# Clinical Manifestations of Congenital Rubella Syndrome: A Review of Our Experience in Vietnam

Michiko Toizumi[1], Hien Minh Vo[2], Duc Anh Dang[3], Hiroyuki Moriuchi[4], Lay-Myint Yoshida[1]

**Affiliations:**

[1]Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan

[2]Department of Pediatrics, Khanh Hoa General Hospital, Nha Trang, Vietnam

[3]National Institute of Hygiene and Epidemiology, Hanoi, Vietnam

[4]Department of Pediatrics, Graduate School of Biomedical Sciences, Nagasaki University

**Address correspondence to:**

Lay-Myint Yoshida, Department of Pediatric Infectious Diseases, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan. E-mail: lmyoshi@nagasaki-u.ac.jp, Tel.: +81-95-819-7764, Fax: +81-95-819-7844

**Funding Source:** Authors' studies reviewed in this paper were supported by NEKKEN collaborative research fund (Institute of Tropical Medicine, Nagasaki University) under Grant Number 27-general-17 and AMED under Grand Number JP18fm0108001.

**Declarations of interest:** none

**Abstract**

Rubella vaccination programs have dramatically reduced the incidence of rubella and congenital rubella syndrome (CRS) in developed countries. However, CRS prevalence is still rising in developing countries where rubella-containing vaccines (RCV) are not included in the immunization program and even in some countries where a part of the population lacks immunity to rubella despite the presence of RCV in the regular immunization program. This review aimed to summarize the clinical features of CRS using data from our studies conducted between 2011 and 2015 in Vietnam, wherein we examined clinical manifestations in Vietnamese children with CRS who were born after the large rubella outbreak of 2011; a series of studies dealing with CRS in North America and Europe after the 1960s epidemic; and those from countries before introduction of RCVs.

This review shows that children with CRS have a variety of disabilities such as hearing, visual, developmental, behavioral, cardiac, and endocrine impairments, which have variable severity and may appear in different combinations. Some of these impairments can appear or worsen later in the lives of these children.

Physicians should thus complete pediatric, cardiac, auditory, ophthalmologic, and neurologic examinations along with laboratory diagnostic testing soon after birth.

These assessments should be repeated during follow-up if congenital rubella infection is suspected in a neonate. Timely intervention for cardiac defects can be lifesaving. Early introduction and continuation of speech, occupational, physical, and behavior therapies and training with appropriate medical interventions by a multidisciplinary team approach are required to maximize quality of life.

**Highlights:**

- The incidence of CRS is still rising in developing countries
- Children with CRS present with a variety of disabilities
- A timely multidisciplinary approach improves the quality of life in children with CRS.
- A timely multidisciplinary approach can be lifesaving in some children with CRS.

**Keywords:** congenital rubella syndrome, rubella vaccine, clinical manifestations

**Abbreviations:** ASD, autism spectrum disorder; ASQ, the Ages and Stages Questionnaire; CARS2, Childhood Autism Rating Scale, second edition; CRS, congenital rubella syndrome; Denver II, the Denver Developmental Screening Test II;

DSM, the Diagnostic and Statistical Manual of Mental Disorders; M-CHAT, Modified Checklist for Autism in Toddlers; PH, pulmonary hypertension; RCV, rubella-containing vaccine; SNHL, sensorineural hearing loss

## Introduction

Rubella is usually a mild infectious disease often accompanied by rash; however, rubella infection in pregnant women can result in miscarriage, stillbirth and a series of disabilities known as congenital rubella syndrome (CRS), characterized by cataracts, hearing impairment, cardiac defects, and damage to the nervous system [1, 2].

Rubella became a focus of major interest in 1944 when Gregg, an Australian ophthalmologist, showed an association between a syndrome including cataracts and heart disease with maternal rubella in early pregnancy [3]. Swan and colleagues expanded Gregg's findings and described the association between rubella and hearing impairment, cataracts, congenital heart disease, low birth weight, failure to thrive, microcephaly, and developmental delay [4].

A rubella pandemic started in Europe in 1962–1963 and spread to the United States in 1964 [5]. The extensive pandemic in the United States resulted in an estimated 20,000 children with CRS, leading to >11,000 spontaneous or therapeutic abortions and 2,100 neonatal deaths [6]. This tragic experience expanded our understanding of CRS, adding numerous other transient or permanent abnormalities to its clinical spectrum. Clinical manifestations and the long-term prognosis of CRS have been well studied since the late 1960s to 1980s.

The first rubella vaccine entered into commercial use in 1969 and 1970 and it has been introduced into the national immunization program in many countries thereafter, which has led to a dramatic worldwide decrease in CRS. However, CRS remains a problem, especially in developing countries where rubella-containing vaccines (RCVs) are not included in the national immunization program, with estimates of more than 100,000 new CRS cases annually worldwide in 2010 [7]. Even in countries where RCVs are included in the national immunization program, CRS can emerge if a considerable portion of the population in the community remain susceptible to rubella. A rubella outbreak occurred in Japan between 2012 and 2013, resulting in the emergence of more than 40 CRS cases. This outbreak occurred because middle-aged males did not receive childhood RCVs and the RCV immunization rate among women of childbearing age was insufficient as mandatory immunization in a school setting was converted into immunization individually at private clinics [8, 9]. In the United States, where endemic rubella was eliminated, several children with CRS were born to mothers from countries where RCVs are not included in the national immunization program and who were therefore presumably unimmunized [10]. The occurrence of CRS increased with the low coverage of regular RCV immunization during childhood, leading to an increase in the proportion of pregnant women susceptible to rubella in Greece in 1993 [11]. Hence,

100 despite being vaccine-preventable, CRS remains non-negligible disease in some countries.

101

102 However, it is difficult to detect CRS in many cases. Many CRS-associated defects
103 can be undetectable or overlooked in the early months of life and some manifestations
104 may occur later in life; during childhood, adolescence, or early adulthood. It is difficult
105 to recognize these manifestations and associate them with CRS not only in rubella-
106 endemic countries where surveillance or screening for each defect in young children are
107 scarce but also in countries where rubella is rarely seen because of the immunization
108 program [12]. Therefore, there have been few studies that comprehensively examined
109 clinical manifestations of CRS using recently established screening or assessment tools.

110

111 In the Khanh Hoa Province, south-central Vietnam, in 2009-2010, when RCVs were
112 not a part of the national vaccination program, 29% (95% confidence interval, 27–31%)
113 of pregnant women were susceptible to rubella [13]. In the following year, a large-scale
114 rubella outbreak occurred throughout Vietnam between January and July 2011, and many
115 CRS cases emerged [14]. To characterize the clinical manifestations of CRS, infants with
116 CRS in the Khanh Hoa Province were examined and followed up prospectively for four
117 years [15, 16]. The first study [15] targeted infants <12 months of age who had

118 manifestations suggesting CRS [17], from October 2011 to September 2012, at the only
119 referral hospital in Khanh Hoa. In the second study [16], we followed up the children with
120 CRS and assessed their developmental, ophthalmological, and otological status in 2013
121 and 2015 [16]. A retrospective survey of children with CRS was also performed, focusing
122 on patent ductus arteriosus (PDA), by reviewing the medical records from 2011 to 2015
123 in a children's hospital in Ho Chi Minh City, Vietnam (Toizumi et al., under review).
124
125 The present paper reviews clinical manifestations of CRS using data from studies in
126 Vietnam from 2011 to 2015 ([15, 16]; Toizumi et al., under review), in which CRS
127 patients were examined using currently available assessment tools. Moreover, data from
128 previous studies examining a substantial number of patients born after a large rubella
129 outbreak in Europe and North America in the 1960s, and from other studies from
130 countries before RCV introduction or from those where RCVs have not been introduced
131 yet were also reviewed.
132
133 **1. Epidemiology of congenital rubella syndrome**
134 Incidences of CRS per 1000 live births during rubella epidemics in countries without
135 RCVs in the national immunization program were 0.6 in Trinidad and Tobago in 1982-83

[18], 0.7 in Oman in 1993 [19], 0.8 in Ghana in 1995-1996 [20], 0.9 in Sri Lanka in 1994-95 [21], 1.5 in Singapore in 1969 [22], 2.2 in Panama in 1986 [23], 3.5 in Russia in 1979-1997 [24], and 20 in the Ryukyu Islands (Okinawa, Japan) after a rubella epidemic in 1964-1965 when Okinawa was under the United States occupation [25] (Table 1). The incidence during non-epidemic periods varied from 0.1 to 0.2 per 1,000 live births [26].

In Khanh Hoa province, Vietnam, 38 CRS cases aged less than 12 months were identified during a one-year period after the rubella outbreak in 2011 (our first CRS study, [15]). In this study, the incidence of CRS was 2.1 per 1000 live births, which peaked up to 7.8 per 1000 live births in the highest epidemic month. The incidence in Nha Trang City, the capital of Khanh Hoa province, was 3.0 per 1000 live births, which was assumed to be more accurate because the surveyed hospital was located in this city, where most of the infants were from.

Difference in seroprevalence among women of childbearing age could reflect variable CRS incidences among the studies (Table 1). Once a rubella outbreak occurs, drastic change in seroprevalence will follow. Difference in CRS incidence also could be influenced by methods detecting CRS (e.g., active/passive surveillance, availability of specific examinations, inclusion of cases of late-onset manifestations, and so on) and the definition of CRS. Therefore, it is difficult to interpret and compare those results directly.

It is interesting to note that the finding in our study in Khanh Hoa was comparable to a CRS incidence of 2.3 (95% CI, 2.1-2.6) cases per 1000 live births in Vietnam that was estimated by mathematical modeling using rubella seroprevalence of pregnant women in Nha Trang between 2009 and 2010 [7, 13].

The incidence of CRS determined in our study may have been underestimated because it did not include those who died in other small district hospitals soon after delivery, those who would develop or reveal CRS manifestations in later life, and those with abortions or stillbirths.

## 2. Clinical manifestations of congenital rubella syndrome

Clinical manifestations of CRS discussed below are summarized in Table 2.

### *2.1. Manifestations of CRS in neonates*

Neonates with CRS can present with transient thrombocytopenia with or without purpura, “blueberry muffin” skin lesions with dermal erythropoiesis, hemolytic anemia, hepatosplenomegaly, hepatitis, jaundice, meningoencephalitis, large anterior fontanelle, interstitial pneumonia, myositis, myocarditis, diarrhea, cloudy cornea, radiolucent bone disease, and adenopathy [26, 27]. Most infants with CRS have some degree of intrauterine growth restriction and may continue to fail to thrive [6, 28].

172 In the prospective CRS surveillance study in Khanh Hoa (our first study [15]), we
173 found 84% of the 38 infants with CRS presented with purpura or "blueberry muffin" skin
174 lesions. Hepatosplenomegaly and thrombocytopenia with platelet counts less than 150 x
175 $10^9$/liter were detected in 68% and 76 % of the subjects, respectively. Seventy-one percent
176 and 72% of the infants with CRS had low birth weight <2500 grams in a prospective
177 surveillance in Khanh Hoa [15] and in a retrospective study in Ho Chi Minh city (Toizumi
178 et al., under review), respectively.
179
180 *2.2. Hearing impairment of congenital rubella syndrome*
181 Sensorineural hearing loss (SNHL) is the single most common finding among
182 children with CRS [6]. Previous reports from the United States and Oman found hearing
183 impairment in 66–90% of children with CRS. This impairment was generally bilateral
184 and sensorineural [29-32]. SNHL may occur following maternal infection up to the 18$^{th}$
185 to 20$^{th}$ week of pregnancy, while other rubella-related defects of organogenesis (i.e.,
186 cataract and heart disease) only occur after infection before the ninth to eleventh
187 gestational week [30, 33].
188 The worldwide burden of SNHL following CRS remains high, and in countries
189 without RCV in the national immunization program, CRS is still the most important cause

of congenital SNHL [34, 35]. However, the burden of hearing impairment among infants with CRS has been underestimated due to late recognition. Otoacoustic emissions and automated auditory brainstem responses [36] are now available for screening infants at risk or all neonates universally in order to detect hearing defects; however, they are still not commonly used in developing countries where CRS often occurs. Delays in detecting hearing impairment can make CRS diagnosis difficult, hinder introduction of education for language acquisition, and lead to misdiagnosis of intellectual developmental delay or autism spectrum disorder (ASD).

A Swedish study reported that hearing impairment in CRS may progressively worsen after the first year of life [37]. Desmond and colleagues, in a United States study, observed two children with CRS whose auditory acuity was normal but later suddenly developed SNHL [38].

Twenty-one children with CRS were evaluated in 2013 and 16 of them was examined again in 2015 (five did not come to the examination in 2015) using automated auditory brainstem responses at the median ages of 23 and 47 months, respectively, in the CRS follow-up study in Khanh Hoa, Vietnam (our second study [16]). Thirteen (62%) showed hearing impairment; among these, 10 had moderate or greater level of bilateral hearing impairment, which would hamper their language acquisition without any appropriate

208 hearing aids or education.

209

210 *2.3. Ophthalmological manifestations of congenital rubella syndrome*

211 Rubella virus can infect every part of the developing fetal eye via the capillary
212 network and slow cell division and maturation [39].

213 Previous studies of CRS arising from the rubella epidemics of 1960s in the United
214 States [30, 40] and the United Kingdom [41] have shown that 53–78% of patients with
215 CRS had ocular problems. A “salt and pepper” pigmentary retinopathy (24–60%) is the
216 most common ocular finding, followed by cataracts (17–63%), nystagmus (13-25%),
217 strabismus (13-24%), microphthalmia (9-23%), amblyopia (16%), and glaucoma (5-12%)
218 [30, 31, 40-42]. A previous study investigated the etiology of childhood cataracts in south
219 India and found that 25% of cataracts in infants aged less than one year were due to CRS
220 and cataract with nuclear morphology had a 75% positive predictive value for CRS [43].

221 A study investigated patients born in the early 1960s in the United States with
222 CRS and prior ocular pathology, followed up until late adolescence [44]. It reported that
223 nearly 10% of the patients developed additional forms of eye defects as delayed
224 manifestations. Some of them had developed late-onset glaucoma and the diagnosis was
225 made 3 to 22 years after birth. Keratic precipitates, keratoconus, corneal hydrops, and

226 spontaneous lens absorption were also reported as late-onset ocular defects [45].

227 Two hundred and forty-three children attending a school for the deaf in Nepal were
228 examined for ocular defects associated with CRS in 2009, of which 18 (7.4%) met the
229 clinical criteria for CRS and all the 18 children presented with pigmentary retinopathy
230 [46]. This indicated that detection of pigmentary retinopathy in children with congenital
231 hearing impairment could be an indicator of CRS first diagnosed in older age.

232 An ophthalmologist examined a total of 21 children with CRS at the median ages of
233 23 months in 2013 and 16 of them were examined again at the median age of 47 months
234 in 2015, in the follow-up study in Khanh Hoa (our second study [16]). Among the 21
235 children, 11 (52%) had abnormal ocular findings; ten (48%) had pigmentary retinopathy
236 and seven had other ocular abnormalities such as cataract (19%), myopia (11%),
237 hyperopia (11%), strabismus (29%), microphthalmia (19%), and nystagmus (10%).
238 Cataract was detected in four children (19%); one was unilateral and three were bilateral
239 (Figure 1). All children with cataracts also had microphthalmia and strabismus. Prognosis
240 after surgery for bilateral cataracts can be poor if associated with microphthalmia [40].

241

242 *2.4. Developmental delay of congenital rubella syndrome*

243 *2.4.1. Global developmental delay*

Chess observed children with CRS born after the rubella epidemic in 1960s in the United States, and found overlapping neurological manifestations such as unspecified, borderline, mild, moderate, severe, or profound intellectual disability (37%), hard signs of physical neurological defects such as spasticity (44%), and soft signs such as clumsy gait (24%) [29]. Ninety-five percent of children with CRS and intellectual disabilities also presented hearing and/or visual defects in the Chess's study [29]. Givens and colleagues also examined patients with CRS after the 1960s epidemic in the United States and found 62% with mild to severe psychomotor impairments, 41% with mild to severe intellectual disabilities, 18% with hyperactivity, 14% with spastic diplegia, 7% with seizure disorder, 2% with spastic quadriplegia, and a small number of hemiparesis cases [30]. Follow-up through 9-12 years of CRS infants without initial neurologic problems revealed that additional sensory, motor, and behavioral problems, including ASD, can appear in later life and develop progressively [6].

In the follow-up study in Khanh Hoa, Vietnam (our second study [16]), a total of 20 children were evaluated for developmental features using developmental screening tests; 17 (median age 24.7 months) in 2013 and 13 (median age 43.5 months) in 2015 including 10 for the second time and 3 for the first time. Nineteen of the 20 children had an "abnormal" score in at least one domain in the Ages and Stages Questionnaire (ASQ)

262 [47] or a “suspect” score in at least one area of the Denver Developmental Screening Test
263 II (Denver II) [48]. The communication domain in the ASQ and the language area of the
264 Denver II were the most frequently impaired in both assessments. The proportion of
265 children with affected problem-solving and personal-social skills increased at the median
266 age of 44 months. High incidence of hearing impairment and ASD (described later)
267 among the study participants could contribute to language and communication disorders
268 [49, 50]. Twelve children (71%) failed in two or more ASQ domains in 2013 (n=17) and
269 could be regarded as having a global developmental delay, which is defined as a
270 significant delay in two or more of the following developmental domains: gross/fine
271 motor, speech/language, cognition, social/personal, and activities of daily living [51].
272 Twelve participants were examined using the same version of the ASQ at the median age
273 of 25 months. A broad range of total ASQ scores (0 to 265) was found, indicating that
274 CRS can present with a wide severity range. In this study, children with CRS had multiple
275 areas of developmental difficulties in various levels of severity, with high prevalence of
276 sensory defects and language or communication problems.
277
278 *2.4.2. Autism Spectrum Disorder*
279 Chess’s study of children with CRS [29] reported a 7.4% prevalence of autism

and “partial syndrome of autism” by Kanner’s classical criteria [52] which is narrower and more exclusive than current ASD diagnostic criteria. A study estimated that 1228 ASD cases were prevented by RCVs in the United States from 2001 to 2010 [53], using the prevalence (7.4%) of CRS cases presenting with ASD obtained from the Chess’s study [29].

In the CRS follow-up study in Khanh Hoa (our second study [16]), 41% of children with CRS at the median age of 25 months failed on the Modified Checklist for Autism in Toddlers (M-CHAT) [54], a tool for screening ASD, in 2013 (n=17), and 12% met the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV [55] for autistic disorder, which is assumed to be a part of ASD according to the DSM-V [56]. Fifteen percent of children tested by the Childhood Autism Rating Scale, second edition (CARS2) [57] at the age of 44 months in 2015 (n=13) were diagnosed as having severe ASD, and met the DSM-IV criteria for autistic disorder. In this study, a combination of sensory or other impairments made it difficult to diagnose ASD correctly; however, 12–15% of the children with CRS was diagnosed as having ASD.

### *2.5. Cardiac diseases of congenital rubella syndrome*

Cardiac defect is also one of the common findings in CRS. It is detected in 38-70%

298 of patients with CRS [30, 31, 41, 58-60]. Patent ductus arteriosus (PDA) has been
299 reported as the most frequently seen congenital vascular malformation with CRS since
300 Gregg's initial report of CRS in 1941 [3]. The widespread use of cardiac catheterization
301 and echocardiography have improved the ability to diagnose other cardiac vascular
302 malformations in association with CRS, especially pulmonary artery stenosis [61]. A
303 review paper confirmed the association of CRS with branch pulmonary artery stenosis
304 and PDA, summarizing that 78% and 62% of 121 cases with CRS and cardiovascular
305 malformations had branch pulmonary artery stenosis and PDA, respectively, in studies
306 that used cardiac catheterization for evaluation of patients with CRS [61].

307 In the prospective survey in Khanh Hoa, Vietnam (our first study [15]), we examined
308 36 children with CRS by echocardiography and detected that 72% of them had
309 cardiovascular malformations, including 67% with PDA (n=24), 19% with atrial septal
310 defect, 8% with pulmonary stenosis, 3% with ventricular septal defect, and 3% with
311 atrioventricular septal defect. Sixteen cases of PDA (n=24) were accompanied by
312 pulmonary hypertension (PH) and nine of them died within one year after birth. PH was
313 significantly associated with mortality (hazard ratio 8.33, 95% confidence interval 1.79-
314 38.7) (Figure 2). Six in 11 children with PDA followed-up regularly by echocardiography
315 underwent transcatheter PDA occlusion therapy and showed a good prognosis without

316 PH.

317 In Vietnam, an experienced pediatric cardiologist empirically noticed that tubular-
318 type PDA was more frequently seen in PDA associated with CRS than in general PDA
319 without CRS (Do TN, personal communication). Transcatheter closure of tubular-type
320 PDA has difficulty in stabilizing the prosthesis due to lack of a sufficient ampulla; there
321 is the risk of displacement, embolization, or aortic protrusion [62, 63]. To clarify the
322 cardiologist's notion and investigate morphological and hemodynamic characteristics of
323 PDA associated with CRS, a retrospective survey of 108 children with CRS and 290
324 children with PDA but without CRS was conducted in Ho Chi Minh City (Toizumi et al.,
325 under review). Echocardiography in 106 children with CRS detected 87% with PDA the
326 most frequently, followed by 65% with tricuspid regurgitation, 50% with atrial septal
327 defect/patent foramen ovale, 44% with pulmonary hypertension, 26% with mitral
328 regurgitation, 23% with pulmonary stenosis, 15% with pulmonary regurgitation, 14%
329 with aortic stenosis, 9% with ventricular septal defect, 7% with aortic regurgitation, 4%
330 with coarctation of aorta and 1% with atrioventricular septal defect. Patients with CRS
331 and PDA (CRS-PDA) (n=50) had pulmonary stenosis and aortic stenosis more frequently.
332 In addition, they had higher main pulmonary artery pressure (PH) and higher aortic
333 pressure (systemic hypertension) compared to those with PDA without CRS (non-CRS-

PDA) (n=290). The diameter on the pulmonary artery side of PDA was larger and the length of PDA was longer significantly in CRS-PDA than in non-CRS-PDA. Proportion of tubular-type PDA (Figure 3) was higher in CRS-PDA (16%) than in non-CRS-PDA (3%) (p=0.020), as the cardiologist noticed. A coil occluder, generally used for small PDA, was more frequently used in those without CRS and a device with double-disk, used to avoid displacing or dropping it in the aorta, was more frequently used in those with CRS, reflecting differences in the morphology and size of PDA between CRS and non-CRS.

Hypertension due to stenosis of renal artery or aorta was previously reported as a late-onset finding in CRS [64]. Obstructive arterial lesions were seen in many vessels in CRS and could cause coronary, cerebral, and peripheral vascular disease in adulthood [65].

Hence, transcatheter closure of PDA in association with CRS needs a more careful choice of device and more detailed follow-up examinations after the intervention.

### *2.6. Other manifestations of congenital rubella syndrome*

We were unable to follow up on long-term prognosis of Vietnamese children with CRS born after the epidemic in 2011. However, it is noted that delayed manifestations can occur in more than 20% of children who have had symptomatic congenital rubella infection [66]. Late-onset diseases of CRS include a variety of endocrine disorders;

352 diabetes mellitus [67, 68], thyroid dysfunction [69], growth hormone deficiency [70], and
353 Addison's disease [71]. It has been reported that diabetes mellitus and impaired glucose
354 tolerance occur in approximately 20% of patients with CRS by the age of 35 [67]. Thyroid
355 dysfunction has been reported in 5% of patients with CRS in a previous study [72]. It
356 manifests variedly as hypothyroidism secondary to Hashimoto's thyroiditis,
357 thyrotoxicosis, or idiopathic hypothyroidism [69].

358 Late-onset interstitial pneumonitis has been detected at the age of 3-12 months and
359 led to death in some cases [6, 26, 73]. Progressive rubella panencephalitis, a slowly
360 progressive disease of the central nervous system that is due to chronic rubella virus
361 infection of the brain, rarely manifests during the second decade of life among patients
362 with CRS [6]. Urogenital anomalies including hypospadias, cryptorchidism, and
363 vesicoureteral reflux may occur in 20% or children with CRS [74].

364

365 **3. Conclusions**

366 In CRS, mortality is high and survivors can have a variety of disabilities in different
367 combination and severity, some of which would appear or worsen in later life.
368 Introduction of RCV into the national immunization program and maintenance of high
369 coverage of RCV immunization are critical to prevent rubella and CRS, while early

detection and management of patients with CRS are also an imperative clinical and public health issue.

Surveillance and reporting system of rubella and CRS are necessary to recognize suspected cases and call attention to high-risk groups (e.g., women of childbearing age and people around them). If a neonate is suspected of rubella infection, the physicians should complete pediatric, cardiac, auditory, ophthalmologic, and neurologic examinations along with laboratory testing and perform frequent follow-up, especially during the first 6 months. Timely intervention in cardiac defects can be lifesaving. Delays in diagnosis and intervention in hearing and ocular impairments can have critical impacts on the development of language and visual acuity, respectively. Early introduction and continuation of speech, occupational, physical, and behavior therapies, as well as appropriate interventions including hearing aids, cochlear implant, ophthalmological surgeries, eyeglasses or contact lens, or other treatments by a multidisciplinary team approach are required.

**Acknowledgement**

Our researches reviewed in this paper were supported by AMED under Grant Number JP18fm0108001.

**Conflict of interest**

The authors declare that they have no conflicts of interest.

391 Table 1. Incidence of congenital rubella syndrome (CRS) and rubella susceptibility in women of childbearing age.

| Country, city | Year | CRS incidence (per 1000 live births) | Reference | Proportion of women of childbearing age susceptible to rubella |
|---|---|---|---|---|
| Khanh Hoa, Vietnam | 2012-2013 | 2.1 | [15] | 29% in 2009-2010 [13] |
| Vietnam (mathematical modeling) | | 2.3 (estimated) | [7, 13] | 29% in 2009-2010 [13] |
| Trinidad and Tobago | 1982-1983 | 0.6 | [18] | 68% [75] |
| Oman | 1993 | 0.7 | [19] | 8% in 1988-89 (4-30% by regions) [19] |
| Ghana | 1995-1996 | 0.8 | [20] | 7% (postepidemic) [20] |
| Sri Lanka | 1994-1995 | 0.9 | [21] | 43% [76] |
| Singapore | 1969 | 1.5 | [22] | 47% [77] |
| Panama | 1986 | 2.2 | [23] | 38% in urban and 64% in rural [75] |
| Russia | 1979-1997 | 3.5 | [24] | 17% [24] |
| Ryukyu (Okinawa, Japan) | 1964-1965 | 20 | [25] | 7-11% in the Ryukyus, 37% in Amami (islands close to the Ryukyus) (postoepidemic) [78] |

392

393 Table 2. Clinical manifestations of congenital rubella

| | Transient | Perma-nent | Development and late-onset[a] | | Transient | Perma-nent | Development and late-onset[a] |
|---|---|---|---|---|---|---|---|
| General | | | | Central nervous system | | | |
| Intrauterine growth restriction | | | | Microcephaly | | + | |
| Delay in postnatal somatic growth | + | + | | Meningoencephalitis | + | | |
| Eyes | | | | Large anterior fontanel | + | | |
| Cataracts | | + | | Psychomotor developmental delay | | + | + |
| Microphthalmia | | + | | Autism spectrum disorder | | + | + |
| Pigmentary retinopathy | | + | | Learning disorder | | + | + |
| Cloudy cornea | | + | | Neurologic defect | | + | + |
| Glaucoma | | + | + | Progressive rubella encephalitis | | + | + |
| Hypoplasia of the iris | | + | | Endocrine | | | |
| Cloudy cornea | + | | | Diabetes mellitus | | + | + |
| Keratic precipitates | | + | + | Thyroid diseases | | + | + |
| Keratoconus | | + | + | Growth hormone deficiency | | + | + |
| Corneal hydrops | | + | + | Addison disease | | + | + |
| Lens absorption | | + | + | Urogenital anomalies | | | |
| Ears | | | | Hypospadias | + | + | |
| Sensorineural hearing impairment | | + | + | Cryptorchidism | + | + | |
| Central hearing impairment | | + | | Vesicoureteral reflux | + | + | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cardiovascular | | | | Others | | | |
| Patent ductus arteriosus | | + | | Dermal erythropoiesis | + | | |
| Pulmonary arterial stenosis | | + | | Thrombocytopenia with/without purpura | + | | |
| Aortic stenosis | | + | | Hepatosplenomegaly | + | | |
| Coarctation of aorta | | + | | Hepatitis | + | | |
| Atrial/ventricular septal defects | | + | | Radiolucent bone disease | + | | |
| Pulmonary hypertension | | + | | Jaundice | + | | |
| Myocarditis | + | | | Adenopathy | + | | |
| Hypertension | | + | + | Interstitial pneumonitis | + | | + |
| | | | | Chronic diarrhea | + | | |

[a] Some occur early.

The clinical features of CRS are grouped into three categories: transient manifestations in newborns and infants; permanent manifestations, which may be present at birth or become apparent during the first year of life; and development and late-onset manifestations, which usually appear and progress during childhood, adolescence, and early adult life [27, 58]. These groupings overlap. “+” suggests the group(s) into which the respective manifestation is categorized commonly.

## Figure legends

Figure 1. Cataracts in bilateral eyes of a 21-month-old boy with CRS.

A clouding of the lens of the bilateral eyes that was detected by the CRS follow-up study in 2013 is shown [16].

Figure 2. Kaplan-Meier survival curves of the CRS patients with and without pulmonary hypertension detected on the echocardiographic study in Khanh Hoa, Vietnam, 2011-2012 (reproduced with permission from *Pediatrics*, Vol. 134(2), Pages e519-e526, Copyright© 2014 by the American Academy of Pediatrics) [15].

The Kaplan-Meier curve clearly shows a significantly higher mortality of the CRS patients with pulmonary hypertension compared with those without, with most deaths having occurred before 6 months of age (log-rank test, p=0.001).

Figure 3. Tubular type PDA of a 4-month-old boy with CRS.

This angiography was taken when he had transcatheter PDA occlusion therapy at Children's Hospital 1 in Ho Chi Minh City, showing a typical tubular type PDA comprising tubular ductus without constriction at the pulmonary insertion (Toizumi *et al*., under review).

413 **References**

414 [1] Rubella vaccines: WHO position paper. Wkly Epidemiol Rec 2011;86:301-16.

415 [2] Plotkin SA. Rubella eradication. Vaccine 2001;19:3311-9.

416 [3] Gregg NM. Congenital cataract following German measles in the mother. T
417 Ophthalmol Soc Aus 1941;3:35-46.

418 [4] Swan C, Tostevin AL, Black GH. Final observations on congenital defects in infants
419 following infectious diseases during pregnancy, with special reference to rubella. Med J
420 Australia 1946;2:889-908.

421 [5] Reef SE, Plotkin SA. Rubella vaccine. In: Plotkin AS, Orenstein WA, Offit PA, editors.
422 Vaccines. 6th ed. Philadelphia: Elsevier; 2013, p. 688-717.

423 [6] Mason WH. Rubella. In: Kliegman RM, Stanton BF, Geme III JWS, Schor NF,
424 Behrman RE, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier;
425 2011, p. 1075-8.

426 [7] Vynnycky E, Adams EJ, Cutts FT, Reef SE, Navar AM, Simons E, et al. Using
427 seroprevalence and immunisation coverage data to estimate the global burden of
428 Congenital Rubella Syndrome, 1996-2010: A systematic review. Plos One 2016;11.

429 [8] Minakami H, Kubo T, Unno N. Causes of a nationwide rubella outbreak in Japan,
430 2012–2013. J Infection 2014;68:99-101.

[9] Saitoh A, Okabe N. Recent progress and concerns regarding the Japanese immunization program: Addressing the "vaccine gap". Vaccine 2014;32:4253-8.

[10] Reef SE, Redd SB, Abernathy E, Zimmerman L, Icenogle JP. The epidemiological profile of rubella and congenital rubella syndrome in the United States, 1998-2004: the evidence for absence of endemic transmission. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006;43 Suppl 3:S126-32.

[11] Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunisation in Greece: Retrospective survey and systematic review. BMJ Brit Med J 1999;319:1462-6.

[12] Strebel PM, Gacic-Dobo M, Reef S, Cochi SL. Global use of Rubella vaccines, 1980-2009. J Infect Dis 2011;204:S579-S84.

[13] Miyakawa M, Yoshino H, Yoshida LM, Vynnycky E, Motomura H, Tho LH, et al. Seroprevalence of rubella in the cord blood of pregnant women and congenital rubella incidence in Nha Trang, Vietnam. Vaccine 2014;32:1192-8.

[14] Toda K, Reef S, Tsuruoka M, Iijima M, Dang TH, Duong TH, et al. Congenital rubella syndrome (CRS) in Vietnam 2011-2012-CRS epidemic after rubella epidemic in 2010-2011. Vaccine 2015;33:3673-7.

[15] Toizumi M, Motomura H, Vo HM, Takahashi K, Pham E, Nguyen HAT, et al.

449 Mortality associated with pulmonary hypertension in congenital rubella syndrome.
450 Pediatrics 2014;134:e519-e26.
451 [16] Toizumi M, Nguyen GTH, Motomura H, Nguyen TH, Pham E, Kaneko KI, et al.
452 Sensory defects and developmental delay among children with congenital rubella
453 syndrome. Sci Rep-UK 2017;7:46483.
454 [17] Lanzieri T, Redd S, Abernathy E, Icenogle J. Chapter 15: Congenital Rubella
455 Syndrome, Manual for the Surveillance of Vaccine-Preventable Diseases (6th Edition,
456 2013). Centers for Disease Control and Prevention,
457 https://www.cdc.gov/vaccines/pubs/surv-manual/chpt15-crs.html [accessed 03 October
458 2018]
459 [18] Ali Z, Hull B, Lewis M. Neonatal manifestation of congenital rubella following an
460 outbreak in Trinidad. J Trop Pediatrics. 1986;32:79-82.
461 [19] World Health Organization EPoI. Rubella outbreak, Oman. Wkly Epidemiol Rec
462 1994;69:333-6.
463 [20] Lawn JE, Reef S, Baffoe-Bonnie B, Adadevoh S, Caul EO, Griffin GE. Unseen
464 blindness, unheard deafness, and unrecorded death and disability: Congenital rubella in
465 Kumasi, Ghana. Am J Public Health 2000;90:1555-61.
466 [21] Gunasekera DP, Gunasekera PC. Rubella immunisation - Learning from developed

467 countries [5]. Lancet 1996;347:1694-5.

468 [22] Tan KL, Wong TT, Chan MC, Chun FY, Lam SK. Congenital rubella in Singapore.

469 J Singapore Paediatr Soc 1970;12:111-25.

470 [23] De Owens CS, De Espino RT. Rubella in Panama: Still a problem. Pediatr Infect Dis

471 J 1989;8:110-5.

472 [24] Semerikov VV, Lavrentyeva IN, Popov VF, Fletcher MA, Kolotov ME. Rubella in

473 the Russian Federation: Epidemiological features and control measures to prevent the

474 congenital rubella syndrome. Epidemiol Infect 2000;125:359-66.

475 [25] Kono R, Hirayama M, Sugishita C, Miyamura K. Epidemiology of rubella and

476 congenital rubella infection in Japan. Rev Infect Dis 1985;7 Suppl 1:S56-63.

477 [26] Cutts FT, Robertson SE, Diaz-Ortega JL, Samuel R. Control of rubella and

478 congenital rubella syndrome (CRS) in developing countries, part 1: Burden of disease

479 from CRS. B World Health Organ. 1997;75:55-68.

480 [27] Reef S, Plotkin SA. Rubella. In: Wilson C, Nizet V, Maldonado YA, Remington JS,

481 LKlein JO, editors. In: Remington and Klein's Infectious Diseases of the Fetus and

482 Newborn. 8th ed. Philadelphia: Elsevier Saunders; 2016, p. 894-932.

483 [28] Cooper LZ, Krugman S. Clinical manifestations of postnatal and congenital rubella.

484 AMA Arch Ophthalmol (Chicago, Ill : 1960) 1967;77:434-9.

485 [29] Chess S. Autism in children with congenital rubella. J Autism Child Schiz 1971;1:33-
486 47.
487 [30] Givens KT, Lee DA, Jones T, Ilstrup DM. Congenital rubella syndrome: Ophthalmic
488 manifestations and associated systemic disorders. Brit J Ophthalmol 1993;77:358-63.
489 [31] Khandekar R, Al Awaidy S, Ganesh A, Bawikar S. An Epidemiological and Clinical
490 Study of Ocular Manifestations of Congenital Rubella Syndrome in Omani Children.
491 AMA Arch Ophthalmol 2004;122:541-5.
492 [32] Reef SE, Plotkin S, Cordero JF, Katz M, Cooper L, Schwartz B, et al. Preparing for
493 Elimination of Congenital Rubella Syndrome (CRS): Summary of a Workshop on CRS
494 Elimination in the United States. Clin Infect Dis 2000;31:85-95.
495 [33] Cooper LZ. The history and medical consequences of rubella. Rev Infect Dis 1985;7
496 Suppl 1:S2-10.
497 [34] Smith RJH, Bale Jr JF, White KR. Sensorineural hearing loss in children. Lancet
498 2005;365:879-90.
499 [35] Banatvala JE, Brown DWG. Rubella. Lancet 2004;363:1127-37.
500 [36] Johnson JL, White KR, Widen JE, Gravel JS, James M, Kennalley T, et al. A
501 multicenter evaluation of how many infants with permanent hearing loss pass a two-stage
502 otoacoustic emissions/automated auditory brainstem response newborn hearing screening

503 protocol. Pediatrics 2005. p. 663-72.

504 [37] Anderson H, Barr B, Wedenberg E. Genetic Disposition—A Prerequisite for

505 Maternal Rubella Deafness. Arch Otolaryngol 1970;91:141-7.

506 [38] Desmond MM, Fisher ES, Vorderman AL, Schaffer HG, Andrew LP, Zion TE, et al.

507 The longitudinal course of congenital rubellaencephalitis in nonretarded children. J

508 Pediatr 1978;93:584-91.

509 [39] Duszak RS. Congenital rubella syndrome-major review. Optometry 2009;80:36-43.

510 [40] Wolff SM. The ocular manifestations of congenital rubella. Trans Am Ophthalmol

511 Soc 1972;70:577-614.

512 [41] Peckham C. Congenital rubella in the United Kingdom before 1970: the prevaccine

513 era. Rev Infect Dis 1985;7 Suppl 1:S11-6.

514 [42] Vijayalakshmi P, Kakkar G, Samprathi A, Banushree R. Ocular manifestations of

515 congenital rubella syndrome in a developing country. Indian J Ophthalmol 2002;50:307-

516 11.

517 [43] Eckstein M, Vijayalakshmi P, Killedar M, Gilbert C, Foster A. Aetiology of

518 childhood cataract in south India. British Journal of Ophthalmology. 1996;80:628-32.

519 [44] Boger WP, III. Late Ocular Complications in Congenital Rubella Syndrome.

520 Ophthalmology 1980;87:1244-52.

[45] Boger WP, III, Petersen RA, Robb RM. Spontaneous absorption of the lens in the congenital rubella syndrome. AMA Arch Ophthalmol 1981;99:433-4.

[46] Upreti SR, Thapa K, Pradhan YV, Shakya G, Sapkota YD, Anand A, et al. Developing rubella vaccination policy in Nepal - Results from rubella surveillance and seroprevalence and congenital rubella syndrome studies. J Infect Dis 2011;204:S433-S8.

[47] Bricker D, Squires J. Ages and Stages Questionnaires. 1999.

[48] Frankenburg WK, Dodds J, Archer P, Shapiro H, Bresnick B. The Denver II: A major revision and restandardization of the Denver Developmental Screening Test. Pediatrics 1992;89:91-7.

[49] Feldman RB, Lajoie R, Mendelson J, Pinsky L. CONGENITAL RUBELLA AND LANGUAGE DISORDERS. Lancet 1971;298:978.

[50] Vernon M. Psychological, educational and physical characteristics associated with post rubella deaf children. Volta Rev 1967;69:176-85.

[51] Shevell M, Ashwal S, Donley D, Flint J, Gingold M, Hirtz D, et al. Practice parameter: Evaluation of the child with global developmental delay: Report of the quality standards subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. Neurology 2003;60:367-80.

[52] Kanner L. Autistic disturbances of affective contact. Nerv Child 1943;2:217-50.

539 [53] Berger BE, Navar-Boggan AM, Omer SB. Congenital rubella syndrome and autism
540 spectrum disorder prevented by rubella vaccination - United States, 2001-2010. BMC
541 Public Health 2011;11,340.
542 [54] Robins DL, Fein D, Barton ML, Green JA. The Modified Checklist for Autism in
543 Toddlers: An Initial Study Investigating the Early Detection of Autism and Pervasive
544 Developmental Disorders. J Autism Dev Disord 2001;31:131-44.
545 [55] American Psychiatric Association. Diagnostic and Statistical Manual of Mental
546 Disorders. 4th ed. 1994.
547 [56] American Psychiatirc Association. Diagnostic and Statistical Manual of Mental
548 Disorders: DSM-5. Fifth ed. 2013.
549 [57] Schopler E, Van Bourgondien ME, Wellman GJ, Love SR. Childhood autism rating
550 scale, second edition (CARS-2). 2010.
551 [58] Cooper LZ, Ziring PR, Ockerse AB, Fedun BA, Kiely B, Krugman S. Rubella:
552 Clinical Manifestations and Management. American Journal of Diseases of Children.
553 1969;118:18-29.
554 [59] Campbeli M. Place of maternal rubella in the aetiology of congenital heart disease.
555 BMJ Brit Med J 1961;1:691-6.
556 [60] Rittler M, López-Camelo J, Castilla EE. Monitoring congenital rubella embryopathy.

557 Birth Defects Research Part A - Clinical and Molecular Teratology. 2004;70:939-43.

558 [61] Oster ME, Riehle-Colarusso T, Correa A. An update on cardiovascular

559 malformations in congenital rubella syndrome. Birth Defects Res A 2010;88:1-8.

560 [62] Krichenko A, Benson LN, Burrows P, Möes CAF, McLaughlin P, Freedom RM.

561 Angiographic classification of the isolated, persistently patent ductus arteriosus and

562 implications for percutaneous catheter occlusion. Am J Cardiol 1989;63:877-80.

563 [63] Masri S, El Rassi I, Arabi M, Tabbakh A, Bitar F. Percutaneous closure of patent

564 ductus arteriosus in children using amplatzer duct occluder II: Relationship between PDA

565 type and risk of device protrusion into the descending aorta. Catheter Cardio Inte

566 2015;86:E66-E72.

567 [64] Fortuin NJ, Morrow AG, Roberts WC. Late vascular manifestations of the rubella

568 syndrome. A roentgenographic-pathologic study. Am J Med 1971;51:134-40.

569 [65] Forrest JM, Menser MA, Reye RD. Obstructive arterial lesions in rubella. Lancet

570 1969;1:1263-4.

571 [66] Sever JL, South MA, Shaver KA. Delayed manifestations of congenital rubella. Rev

572 Infect Dis 1985;7 Suppl 1:S164-9.

573 [67] Forrest J, Menser M, Burgess JA. High frequency of diabetes mellitus in young

574 adults with congenital rubella. Lancet 1971;298:332-4.

575 [68] Menser M, Forrest J, Bransby R. Rubella infection and diabetes mellitus. Lancet
576 1978;311:57-60.
577 [69] Tomer Y, Davies TF. Infection, thyroid disease, and autoimmunity. Endocr Rev
578 1993;14:107-20.
579 [70] Preece MA, Kearney PJ, Marshall WC. Growth-hormone dificiency in congenital
580 rubella. Lancet 1977;310:842-4.
581 [71] Ziring PR, Gallo G, Finegold M, Buimovici-Klein E, Ogra P. Chronic lymphocytic
582 thyroiditis: Identification of rubella virus antigen in the thyroid of a child with congenital
583 rubella. J Pediatr 1977;90:419-20.
584 [72] Clarke WL, Shaver KA, Bright GM, Rogol AD, Nance WE. Autoimmunity in
585 congenital rubella syndrome. J Pediatr 1984;104:370-3.
586 [73] Mizuno Y, Yokoi K, Suzuki S. Congenital rubella syndrome with death from
587 interstitial pneumonia. Pediatr Int 2016;58:490-3.
588 [74] Kaplan GW, McLaughlin AP. Urogenital anomalies and congenital rubella syndrome.
589 Urology 1973;2:148-52.
590 [75] Dowdle WR, Ferrera W, De Salles Gomes LF, King D, Kourany M, Madalengoitia
591 J, et al. WHO collaborative study on the sero-epidemiology of rubella in Caribbean and
592 Middle and South American populations in 1968. B World Health Organ. 1970;42:419-

593 22.

594 [76] Mendis L. Susceptibility to rubella virus among Sri Lankan women. Ceylon Med J

595 1989;34:73-5.

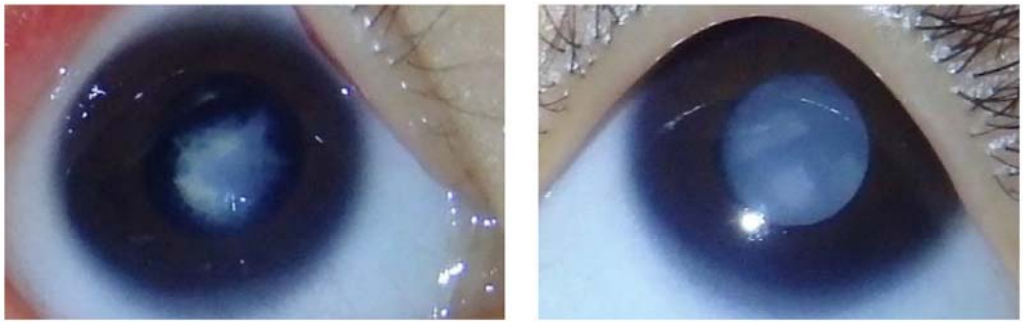
596 [77] Doraisingham S, Goh KT. The rubella immunity of women of child-bearing age in

597 Singapore. Ann Acad Med Singapore 1981;10:238-41.

598 [78] Ueda K, Nishida Y, Oshima K, Yoshikawa H, Nonaka S. An explanation for the high

599 incidence of congenital rubella syndrome in ryukyu. Am J Epidemiol 1978;107:344-51.

Figure 1.



Right eye Left eye

Figure 2.

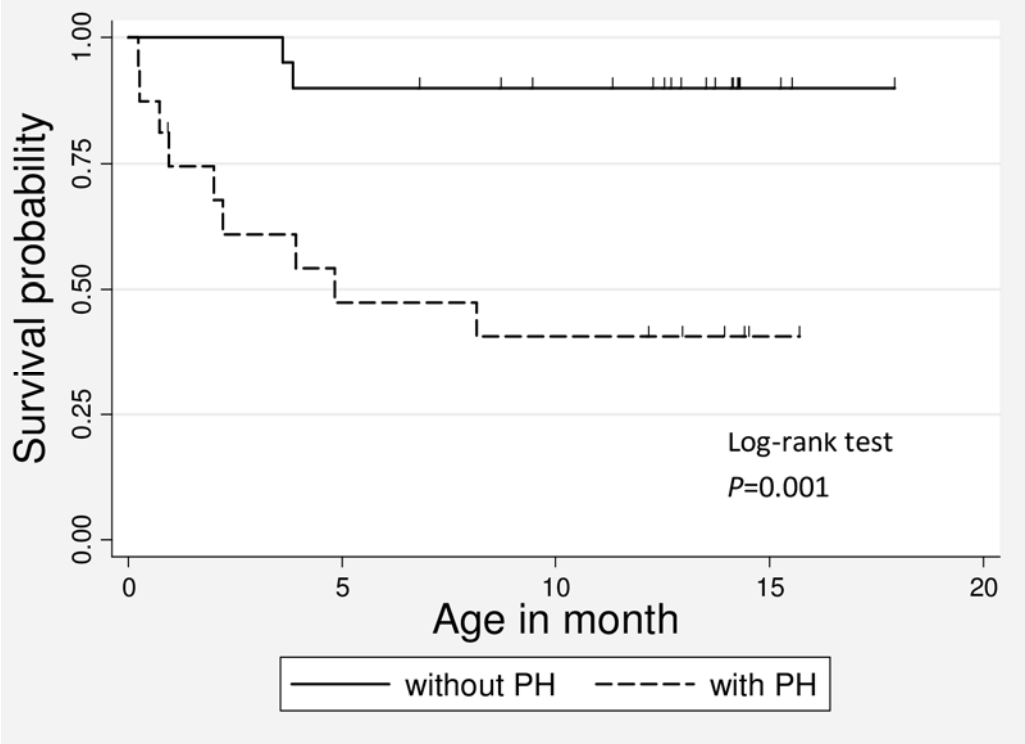
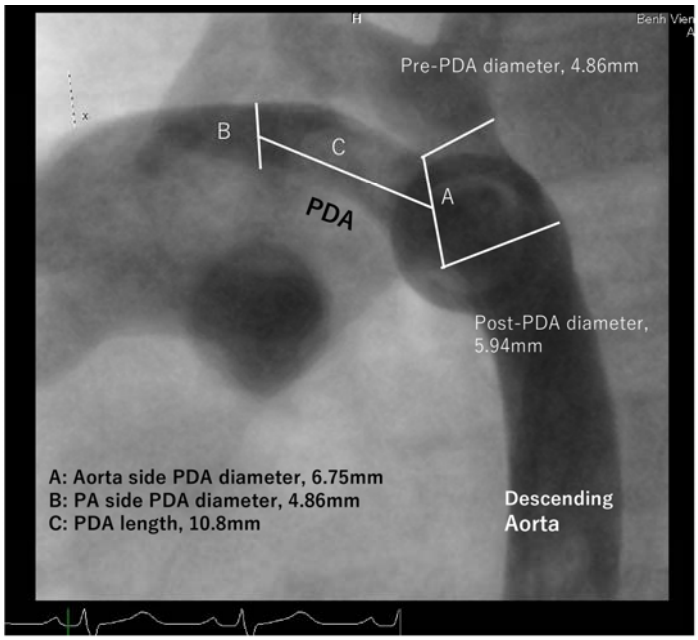


Figure 3.


Pre-PDA diameter, 4.86mm
B
C
A
PDA
Post-PDA diameter,
5.94mm
A: Aorta side PDA diameter, 6.75mm
B: PA side PDA diameter, 4.86mm
C: PDA length, 10.8mm
Descending
Aorta