, ptosis, developmental delay	LA: severe SNHL RA: moderate SNHL	0.16	4	Discarded
7.	AAH	M	10	Cataract, PDA, hearing impairment, microcephaly, developmental delay	LA and RA: profound SNHL	0.14	1	Discarded
8.	AF	M	4	cataract, hearing impairment, microcephaly	LA and RA: profound SNHL	7.05	–	Laboratory-confirmed CRS
9.	DA	F	6	Cataract, hearing impairment, microcephaly	LA: profound SNHL RA: severe SNHL	0.21	67 →1-48	Laboratory-confirmed CRS
10.	AN	M	7	Hearing impairment, hydrocephalus	LA: moderate SNHL RA: severe SNHL	0.19	1	Discarded
11.	AAD	M	5	Hearing impairment	LA: severe SNHL RA: mild SNHL	0.29	–	Discarded
12.	XH	M	10	Cataract, hearing impairment, microcephaly	LA and RA: profound	0.28	214	Clinically compatible
13.	YT	M	4	ASD, microcephaly, hepatomegaly	LA and RA: moderate SNHL	0.12	–	Discarded
14.	SW	F	7	VSD, hearing impairment, microcephaly, hepatosplenomegaly	LA and RA: moderate SNHL	0.17	10	Discarded
15.	A	M	8	Hearing impairment, microcephaly	LA: moderate SNHL RA: severe SNHL	0.16	7	Discarded
16.	J	M	9	Hearing impairment, developmental delay, hydrocephalus	LA and RA: profound SNHL	0.27	396	Clinically compatible
17.	ZH	F	4	Hearing impairment, atrophy nervus II, hidrancephaly	LA: severe SNHL RA: moderate SNHL	0.11	–	Discarded
18.	ANA	F	10	Hearing impairment, developmental delay	LA: severe SNHL RA: moderate SNHL	0.16	5	Discarded
19.	NZ	F	<1	PDA, hearing impairment, craniosinostosis	LA: severe SNHL RA: moderate SNHL	6.44	–	Laboratory-confirmed CRS
20.	RAP	M	11	PDA, hearing impairment, microcephaly	LA and RA: profound SNHL	0.87	231	Clinically compatible
21.	B	F	4	PDA, hearing impairment, microcephaly	LA and RA: profound SNHL	0.10	–	Discarded
22.	SN	F	2	cataract, PDA, hearing impairment	LA and RA: profound SNHL	13.08	–	Laboratory-confirmed CRS
23.	ABH	M	3	Hearing impairment, hydrocephalus	LA and RA: profound SNHL	0.07	–	Discarded
24.	SP	F	9	ASD, PDA, developmental delay, hearing impairment	LA and RA: profound SNHL	3.48	207	Laboratory-confirmed CRS ([a])
25.	R	F	11	PDA, hearing impairment, microcephaly, developmental delay	LA: moderate SNHL RA: severe SNHL	0.23	307	Clinically compatible
26.	SL	F	5	Cataract, PDA, , hearing impairment, microcephaly	LA and RA: profound SNHL	8.79	–	Laboratory-confirmed CRS
27.	AK	F	3	PDA, microcephaly	LA: wnl RA: moderate SNHL	0.12	–	Discarded
28.	EA	M	<1	Hearing impairment, microcephaly	LA: severe SNHL RA: moderate SNHL	0.15	–	Clinically compatible
29.	INR	M	5	Cataract, ASD, hearing impairment	LA: severe SNHL RA: moderate SNHL	0.21	–	Discarded
30.	AR	F	4	Hearing impairment, VSD, TI, PH, single atrium, microcephaly, hepatomegaly	LA: mild SNHL RA: moderate SNHL	0.12	–	Discarded
31.	KR	M	8	DORV, ASD, TGA, hearing impairment, microcephaly, hepatomegaly	LA: severe SNHL RA: moderate SNHL	0.12	0	Discarded
32.	D	F	4	VSD, hearing impairment, microcephaly	LA: moderate SNHL RA: severe SNHL	0.16	–	Discarded
33.	FA	M	8	VSD, hearing impairment, hepatosplenomegaly	LA: mild SNHL RA: mild SNHL	0.12	2	Discarded
34	WS	M	9	ASD, VSD, hearing impairment	LA and RA: severe SNHL	0.16	0	Discarded
35.	ID	M	3	Cataract, hearing impairment, microcephaly, splenomegaly	LA and RA: profound SNHL	4.12	–	Laboratory-confirmed CRS
36.	CB	F	<1	Hearing impairment, microcephaly	LA and RA: moderate SNHL	0.14	–	Clinically compatible

Table 3 (continued)

No	Identity	Sex	Age (mo)	Clinical manifestation	ABR test	Serology test		Final diagnosis
						IgM (index)	IgG (IU/mL)	
37.	TTN	M	2	ASD, VSD, hearing impairment	LA and RA: mild SNHL	0.53	–	Discarded
38.	DA	F	3	Cataract, hearing impairment, microcephaly, hepatoslenomegaly	LA and RA: profound SNHL	16.72	–	Laboratory-confirmed CRS
39.	MIA	M	3	Hearing impairment, microcephaly, hepatosplenomegaly	LA and RA: mild SNHL	0.35	–	Discarded
40.	KT	M	4	Hearing impairment, microcephaly	LA and RA: moderate SNHL	0.13	–	Discarded
41.	DR	M	7	Hearing impairment, microcephaly	LA and RA: moderate SNHL	0.15	2	Discarded
42.	MJ	F	5	Hearing impairment, microcephaly, PDA	LA and RA: moderate SNHL	0.16	–	Discarded
43.	ZF	F	2	Cataract, ASD, hearing impairment, microcephaly	LA and RA: profound SNHL	15.6	–	Laboratory-confirmed CRS
44.	LN	F	3	Hearing impairment, microcephaly	LA: profound SNHL RA: severe SNHL	0.1	–	Discarded
45.	ANI	F	6	Cataract, hearing impairment	LA and RA: mild SNHL	0.25	5	Discarded
46.	NKA	F	6	Hearing impairment, cataract	LA and RA: profound SNHL	12.27	–	Laboratory-confirmed CRS
47.	AR	M	2	Hearing impairment, microcephaly	LA and RA: profound SNHL	11.86	–	Laboratory-confirmed CRS

ABR auditory brainstem response, *ASD* atrium septal defect, *DORV* double outlet right ventricle, *F* female, *Ig* immunoglobulin, *LA* left auditory, *M* male, *mo* month, *n/a* not determined, *PDA* patent ductus arteriosus, *PH* pulmonary hypertension, *RA* right auditory, *SNHL* sensorineural hearing loss, *TGA* transposition of great arteries, *TI* tricuspid insufficiency, *VSD* ventricular septal defect, *wnl* within normal limit, cut-off IgM: index < 0.8 (negative), 0.8–1.1 (borderline), >1.1 (positive), cut-off IgG: <10 IU/mL (negative), 10–14 IU/mL (borderline), >14 IU/mL (positive)

[a] Died

laboratory-confirmed cases of CRS were in the 1–5 month age group of infants, of whom 3/11 (27.3%) were boys and 8/11 (72.7%) were girls (Table 2). From September to December 2013, the number of newborns in Yogyakarta Province was 16,569 [13]. Therefore, the estimated incidence of CRS in Yogyakarta, Indonesia during the study period was 1:1500.

The most common clinical manifestation among CRS cases was hearing impairment (100%), followed by congenital cataracts (72.7%), microcephaly (72.7%), and congenital heart defects (45.5%). Other clinical features of CRS cases included hepatosplenomegaly (18.2%) and global developmental delay (9.1%) (Table 2).

Analysis of the maternal history showed that the median age of the mothers was 27 years (range, 21–34 years). None of the mothers had been vaccinated against rubella, and only five (33.3%) mothers had febrile rashes during their pregnancy. However, we could not classify the mothers' infection according to the WHO definition of rubella cases because of a lack of information on the mothers' infections.

Discussion

In this study, we showed that the incidence of CRS in Indonesian infants was high, and 23.4% of the patients during our short period of surveillance were laboratory-confirmed CRS. The reason for this finding may be that rubella vaccination has not been implemented in the national immunization program in Indonesia. There are no data on the incidence of CRS in Indonesia. However, notably, the incidence of CRS estimated in this study was solely based on one tertiary hospital in Yogyakarta Province. Therefore, our estimate may not reflect the incidence of CRS in Indonesia.

Our method of surveillance will be implemented in other hospitals as a basis for implementation of rubella vaccine in Indonesia. Our hospital is one of the tertiary referral hospitals in Indonesia for Yogyakarta and the South of Central Java region. The Indonesian government is considering rubella vaccine in the national immunization program in the near future.

Our study showed different results from previous studies of developed countries [2, 6, 9, 14, 16, 22]. The incidence of CRS in most developed countries has greatly decreased since the implementation of rubella vaccination [2, 6, 9]. However, our study showed similar results to studies from Asian countries [13, 15, 17]. Rubella IgG antibodies were detected in 74% of hearing-impaired children in Bangladesh [15]. By screening with real-time PCR, rubella virus RNA was detected in throat swabs and placental tissues in all cases (100%) of fetuses/newborns with congenital cataracts in Vietnam [13]. Bangladesh and Vietnam have not yet implemented rubella vaccine in the national immunization program [13, 15]. Only a few Asian countries have implemented rubella vaccination into national immunization programs. Therefore, rubella still remains poorly controlled in many countries in Asia, especially in the Southeast Asian continent [18]. Furthermore,

according to WHO surveillance data regarding the incidence of rubella in 2012, Indonesia was one of the countries that reported most of the rubella cases in the Asia-Pacific region [9]. Sudan is one of the developing countries that have not implemented a rubella vaccination program. Interestingly, in Sudan, surveillance only detected 7.1% of laboratory-confirmed CRS among 98 infants with suspected and clinically confirmed CRS [1]. The most likely explanation for this finding is that the observed defects in those infants were caused by other pathogens involved in congenital disorders, such as *Toxoplasma gondii*, cytomegalovirus, or *Herpes simplex* virus [4]. In accordance with those findings, Villagra et al. suggested performing an integrated surveillance for CRS, with screening for TORCH pathogens to strengthen CRS surveillance and avoid missing rubella cases [19]. Furthermore, in our study, some infants had clinical CRS, but this was not confirmed by laboratory criteria. The most likely explanation for this finding is that the affected infants had infections or pathology other than rubella infection, such as *T. gondii*, cytomegalovirus, or *H. simplex* virus [4].

Notably, a 4-month period is too short for prospective surveillance for a condition such as CRS. We conducted surveillance during this short period because of a limitation of funding. Additionally, this surveillance was a pilot study for CRS surveillance in other hospitals in Indonesia.

The ELISA test, which is used to identify virus-specific IgM and/or IgG antibodies, is a popular method for diagnosing CRS in developing countries because of its simplicity and reliability. Almost 100% of infected infants aged younger than 3 months will show rubella-specific IgM. However, this antibody gradually decreases to less than 50% by 12 to 18 months of age [17]. In our study, 9/10 (90%) infants showed rubella-specific IgM antibodies at <6 months of age, while only 1/10 (10%) infants showed rubella-specific IgM antibodies at ≥6 months of age (Table 3). A limitation of our study is that IgM-negative infants (at birth) with suspected CRS did not undergo a second test at 1 month old or shortly after. Furthermore, a diagnosis of CRS based only on the presence of rubella IgG antibodies should be carefully determined because the test does not differentiate between maternal-induced immunity and acquisition of infection during early gestation. A diagnosis of CRS based solely on rubella IgG may only be confirmed if the antibodies persist beyond 4–6 months old in infants [8]. Additionally, the presence of IgG antibodies to qualify as laboratory-confirmed CRS would potentially allow an infant who acquired rubella postnatally and who had IgG antibodies as a consequence, to be falsely identified as having CRS. However, clinical manifestation of postnatal rubella infection is usually a mild and self-limited disease, but CRS has severe consequences, such as miscarriage, stillbirth, and severe birth defects [11]. Additionally, postnatally, rubella-infected infants show a rubella-specific IgG response from 7 to 10 days after onset of a rash, whereas infants with CRS demonstrate high/increasing rubella-specific IgG levels in the first year of life [5].

Our results are similar to previous studies, which showed that hearing impairment was the most frequent defect of CRS [7, 9]. However, Zimmerman et al. showed that congenital heart defects were the most common clinical manifestations in CRS cases [22]. Clinical diagnosis of CRS is difficult, particularly in infants with single and mild defects. Early diagnosis of CRS is essential for prompt intervention for specific impairments and also to prevent further dissemination of the virus because infants with CRS might shed the virus for long periods. Therefore, the ELISA test is important for confirming CRS, especially in single and mild deficit cases [17].

In conclusion, the number of laboratory-confirmed CRS cases among Indonesian infants is high. Furthermore, hearing impairment is the most common clinical feature found in infants with CRS. Our findings indicate the importance of implementation of rubella vaccination in the national immunization program in Indonesia. Our results also suggest that a CRS hospital-based surveillance program should be conducted in other hospitals in Indonesia.

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Author' contributions ESH conceived the study, and AT and AWEM participated in its design and coordination. AT provided key technical guidance, ESH and G drafted the manuscript, and NM, R, YS, and SER critically revised the manuscript for important intellectual content.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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