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Congenital rubella syndrome (CRS) in Vietnam 2011–2012—CRS epidemic after rubella epidemic in 2010–2011

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Abstract

Background: Rubella is endemic in Vietnam with epidemics occurring every 4–5 years. In 2011, Vietnam experienced the large nationwide rubella epidemic. During the rubella epidemic, many infants born with congenital rubella syndrome (CRS) were identified and reported from the neonatal units or cardiology departments of the national hospitals. To understand the burden of CRS, National Expanded Program on Immunization (NEPI) established sentinel CRS surveillance system.

Method: Three national paediatric hospitals in Hanoi and Ho Chi Minh City (HCMC) were selected as CRS sentinel surveillance sites. Blood specimens from the infants were collected for rubella specific IgM and ELISA testing was performed at the national measles and rubella laboratory.

Results: From January 2011 to December 2012, 424 infants with suspected CRS were identified and reported. Among them 406 (96%) had specimens obtained, 284 (70%) cases were IgM positive including 279 laboratory confirmed CRS and 5 Congenital Rubella Infection (CRI). 13 cases were clinically confirmed and 127 (30%) were discarded. Total 292 infants were confirmed as CRS. Of the 292 infants with CRS, 69% of mothers had a history of “fever and rash” during pregnancy, of which 85% was in the first trimester. The most common clinical defects were congenital heart disease and cataract(s). However, 81.9% of the infants had a combination of major and minor signs and symptoms. Low birth weight in full term infants with confirmed CRS was observed in 114 infants (39%).

Conclusions: The newly established CRS sentinel surveillance system documented the significant burden of CRS in Vietnam and provided evidence to the policy makers for the introduction of rubella containing vaccine (RCV) into Vietnam. This report highlights the importance of countries with rubella epidemic to establish CRS surveillance rapidly in order to support the introduction of RCV into the routine Expanded Programme on Immunization (EPI) immunization.

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Conflict of interest statement

None of authors have financial or other conflict of interest.

Keywords

Congenital rubella syndrome; CRS; CRS surveillance; Rubella; RCV; Routine EPI immunization

1. Introduction

Rubella virus infection in adults and children usually causes a mild and self-limited rash illness with few complications. However, rubella in pregnant women, especially during the first trimester, can result in devastating consequences including miscarriages, foetal deaths and infants born with congenital rubella syndrome (CRS). CRS is characterized by a pattern of congenital anomalies which includes hearing impairment, cataracts, and cardiac abnormalities [1,2].

Even though the risk of CRS is known in relationship to the timing of maternal infection and gestational age, the identification of suspected CRS cases is challenging due to the variation of the clinical manifestations, the distance between the birth of the infant with CRS and maternal infection and the lack of specific diagnostic equipment for CRS-related (e.g., hearing, cardiac) defects in many developing countries. Globally it is estimated that over 103,000 infants with CRS was born in 2010; however, during 2009–2011, globally only 406 infants with CRS were reported to the WHO [3]. Without documenting the burden of CRS, policy makers may not understand the importance of introducing rubella-containing vaccine resulting in the delay of the introduction of the rubella vaccine into the national programme [4].

As of 2014, rubella containing vaccine (RCV) has not been introduced completely in Vietnam. In 2005, through the fever and rash surveillance system, a rubella epidemic was detected with over 22,000 cases (13% confirmed by lab) reported. Of these cases, approximately 60% occurred among persons 10–25 years old. The outbreak occurred mainly in factories, schools, military barracks and prisons (Annual EPI report, Vietnam 2005). In one factory with over 400 pregnant women workers, 100 (25%) of these women were rubella IgM positive. However, many were lost in follow up, even those followed-up showed only a few suspect CRS clinically. CRS surveillance was not yet established in 2005.

In 2010–2011, Vietnam experienced another rubella epidemic. In 2010, 6492 cases were tested for rubella IgM antibodies and 2300 (35%) were rubella IgM positive. Of these 2300 IgM positive cases, 1380 cases (60%) were child bearing age women. In 2011, a total of 7259 rubella cases were reported with 2924 (56%) of the 5259 tested were rubella IgM positive, and 4335 cases were clinically confirmed (Annual EPI report, Vietnam 2010, 2011). However, 6–8 months after the peak of the rubella epidemic, the department of neonatology in the main national paediatric hospitals in Hanoi and Ho Chi Minh City (HCMC) identified several clusters of newborn with suspected CRS. These infants presented with cataracts and various congenital heart abnormalities. Even though the Ministry of Health (MoH) recognized the need of introduction of RCV, they needed the evidence for decision making. National Expanded Program on Immunization (NEPI) established CRS sentinel surveillance system with the assistance of WHO to clarify the diseases burden of CRS.

This report aims to share the experience of Vietnam in establishing a CRS sentinel surveillance system, and discuss the epidemiological and clinical features of CRS from the rubella outbreak 2010–2011.

2. Method

2.1. Surveillance system

In 2011, CRS sentinel surveillance system was established by MoH in collaboration with NEPI, regional Expanded Programme on Immunization (EPI), three sentinel hospitals and two national measles-rubella laboratories. Three national paediatric hospitals located in the two biggest cities in Vietnam, Hanoi (national paediatric hospital) and HCMC (children hospital No. 1 and 2), were selected as the sentinel sites. The two national measles and rubella laboratories accredited by WHO (National Institute of Hygiene and Epidemiology in Hanoi, Pasteur Institute in HCMC) also contributed to serological test using commercial ELISA kit for rubella-specific IgM (Siemens Enzygnost®, Marburg, Germany). To establish surveillance system, a guideline was developed using the WHO guidelines. In mid-2011, training for the hospital staff from neonatology, cardiology and administrative department was conducted. After surveillance system was established, periodic supervision visits were conducted not only for clinical departments but also administrative department in the sentinel hospitals. In addition, NEPI organized the annual workshop to provide feedback of data analysis and surveillance performance for regional EPI, sentinel hospitals and national labs. The cases reported in the first half of 2011 were retrospectively enrolled into surveillance data. Those retrospective data was only available from children hospital No. 2 in HCMC where the basic investigation was conducted by themselves with some laboratory data. The period of the surveillance data reviewed was during January 2011–December 2012.

2.2. Criteria of case enrolment

A suspected case of CRS was defined as an infant aged less than 12 months with at least one condition of congenital heart disease, cataract(s) or hearing impairment and/or those mothers had history of suspected or confirmed rubella infection in pregnancy. Using the same entry criteria for suspected CRS cases, medical records at each of the sentinel sites were searched retrospectively.

2.3. Case investigation and classification

Infants with suspected CRS had a case investigation form completed and blood specimens obtained for rubella-specific IgM testing. Based on the result of laboratory test, cases were classified laboratory confirmed, congenital rubella infection (CRI) or discarded case (Fig. 1). Suspected cases without blood sample were classified as clinically confirmed or discarded case based on their clinical symptoms. The clinical symptom is divided into two groups: Group A as major symptom (congenital heart disease, cataract(s), hearing impairment, congenital glaucoma, pigmentary retinopathy) and Group B as minor symptom (purpura, splenomegaly, microcephaly, developmental delay, meningo-encephalitis, radiolucent bone disease, jaundice within 24 h after birth). Clinical confirmation needs at least two in Group A or one in Group A and Group B, respectively [5].

There was no standardized protocol for clinical diagnosis for CRS. Congenital heart disease was mainly diagnosed by echocardiography. Hearing impairment was diagnosed by automated auditory brainstem response (AABR) or otoacoustic emission (OAE), but use was limited.

2.4. Data management and analysis

Data entry and analysis were conducted using software of Microsoft Office Access 2010, Microsoft Office Excel 2010 and STATA 11.1 (StataCorp, Texas, USA).

2.5. Ethical consideration

Before case investigation, signed consent was obtained from family of suspected cases. Results of laboratory test were informed family with reporting documents.

3. Results

From January 2011 to December 2012, a total of 424 suspected CRS cases were reported from sentinel hospitals including 71 cases retrospectively discovered during first half of 2011 from children hospital No. 2. The number of classified is shown in Fig. 1. The laboratory test used for the retrospective enrolment in children hospital No. 2 was the commercial kits, not the WHO standard ELISA kits. Of the 406 (95.7%) cases with sera collected and tested for rubella-specific IgM, 284 (70.0%) cases were IgM positive including 279 laboratory confirmed CRS and 5 CRI. Among 18 investigated cases without samples, 13 met criteria of clinically confirmed CRS. Total 292 (68.9%) infants were confirmed as CRS by laboratory and clinically. While most suspected cases were detected in neonatology (56.1%) or cardiology (39.2%) department, other cases were reported from several other departments especially at children hospital No. 2 (Table 1).

Of the 292 CRS cases, 142 (48.6%) were male. Five infants with CRS died aged between 0 to 3 months of age. Two hundred two (69.2%) mothers had history of fever and rash during pregnancy and 85% of them had experienced the episode during the first trimester (Fig. 2). Of available maternal data, the median age of mothers of the 130 confirmed CRS cases was 25 years (range 18 years, 39 years).

The number of laboratory-confirmed rubella through fever and rash surveillance in all ages of population including adults and pregnant women and confirmed CRS cases by month is shown in Fig. 3. The peak of reported CRS cases is seen after 6–8 months of the peak of rubella epidemic. Additionally, small clusters of CRS cases in early 2011 were identified through the retrospective search which followed the rubella outbreak in early 2010.

Laboratory confirmed CRS cases by months of age are shown in Fig. 4. Of the infants older than 7 months of age, rubella-specific IgM antibody was detected from 16 cases. However, there were 6 additional cases that were 7–9 months of age and were IgM negative but met the clinical compatible case definition. These infants did not receive any additional serological workup.

The most common clinical symptoms among confirmed CRS cases were congenital heart disease (91.4%), cataract(s) (45.2%), splenomegaly (38.7%) and purpura (32.9%) (Table 2). Of the 240 (82.2%) cases with multiple complications, 18 (6.2%) had the triad of heart, eye, and hearing defects and 125 (42.8%) had combination of two signs of heart and eye defects. A birth weight under 2500 g was found in 218 (74.7%) of infants with confirmed CRS and 52.3% were term deliveries.

4. Discussion

This is the first CRS data in Vietnam generated by the national CRS sentinel surveillance system which showed that CRS is a significant public health issue in Vietnam. The recent study showed that the estimated national number of CRS and incidence modelling from one province in Vietnam in non-epidemic year in 2009 were 3788 (95% CI: 3283–4143) and 234 (95% CI: 207–262), respectively [4,9]. This suggests that the reported CRS in this sentinel surveillance system is still much under-reported and the tip of iceberg of real magnitude of CRS situation in Vietnam. Since this surveillance has been conducted at only tertiary hospitals in the two biggest cities in Vietnam, the number of reported cases was limited by factors such as geographical accessibility and financial feature of patients.

This CRS surveillance system used two different approaches (e.g., retrospective and prospective search) to identify suspected infants with CRS. They identified many CRS cases by retrospective search for infants with symptoms associated with CRS with the record of laboratory test result. Approximately 25% of the confirmed cases were identified using this methodology. If an infant is identified before 1 year of age or before the first dose of MR vaccination, CRS can be confirmed using laboratory testing. Prospective CRS surveillance includes the identification and follow-up of the pregnant women with confirmed rubella infection and the identification of infants with congenital defects associated with CRS. However, for the initial CRS surveillance, pregnant women were often not followed up due to various difficulties, such as abortions, limited access to the test for pregnant women, and limited capacity to follow up those women with confirmed rubella infection at large gynaecological hospitals. Therefore the prospective search for infants with CRS is more practical in the setting of developing country [6–8].

The median maternal age was 25 years, highlighting the susceptibility in age groups. This information may be used to tailor the vaccination strategy to target certain age groups of women of childbearing age [9].

In this surveillance, 16 CRS cases were confirmed by IgM laboratory testing after 7 months of age. However, there were 6 clinically compatible cases that were not confirmed in the same period. Additional laboratory testing can be conducted which include persistent IgG titres or RT-PCR or virus isolation. These additional tests may help in the diagnosis of the CRS case. In addition, virus isolation and RT-PCR may help in determining the infectiousness of the infant. Jin et al. detected rubella IgM and genome from two infants aged 12 and 24 months of age using blood samples and Rajasundari isolated virus from serum and lens samples of infants with CRS at 11 months of age [10,11]. According to these studies, infants with CRS shed virus for up to 12 months. Since some infants with

CRS are admitted to hospital for several months, this information is important to prevent nosocomial spread of rubella virus from the infants with CRS. Prevention of nosocomial infection among patients, families and also medical staff, especially pregnant medical staff without vaccination history against rubella, should be conducted. In 2013, WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommended that all health workers should be immune to measles and rubella (once rubella has been introduced). This will also prevent nosocomial spread of rubella.

One of the challenges of this surveillance system in developing country is the lack of equipment to confirm the diagnosis of infants with hearing and cardiac defects. From the surveillance data, hearing impairment was seen in only 9.6% of total confirmed CRS cases. Hearing impairment is one of the most common symptoms of CRS; however, in reports from the USA, Panama and Myanmar, hearing impairment among CRS infants were identified in 60%, 30% and 17%, respectively [7,12,13]. Hearing impairment is usually identified in the second year of life or later without standardized newborn hearing screening or hearing equipment available, so it is usually under-reported in CRS surveillance. This would cause the underreporting of CRS, especially in developing countries where the sophisticated medical equipment for detection of hearing impairment is needed. In some countries, newborn hearing screening has been established using oto-acoustic emission testing as a screen. This may improve the identification of infants with hearing impairment.

Successful establishment of CRS surveillance system mainly relied on good management system in the sentinel hospitals. Since the clinical presentation of CRS involves multi-organs, multiple clinical assessments from different departments are involved in the identification of the suspected CRS cases. To ensure complete reporting of suspected cases, two routine practices were used. One was the daily reporting system by the doctor's conference in every morning. Sharing the information of suspected CRS during doctor's conference encouraged doctors from different departments to report continuously. The other practice was the supervision of administrative department. They compiled data from various departments and worked as a contact point of the hospital to regional EPI, sending the reports and lab samples. Besides above two practices, timely sample testing and feedback by national measles and rubella laboratory contributed to smooth workflow and helped clinicians for providing accurate diagnosis.

Based on the results of this CRS surveillance and cost effectiveness analysis of RCV [13], the government of Vietnam is in the process of introducing RCV into Vietnamese national immunization programme. RCV is being introduced by an unprecedented catch-up campaign of Measles-Rubella combination vaccine targeting children aged from 9 months to 14 years in 2014–2015 by the support of Global Alliance of Vaccine Initiatives followed by introduction into the routine immunization programme. Through this national sentinel CRS surveillance system, the impact of MR vaccine introduction into routine EPI will be monitored.

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Abbreviations:

CRS	congenital rubella syndrome
CRI	congenital rubella infection
RCV	rubella containing vaccine
EPI	Expanded Programme on Immunization
NEPI	National Expanded Programme on Immunization
MoH	Ministry of Health
SAGE	Strategic Advisory Group of Experts on Immunization

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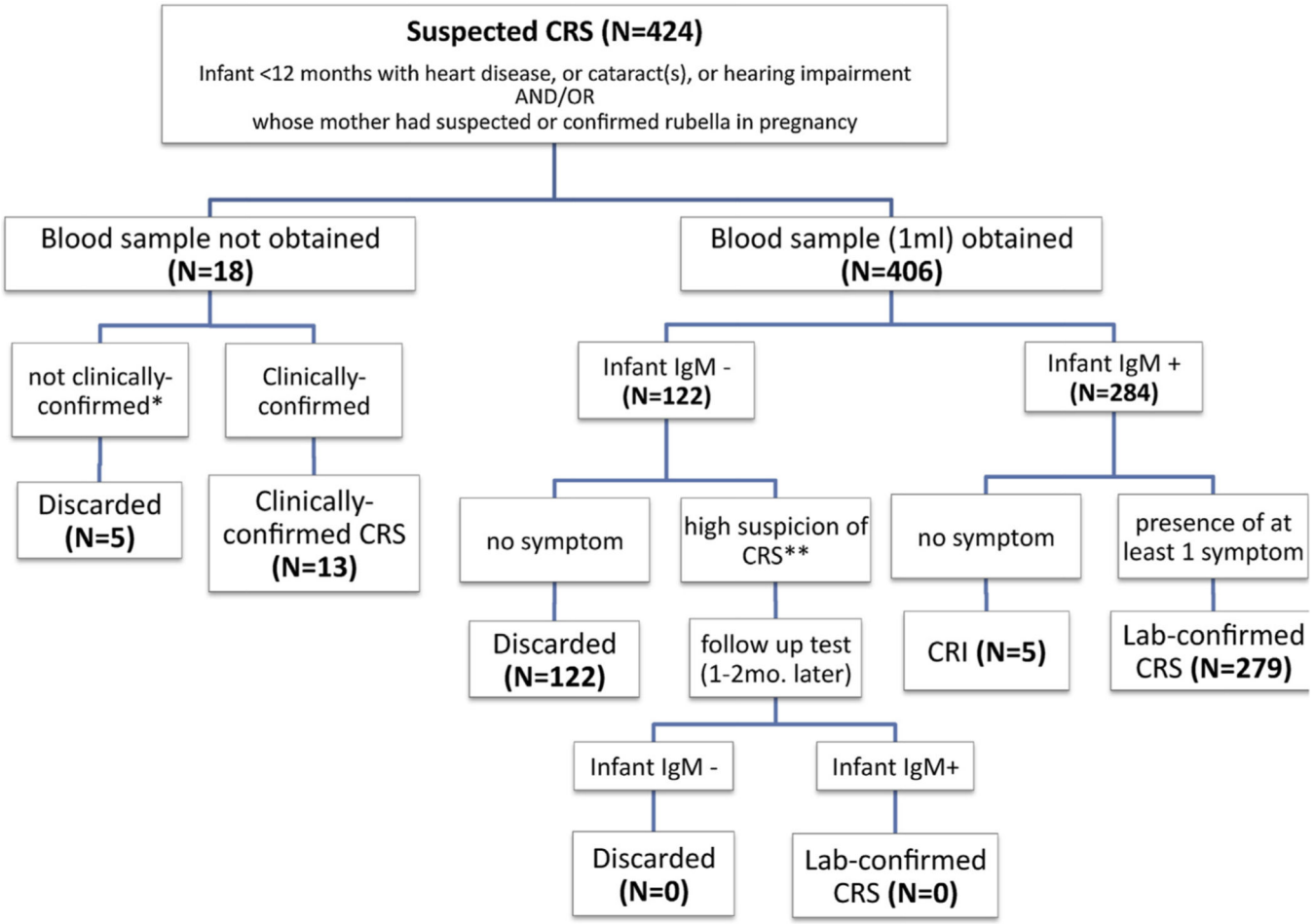

Fig. 1.

CRS surveillance algorithm. * Not clinically-confirmed: After a thorough work-up including hearing test (if possible). ** High suspicion of CRS: clinically-confirmed OR mother's history. (): Number of cases classified in results.

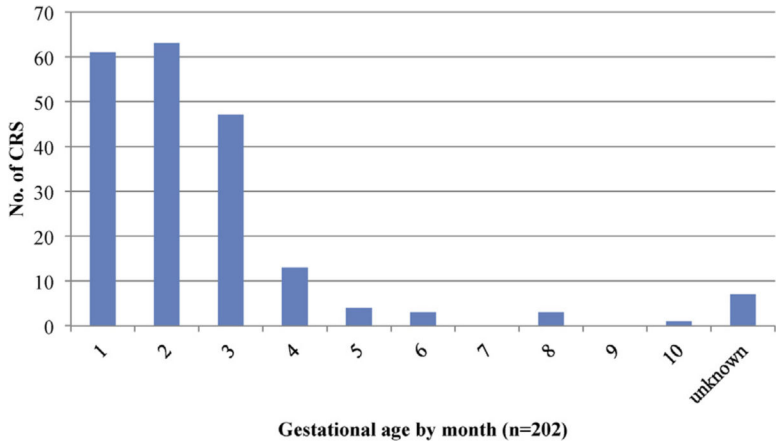

Fig. 2.
Gestational age at mother's history of fever and rash (n = 202).

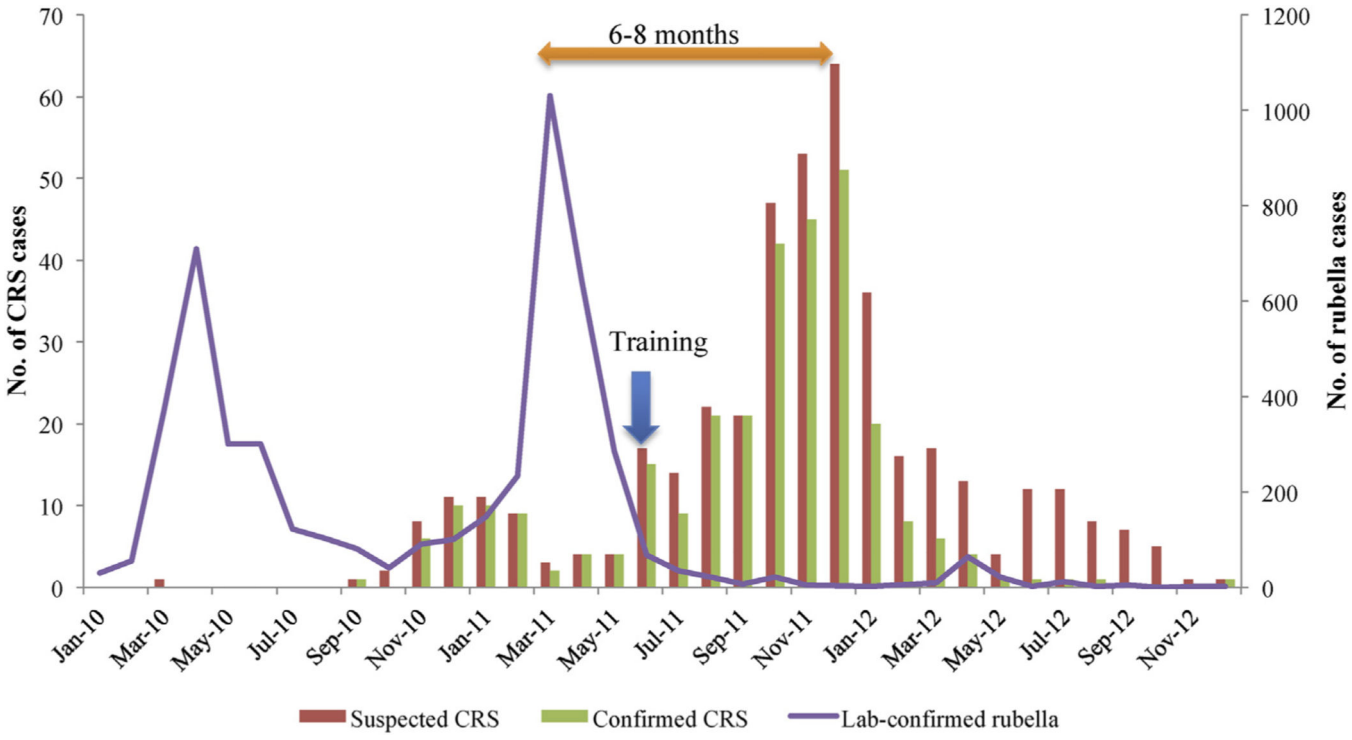

Fig. 3.
Laboratory-confirmed rubella and confirmed CRS cases, by month.

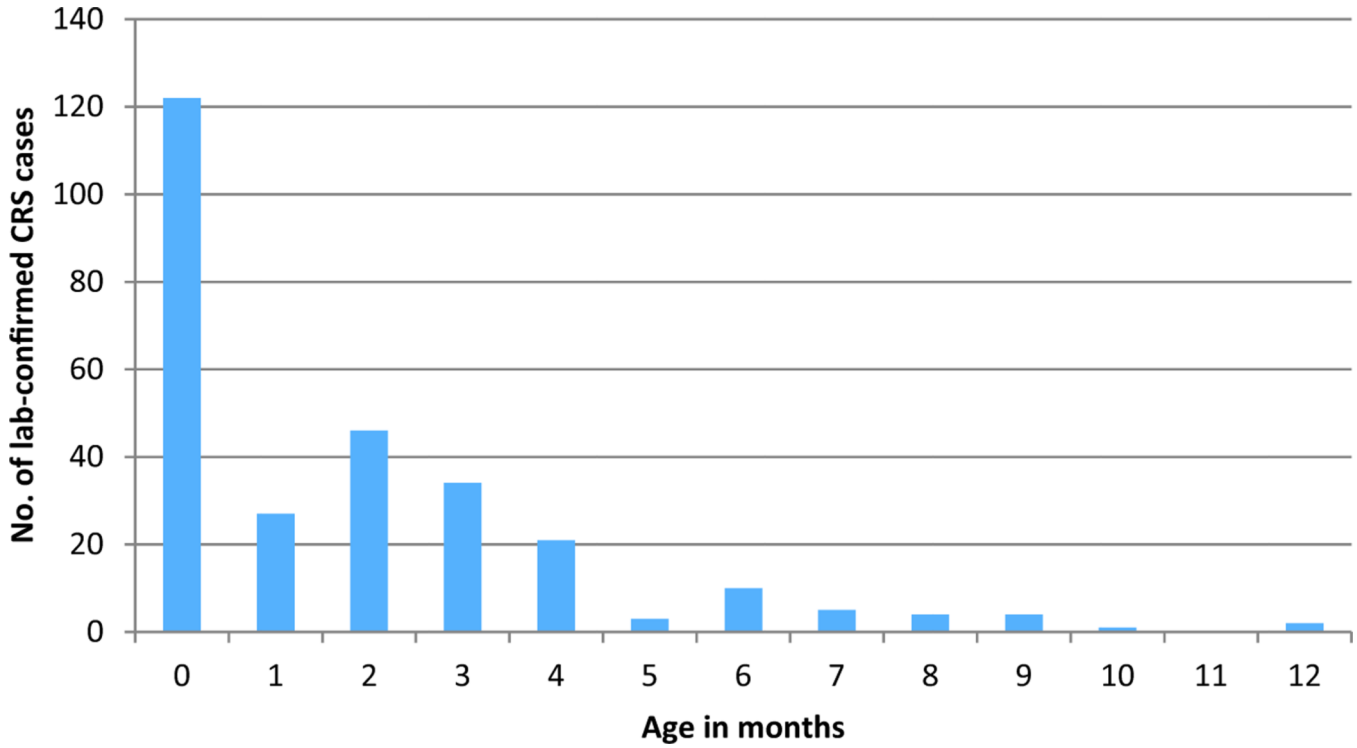

Fig. 4.
Age in months of IgM positive cases at investigation (n = 279).

Table 1

Number of suspected cases by department at hospital.

Hospital	Total	Neonatology	Cardiology	Infection	Gastroenterology	Kidney	Emergency	Respiratory	Neurology	Unknown
NPH*	79	51	28	0	0	0	0	0	0	0
CH1**	143	105	36	1	1	0	0	0	0	0
CH2***	202	82	102	3	0	2	5	5	1	2
Total	424	238	166	4	1	2	5	5	1	2

*NPH: National Paediatric hospital in Hanoi.

**CH1: Children hospital No.1 in Ho Chi Minh City.

***CH2: Children hospital No. 2 in Ho Chi Minh City.

Table 2

Clinical complications of confirmed CRS cases (n = 292).

Clinical signs	No.	(%)
Congenital heart disease	267	91.4
Low birth weight (<2500 g)	218	74.7
Cataract(s)	132	45.2
Splenomegaly	113	38.7
Purpura	96	32.9
Jaundice	46	15.8
Development delay	35	12.0
Microcephaly	33	11.3
Hearing impairment	28	9.6
Pigmentary retinopathy	5	1.7
Meningoencephalitis	3	1.0
Glaucoma	0	0.0
Radiolucent bone disease	0	0.0
Combination of signs		
Heart, eye and hearing	18	6.2
Heart and eye	125	42.8