Late Clinical Manifestations of Congenital Rubella Syndrome (CRS), an experience from Oman, 1980-2015

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Abstract

Background

Congenital rubella syndrome (CRS) is a major cause of severe birth and late onset defects worldwide. A national CRS registry was established in Oman to conduct long term follow-up of CRS cases.

Methods

The CRS national registry includes all CRS cases reported to the Ministry of Health since 1980 and are based on the WHO CRS case definition. CRS patients received annual clinical assessments.

Results

Of 104 reported CRS cases, 85 (82%) were clinically or laboratory-confirmed. Out of the confirmed cases, 46 (54%) patients were successfully contacted and received clinical evaluation. Twenty (24%) of the confirmed cases were lost to follow-up and 19 (22%) were deceased. Among deceased cases, 7 (28%) died from cardiovascular causes, 3 (12%) from meningitis/encephalitis, 2 (9%) from pneumonia, 1 (3%) from, head injury and 12 (48%) had unknown causes.

Out of the evaluable patients, 19 (41%) had late-onset symptoms manifestations of CRS detected from 8-23 years of age; 3 (16%) had endocrine function defects: 2 (11%) had thyroid disorders and 1 (5%) had type 2 diabetes mellitus, 3 (16%) had seizures disorders, One (5%) case each of systolic murmur, elevated blood pressure, pulmonary atresia and left ventricular failure were reported. Three (16%) hepatosplenomegaly, 1 (5%) late onset sensorineural hearing impairment, 1 (5%) hypospadias and 1(5%) autism (reported as CRS-related), 18 (39%) had cerebral palsy, 10 (22%) and 5 (11%) had severe to profound and moderate mental retardation reported, respectively. Seventy two percent of the CRS cases survived up to 30 years.

Conclusions

Cardiovascular, neurological manifestations and endocrine function defects were the most common late CRS manifestations. The long survival of CRS cases were attributed to early medical and rehabilitation interventions. Identification and follow-up of the CRS cases provided an opportunity to assess late or unrecognized manifestations of congenital rubella and support earlier clinical intervention.

Keywords

Congenital Rubella Syndrome; CRS; late manifestations of CRS; disability; Expanded Program on Immunization; Oman

1. Introduction

The World Health Organization (WHO) has estimated that more than 100,000 infants are born annually with congenital rubella syndrome (CRS) worldwide [1]. CRS comprises various birth defects, most importantly deafness, congenital heart disease, cataracts or blindness, and mental retardation. Many of the CRS manifestations are readily identified during infancy, but others are hard to diagnose until older ages, such as sensorineural deafness. Some cases of CRS are known to have a late onset, for example type 2 diabetes mellitus and thyroiditis [2].

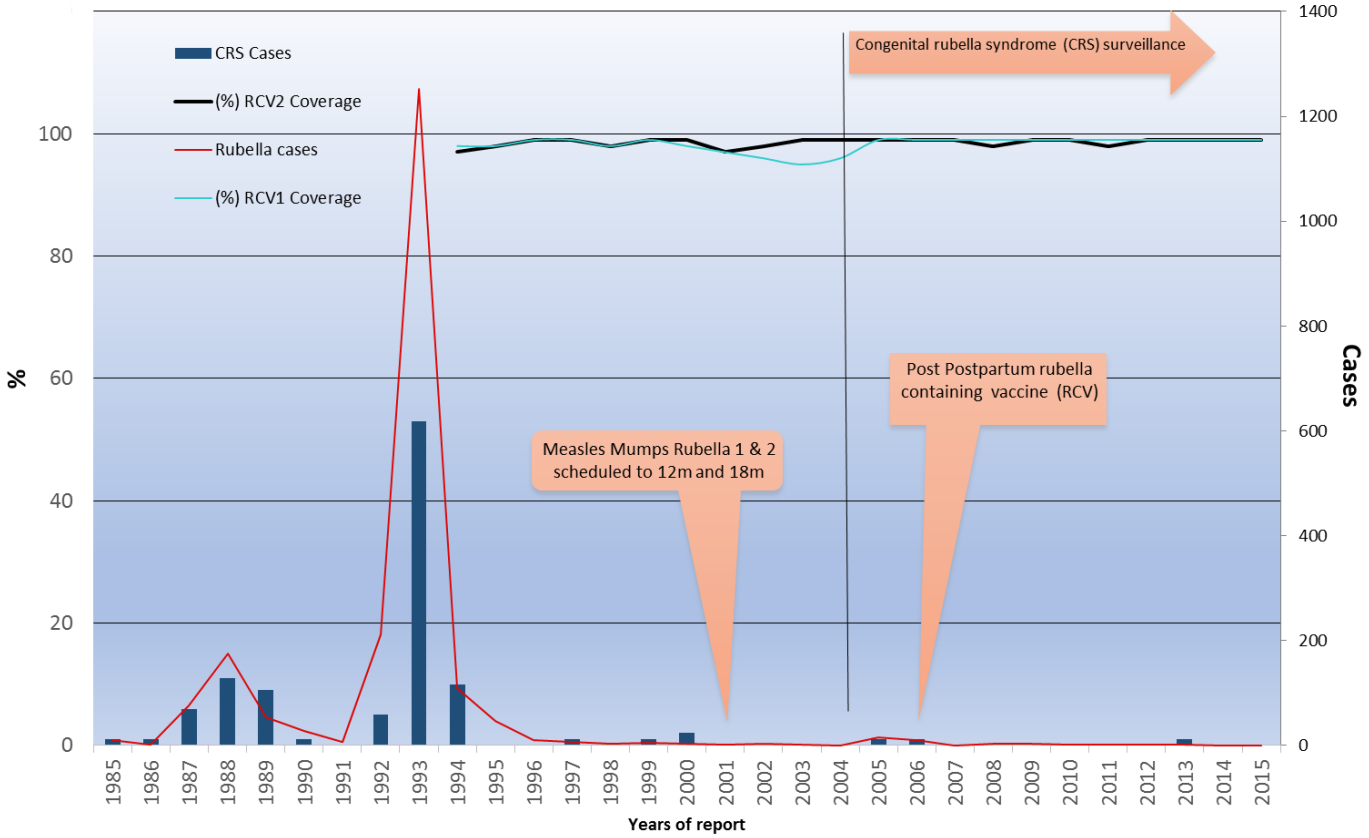
Oman has experienced significant rubella epidemics, from 1987 to 1989 and from 1992 to 1996 [Figure 1]. In 1994, the first dose of rubella-containing vaccine (RCV1) was introduced into the national expanded programme of immunization (EPI) as measles-rubella vaccine (MR) at 15 months of age. In October 1997, MR vaccine was replaced by single-dose measles-mumps–rubella vaccine (MMR), and in 2001, a policy of two doses was introduced for MMR vaccination at 12 and 18 months of age, both vaccines coverages were maintained above 95% since 1999. The widespread use of rubella vaccine and the first-dose coverages of more than 95% had led to a dramatic decline in the incidence of rubella and CRS. Additionally, since 2001, post-partum rubella vaccination of susceptible mothers with RCV at the time when their infants receive hepatitis B vaccine birth dose and BCG has been a national priority resulting in achievement of above 99% coverage. Further, newly employed health care workers (HCWs) receive counseling and education about the benefits of vaccination and offered serological testing and free cost vaccination to those who lack evidence of immunity. Further, infection control practices are widely adhered to at delivery, and on paediatric, ophthalmology and neonatology wards [3].

In 2005, Oman established a policy for interrupting indigenous rubella virus transmission. Rubella elimination was defined as the absence of endemic rubella transmission in a defined geographical area (e.g. region) for ≥12 months and the

absence of CRS cases associated with endemic transmission in the presence of a high-quality surveillance system.

Oman has demonstrated exemplary progress towards elimination of rubella and CRS and has fully committed to the national elimination goal and strategies. Since 2001, only 1 case of CRS was reported from local transmission and 2 CRS cases were imported [Figure 1].

Figure 1: Trend of rubella cases, congenital rubella syndrome (CRS), first and second dose of rubella-containing vaccine (RCV1, RCV2), Oman, 1985-2015



In 2004, the CRS surveillance system was implemented in Oman. This program mandates that every suspected case of CRS should be reported within 24 hours of identification and should be investigated within 48 hours of identification. National surveillance includes both active and passive reporting from all health institutions to the governorate communicable diseases surveillance unit. Every clinician, staff nurse, hospital, and laboratory is required to report CRS cases to their respective governorate.

Further, the surveillance system includes a CRS registry with a process for follow-up of all CRS-registered cases to monitor for and document late CRS manifestations.

This paper reports the findings of long term follow-up and clinical assessments of CRS cases from 1980 to 2015 in order to document late emerging CRS manifestations and to create an important resource for health professionals for planning and early intervention.

2. Methods

2.1. Congenital Rubella Syndrome Registry

A national registry of CRS cases was implemented in 2000. All patients with CRS who had been reported to the health and non-health institutions since 1980 were included, in addition to prospectively reported cases.

2.2. Case ascertainment

Since 2000, both active & passive CRS surveillance were intensified in Oman. In this program, CRS cases are classified according to WHO CRS case definition which included suspected CRS case; clinically confirmed CRS case; and laboratory confirmed CRS case [4].

Suspected CRS: A suspected case is any infant less than one year of age in whom a health worker suspects CRS and who presents with heart disease and/or suspicion of deafness and/or one or more of the following eye signs: white pupil (cataract), diminished vision, pendular movement of the eyes (nystagmus), squint, smaller eye ball (microphthalmos), or larger eye ball (congenital glaucoma), or the infant's mother has a history of suspected or confirmed rubella during pregnancy, even when the infant shows no signs of CRS.

Clinically Confirmed CRS: A clinically confirmed case is an infant in whom a qualified physician either detects two or more of the complications from list "A" below or detects one from list A and one from list "B." List A includes: cataract(s), congenital glaucoma, congenital heart disease, loss of hearing, or pigmentary retinopathy. List B includes: purpura, splenomegaly, microcephaly,

mental retardation, meningo-encephalitis, radiolucent bone disease, or jaundice that begins within 24 hours after birth.

Laboratory Confirmed CRS: A laboratory-confirmed case is an infant with clinically confirmed CRS who has a positive blood test for rubella-specific immunoglobulin M (IgM) obtained as early as possible within the first year of life.

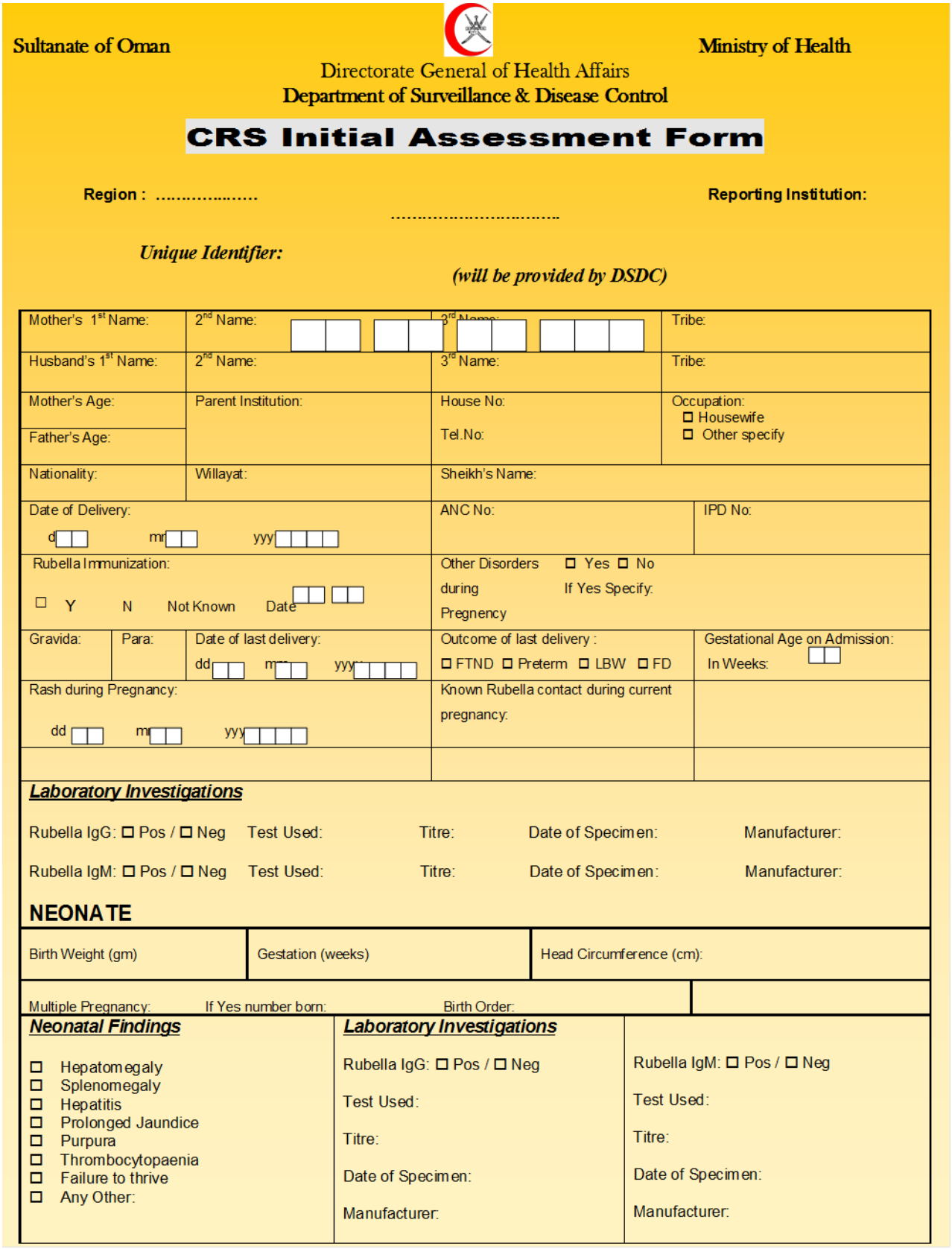
Congenital rubella infection (CRI): A case with positive serology, but without manifestations that meet clinically confirmed case criteria.

2.3. Case investigation and long term follow-up

All surviving patients with CRS were identified and contacted, to schedule annual detailed clinical assessments using standardized forms. CRS patients received clinical assessments annually from 2000 until 2010 and biannually thereafter. The clinical assessments included a general physical examination and examinations [Figure 2] by specialists in cardiology, endocrinology, ophthalmology, neurology [Figure 3], audiology, and otorhinolaryngology [Figure 4].

The following information was obtained during annual and biannual examinations: age, sex, year of birth, history of rash during pregnancy or contact with rubella case, rubella virus testing results and neonatal outcomes. An ophthalmologist performed a complete eye examination, including dilated retinal assessment, on each child with CRS for ocular manifestations. Inpatient medical records for CRS patients who had eye surgery were reviewed when available. Otorhino-laryngologic evaluations included audiologist-performed testing for hearing loss and assessment for speech impairment. Pure tone audiometric testing was carried out when possible. Hearing impairments were classified as sensorineural, conductive, or mixed. Patients with hearing aids required examination at the ear clinic once every 6 months for the first 15 years and every 5 years thereafter. Speech was assessed for impairments and delays.

Figure 2: Congenital rubella syndrome (CRS) initial assessment form for general examination, Oman, 2015



Sultanate of Oman — Ministry of Health

Directorate General of Health Affairs

Department of Surveillance & Disease Control

CRS Initial Assessment Form

Region : ……..…… **Reporting Institution:** ……..……..……..

Unique Identifier: ***(will be provided by DSDC)***

Mother's 1st Name:	2nd Name:	3rd Name:	Tribe:
Husband's 1st Name:	2nd Name:	3rd Name:	Tribe:
Mother's Age: Father's Age:	Parent Institution:	House No: Tel.No:	Occupation: ☐ Housewife ☐ Other specify
Nationality:	Willayat:	Sheikh's Name:	
Date of Delivery: dd mm yyyy		ANC No:	IPD No:
Rubella Immunization: ☐ Y N Not Known Date		Other Disorders during Pregnency ☐ Yes ☐ No If Yes Specify:	
Gravida: / Para:	Date of last delivery: dd mm yyyy	Outcome of last delivery : ☐ FTND ☐ Preterm ☐ LBW ☐ FD	Gestational Age on Admission: In Weeks:
Rash during Pregnancy: dd mm yyyy		Known Rubella contact during current pregnancy:	

Laboratory Investigations

Rubella IgG: ☐ Pos / ☐ Neg Test Used: Titre: Date of Specimen: Manufacturer:

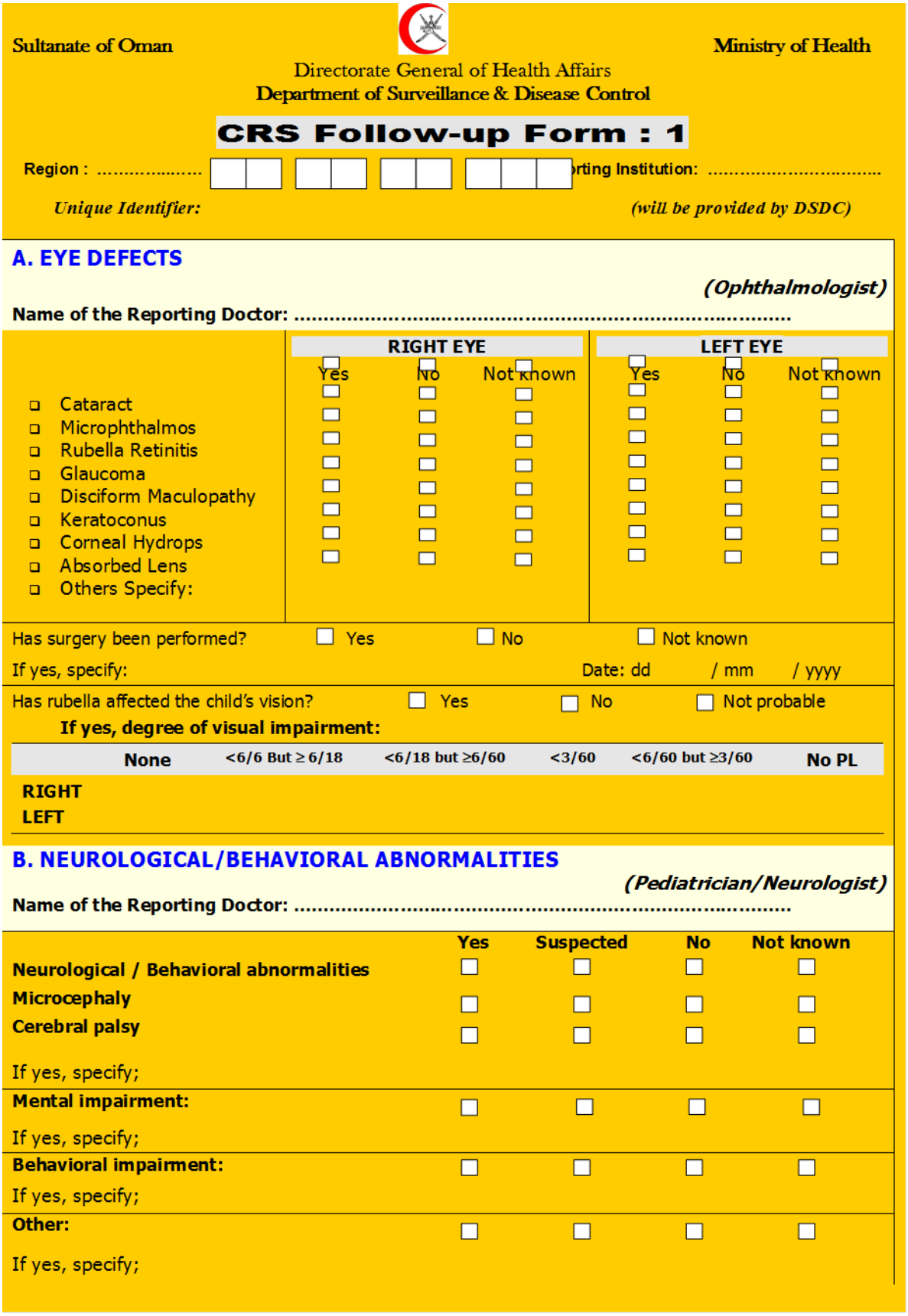
Rubella IgM: ☐ Pos / ☐ Neg Test Used: Titre: Date of Specimen: Manufacturer:

NEONATE

Birth Weight (gm)	Gestation (weeks)	Head Circumference (cm):
Multiple Pregnancy: If Yes number born:	Birth Order:	

Neonatal Findings	***Laboratory Investigations***	
☐ Hepatomegaly ☐ Splenomegaly ☐ Hepatitis ☐ Prolonged Jaundice ☐ Purpura ☐ Thrombocytopaenia ☐ Failure to thrive ☐ Any Other:	Rubella IgG: ☐ Pos / ☐ Neg Test Used: Titre: Date of Specimen: Manufacturer:	Rubella IgM: ☐ Pos / ☐ Neg Test Used: Titre: Date of Specimen: Manufacturer:

Figure 3: Congenital rubella syndrome (CRS) follow-up form for ocular and neurological manifestation, Oman, 2015



Sultanate of Oman — Ministry of Health

Directorate General of Health Affairs
Department of Surveillance & Disease Control

CRS Follow-up Form : 1

Region : ..... ☐☐ ☐☐ ☐☐ ☐☐☐ rting Institution: .....

Unique Identifier: *(will be provided by DSDC)*

A. EYE DEFECTS

(Ophthalmologist)

Name of the Reporting Doctor: .....

	RIGHT EYE			LEFT EYE		
	Yes	No	Not known	Yes	No	Not known
☐ Cataract	☐	☐	☐	☐	☐	☐
☐ Microphthalmos	☐	☐	☐	☐	☐	☐
☐ Rubella Retinitis	☐	☐	☐	☐	☐	☐
☐ Glaucoma	☐	☐	☐	☐	☐	☐
☐ Disciform Maculopathy	☐	☐	☐	☐	☐	☐
☐ Keratoconus	☐	☐	☐	☐	☐	☐
☐ Corneal Hydrops	☐	☐	☐	☐	☐	☐
☐ Absorbed Lens	☐	☐	☐	☐	☐	☐
☐ Others Specify:	☐	☐	☐	☐	☐	☐

Has surgery been performed? ☐ Yes ☐ No ☐ Not known

If yes, specify: Date: dd / mm / yyyy

Has rubella affected the child's vision? ☐ Yes ☐ No ☐ Not probable

If yes, degree of visual impairment:

	None	<6/6 But ≥ 6/18	<6/18 but ≥6/60	<3/60	<6/60 but ≥3/60	No PL
RIGHT						
LEFT						

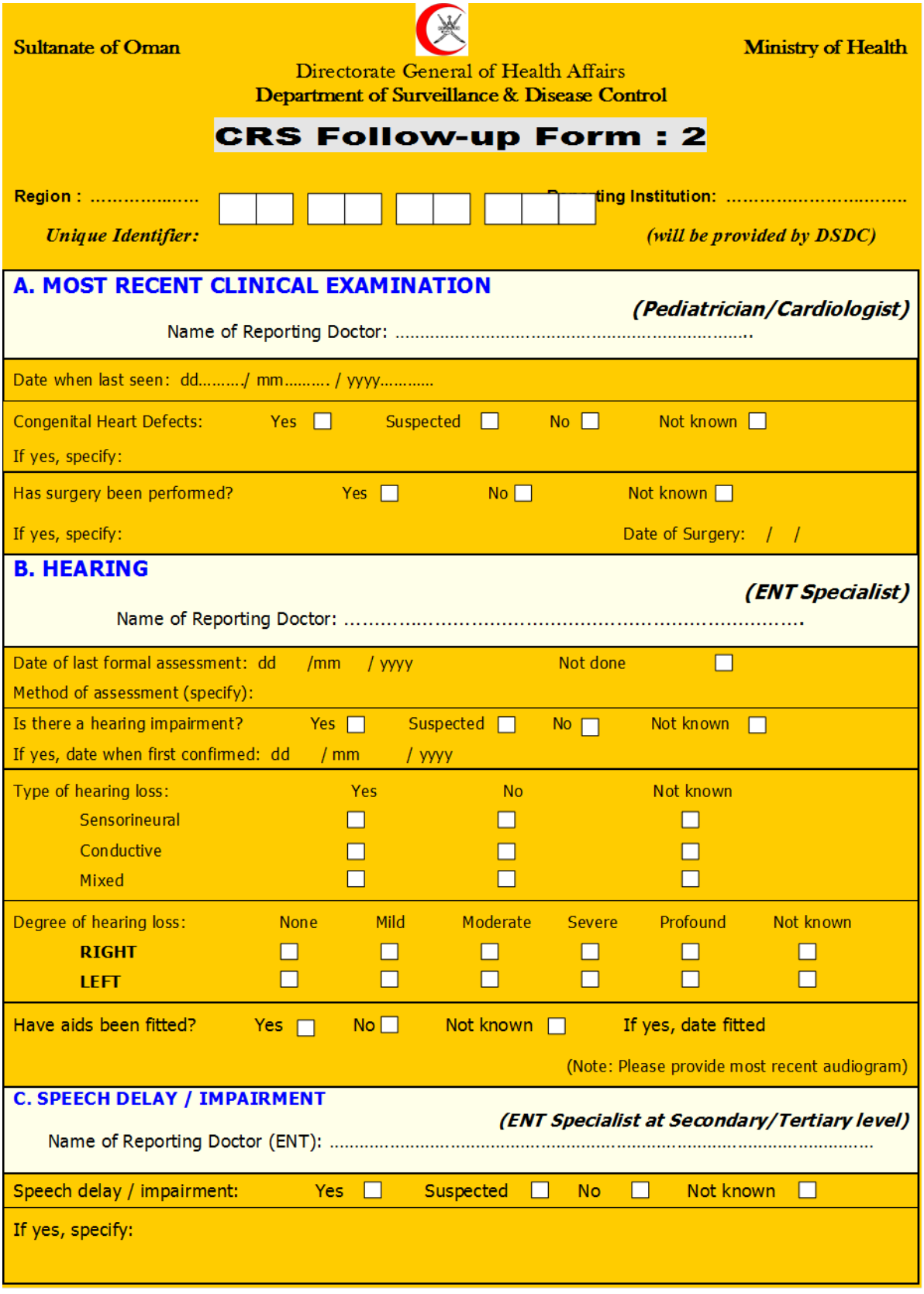
B. NEUROLOGICAL/BEHAVIORAL ABNORMALITIES

(Pediatrician/Neurologist)

Name of the Reporting Doctor: .....

	Yes	Suspected	No	Not known
Neurological / Behavioral abnormalities	☐	☐	☐	☐
Microcephaly	☐	☐	☐	☐
Cerebral palsy	☐	☐	☐	☐
If yes, specify;				
Mental impairment:	☐	☐	☐	☐
If yes, specify;				
Behavioral impairment:	☐	☐	☐	☐
If yes, specify;				
Other:	☐	☐	☐	☐
If yes, specify;				

Figure 4: Congenital rubella syndrome (CRS) examination and data collection form for hearing and speech impairment, Oman, 2015



Sultanate of Oman — Ministry of Health

Directorate General of Health Affairs
Department of Surveillance & Disease Control

CRS Follow-up Form : 2

Region : ..... Reporting Institution: .....

Unique Identifier: ☐☐ ☐☐ ☐☐ ☐☐☐ *(will be provided by DSDC)*

A. MOST RECENT CLINICAL EXAMINATION *(Pediatrician/Cardiologist)*

Name of Reporting Doctor: .....

Date when last seen: dd...../ mm..... / yyyy.....

Congenital Heart Defects: Yes ☐ Suspected ☐ No ☐ Not known ☐

If yes, specify:

Has surgery been performed? Yes ☐ No ☐ Not known ☐

If yes, specify: Date of Surgery: / /

B. HEARING *(ENT Specialist)*

Name of Reporting Doctor: .....

Date of last formal assessment: dd /mm / yyyy Not done ☐

Method of assessment (specify):

Is there a hearing impairment? Yes ☐ Suspected ☐ No ☐ Not known ☐

If yes, date when first confirmed: dd / mm / yyyy

Type of hearing loss:	Yes	No	Not known
Sensorineural	☐	☐	☐
Conductive	☐	☐	☐
Mixed	☐	☐	☐

Degree of hearing loss:	None	Mild	Moderate	Severe	Profound	Not known
RIGHT	☐	☐	☐	☐	☐	☐
LEFT	☐	☐	☐	☐	☐	☐

Have aids been fitted? Yes ☐ No ☐ Not known ☐ If yes, date fitted

(Note: Please provide most recent audiogram)

C. SPEECH DELAY / IMPAIRMENT *(ENT Specialist at Secondary/Tertiary level)*

Name of Reporting Doctor (ENT): .....

Speech delay / impairment: Yes ☐ Suspected ☐ No ☐ Not known ☐

If yes, specify:

Each patient with CRS was assessed by a paediatrician or cardiologist for a cardiovascular disease history and current cardiac status. Inpatient medical records for CRS patients who have had cardiac surgery were reviewed when available. Each child with CRS was assessed by a paediatrician or a neurologist for microcephaly, cerebral palsy, seizure disorder, mental impairment, and any other neurological disease. The assessment included collection of information on whether the child required enrolling into special social- (community) based rehabilitation centers. Additionally, each child with CRS was assessed by a paediatrician for diabetes, other endocrine disorders, and any other medical or surgical disorders. Survival curve of CRS cases were performed using Kaplan-Meier survival estimates [4].

2.4. Rehabilitation

The Omani Ministry of Social Development has established more than 23 Al Wafa community-based rehabilitation centers and special schools across the country, which offer, day-care services, outreach and easy access services free of charge to some 1708 disabled individuals nationwide up to 14 years, including CRS-related disabilities. These included free of charge day-care services, outreach and easy access services to the disabled, those with handicaps, autism and individuals with special needs. An Omani non-governmental organization, the Association for the Welfare of Handicapped Individuals, has also established 4 centers, mainly in large cities, that also offer day-care services for some 450 disabled individuals. In addition, a non-governmental organization has also established centers mainly at large cities that also offer day-care services for disabled individuals. The services are directed towards these individuals and their families. Care and rehabilitation programs include medical and health care, physiotherapy to enhance physical dexterity, social and psychological programs, enhance speech and pronunciation skills emphasized, special education and skill development programs and support individuals to maximize their abilities to be independent in relation to daily life skills. The services also provide on-the-job training to improve basic and functional skills. Further, these institutions also provide guidance, advice and any

other support required for the individuals and their families.

Further, the care and rehabilitation center for the disabled individuals receives persons with disabilities of the age (14-24 years) and provides them with comprehensive social welfare of housing, nutrition, treatment, and entertainment, in addition to educational, training and rehabilitation programs in various professions and disciplines such as tailoring, blacksmithing, carpentry, paint, computers, family education, ornamentation, and decoration.

2.5. Ethics Approval

This study was approved by the national immunization technical advisory committees. Patient identities were kept confidential. Only anonymized results of the study were shared with regional health administrators to guide recommendations to improve the CRS patient care.

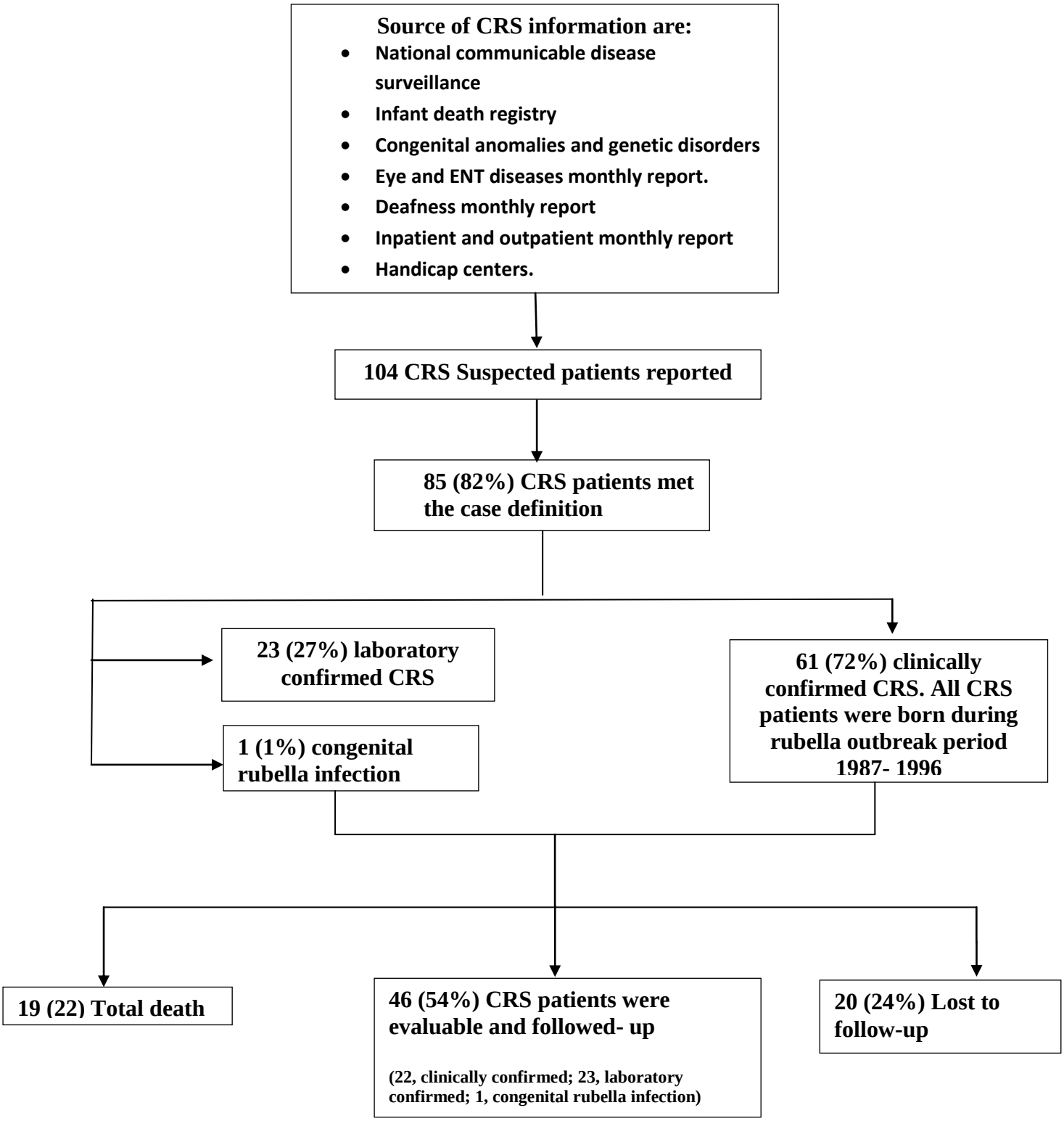
3. Results

3.1. CRS patient registration

A total of 104 suspected CRS patients were identified from 1980-2015. Eighty-five (82%) CRS cases were clinically or laboratory-confirmed and 19 (18%) were discarded. Of the 85 confirmed cases, 61 (72%) were clinically confirmed after being epidemiologically linked to a rubella outbreak from 1987-1996 [Figure 1], 23 (27%) had laboratory confirmed CRS based on a positive rubella virus-specific IgM test and 1 (1%) had congenital rubella infection (rubella IgM-positive but without manifestations that meet clinically confirmed case criteria) [Figure 5].

Of the 85 confirmed cases, 46 (54%) CRS patients were evaluable (i.e. those found and who then consented to be included for in-depth evaluation) as of 2015, 19 (22%) had died and 20 (24%) were lost to follow-up. Of the deceased CRS cases, 7 (37%) died from cardiovascular causes, 3 (16%), from meningitis/encephalitis, 2 (11%) from pneumonia, 1 (5%), from head injury and 6 (31%) had unknown or unreported causes. Fifty eight (68%) of the confirmed cases were reported from tertiary care hospitals and 27 (32%) from regional/governorate hospitals.

Figure 5. Congenital rubella syndrome (CRS) surveillance, Oman, 1980-2015



As of 2015, 46 (54%) CRS-confirmed patients were evaluable and constituted our study group. Of those, 28 (61%) were male and 18 (39%) female, the mean age of this group was 17.9 years (range 8-33 years). Verbal consent was obtained by the families of CRS patients

to perform follow-up examinations and to allow hospital records review.

Of 39 (46%) CRS patients unavailable, 19 (46%) died and 20 (24%) were lost to follow-up. The age at deceased cases were ranged from 6 months to 20 years, i.e. 12 (64%) were 6 months-5years, 5 (26%) were 5-10 years, 1 (5%) were 10-15 years, and 1 (5%) were 15-20 years.

Of the deceased CRS cases, some had symptoms prior to death, i.e. 13 (68%) had cardiovascular symptoms, 2 (11%), had mental retardation and 4 (21%) had unknown or unreported causes.

Initial clinical examination of the 46 evaluable CRS patients revealed that 18 (39%) had cardiac defects, 29 (63%) had ocular manifestations, 27 (59%) had auditory manifestations, 20 (43%) had speech manifestation, 25 (54%) had neurological manifestations, 24 (52%) had microcephaly, 11 (24%) were of low birth weight (≤ 2.5Kg), 3 (6%) had hepatosplenomegaly and 1 (2%) had hypospadias [Table 1].

Table 1. Congenital rubella syndrome (CRS) clinical manifestations identified upon diagnosis among evaluable patients, Oman, 1980-2015

Type of birth defect	Early clinical manifestations, incidence among evaluable CRS patients, No. (%)
Cardiovascular defect	**18 (39)**
Congenital ocular defect	**29 (63)**
Congenital cataract or glaucoma	**19 (41)**
Congenital hearing impairment	**27 (59)**
Microphthalmia	**7 (15)**
Neurological defects	**25 (54)**
Microcephaly	**24 (52)**
Low birth weight(≤ 2.5Kg)	**11 (24)**
Hepatosplenomegaly	**3 (6)**
Purpura	**-**
Hypospadias*	**1 (2)**
Unknown	**-**
Total evaluable CRS patients	**46**

- **Not included in CRS case definition**

3.2. Symptoms and signs upon CRS case diagnosis

Ocular manifestations. A total of 29 (63%) patients had any ocular manifestation, out of which, 16 (55%) had retinitis, 14 (48%) with cataract(s) and 5 (17%) with glaucoma.

6 (43%) of the children with cataracts had bilateral involvement. Microphthalmos (axial length <17 mm) was found in 6 patients (21%), and glaucoma in 5 patients (29%). A case of each of aphakia, corneal hydrops, hypermetropia, keratoconus, and absorbed lens were notified.

Of the 60 eyes in 33 CRS patients, 20 eyes (30%) had undergone some sort of eye surgery. With the exception of a CRS case notified in 2013, the outcome of the surgery was published [5] [Table 2a].

Hearing and speech impairment manifestations. Of the 46 CRS patients, 27 (59%) reported hearing loss, 22 (81% bilateral hearing loss), 21 (78%) had sensorineural hearing impairment, 1 (4%) had conductive hearing impairment, 1 (4%) had mixed hearing impairment and there was speech impairment delay in 20 (74%) [Table 2b]. Of the total patients with hearing loss, 3 (11%) use hearing devices.

Cardiovascular system manifestations. Of the 46 CRS patients, 18 (39%) children had congenital heart disease (CHD). Of these, 12 (67%) had patent ductus arteriosus (PDA), 5 (28%) had a ventricular septal defect (VSD) and one case each of pulmonary stenosis (PS) and pulmonary atresia were detected [Table 2c]. Thirteen (72%) underwent surgery (11 PDA, 1VSD and 1PS) and all eventually got well.

Neurological manifestations. Of the 46 CRS patients, 22 (48%) had mental retardation and 24 (52%) had microcephaly [Table 2d].

Out of the total, 19 (41%) had congenital hearing and visual loss, 12 (26%) had combination of congenital hearing loss, visual loss, and heart defect, 9 (20%) had congenital hearing and visual loss, heart defect(s) and microcephaly.

Table 2a. Causes of visual loss among evaluable congenital rubella syndrome patients upon diagnosis, Oman, 1980-2015

Type of ocular lost	No. (%)
Ocular Cataract	**14 (48)**
Ocular cataracts one eye	8 (57)
Ocular cataract both eyes	6 (43)
Ocular glaucoma	**5 (29)**
Ocular glaucoma one eye	1(20)
Ocular glaucoma both eyes	4 (80)
Retinitis	**16 (55)**
Microphthalmos	**6 (21)**
Aphakia	**3(10)**
Corneal hydrops	**1 (3)**
Hypermetropia	**1(3)**
Keratoconus	**1 (3)**
Absorbed lens	**1(3)**
Eye surgery	
Total surgeries	**20/60 (30)**
Total ocular defects	**29**

Table 2b. Causes of hearing lost among evaluable congenital rubella syndrome patients upon diagnosis, Oman, 1980-2015

Type of hearing lost	No. (%)
Reporting hearing lost both ears	**22 (81)**
Sensorineural hearing impairment	**21 (78)**
Conductive hearing impairment	**1 (4)**
Mixed hearing impairment	**1 (4)**
No ocular anomaly	**4 (15)**
Speech impairment delay	**20 (74)**
Use hearing device	**3 (11)**
Unable to test for hearing loss	**3 (11)**
Total hearing lost	**27**

Table 2c. Cardiovascular system defects among evaluable congenital rubella syndrome patients upon diagnosis, Oman, 1980-2015

Defect	No. (%)
Patent ductus arteriosus (PDA)	12 (66)
Ventricular septal defect (VSD)	5 (28)
Organic systolic murmur	3 (17)
Pulmonary stenosis	1 (5)
Pulmonary atresia	1 (5)
Total	18

Table 2d. Neurological developmental defects among evaluable congenital rubella syndrome patients upon diagnosis, Oman, 1980-2015

Defect	No. (%)
Normal intelligence	**23 (50)**
Microcephaly	**24 (52)**
Mental retardation	**22(48)**
Total CRS cases	**46**

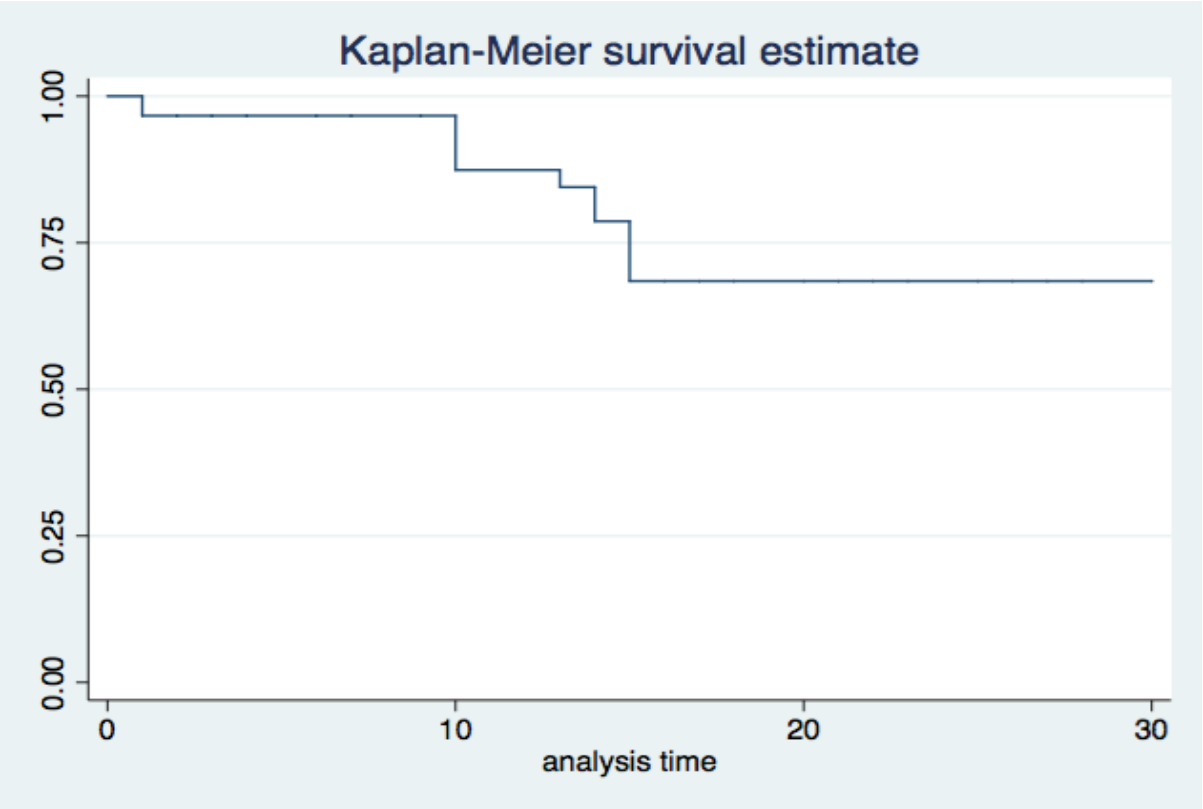
3.3. Late-onset symptoms manifestation of CRS: A follow-up results and support

Out of the CRS patients, 19 (41%) had late CRS manifestations detected from 8-23 years of age; 3 (16%) had endocrine function defects: 2 (11%) had thyroid disorders and 1 (5%) had type 2 diabetes mellitus, 3 (16%) had seizures disorders, 1 (5%) case had each of systolic murmur, elevated blood pressure, pulmonary atresia and left ventricular failure. Three (16%) hepatosplenomegaly, 1 (5%) late-onset sensorineural hearing impairment, 1 (5%) hypospadias and 1 (5%) autism (reported as CRS-related) were reported.

Of the 46 evaluable patients, 18 (39%) had cerebral palsy, 10 (22%) and 5 (11%) had severe to profound and moderate mental retardation respectively.

~20% mortality of CRS cases were in the first 10 years of life and 72 percent of the CRS cases survived up to 30 years [Figure 6].

Figure 6. Survival curse of all CRS cases, Oman, 1980-2015



Forty-three (93%) of the CRS patients in this study were participating in these governmental or nongovernmental community-based rehabilitation centers for handicapped, disabled and autism services, at the time of CRS evaluation. Ten (22%) evaluable CRS patients were benefitting from home care services. Further, these institutions provide guidance, advice and any support required for the individuals and their families.

4. Discussion

Congenital rubella syndrome is a principal contributor to the global burden of preventable blindness, deafness, cardiovascular defects and mental retardation [2] Previous publications based on Oman national CRS registry addressed the importance of the National Omani CRS registry, [4, 6], CRS-related ocular manifestations [5] and CRS-related costs [7].

In the current study, we described late clinical manifestations after a mean 30-year of follow-up of all evaluable CRS patients from 1980 to 2015 who received comprehensive general and specialty clinical assessments. There have been prior publications of late manifestations of

CRS in Australia, Canada, Israel and the United Kingdom, but not in the Middle East. [8-14]. Late CRS manifestations recorded by our CRS registry included endocrine function defects (type 2 diabetes mellitus and thyroid dysfunction) in 6.5% of evaluable cases. CRS-related endocrine defects were also observed in a Canadian study after a mean 34 years of follow-up (12% type 2 diabetes mellitus; 10% thyroid dysfunction) [10], and in an Australian study after 60 years of follow-up (22% type 2 diabetes mellitus; 19% thyroid dysfunction) [11]. The higher prevalence of endocrine disorders observed in these studies compared with our findings might be attributed to the older mean age of patients in these cohorts. The Oman national registry recorded a patient with CRS-related autism; autism is one of the many outcomes associated with CRS [12]

Among the 19 deaths recorded in the Oman CRS registry, 15 (79%) were born between 1980-1993 and rubella-related heart defects were recorded as the most common contributing cause of death. This was not unexpected given that correction of major congenital heart defects was not yet available in Oman for children born between 1980-1993. Of 19 CRS deaths, 6 (31%) had no known cause of death. This could be attributed to the absence of a standardized central death registry until 2005. Additionally, a common ritual is to bury the deceased as soon as possible and this can occur without notification of the healthcare system. Until 1990, there was not a formal requirement to report deaths to health authorities.

CRS cases reported to our registry likely represent only the "tip of the iceberg" of all individuals in the country who developed CRS prior to 1994, when rubella vaccine was first introduced in Oman, for the following reasons: 1) Oman experienced large outbreaks of rubella between 1987-1996 that resulted in more than 1,700 cases; 2) the CRS surveillance system wasn’t established in Oman until 2000 and therefore CRS reporting prior to this year was poor; 3) during the period from1980-1990, Oman had few specialists or specialty departments to support CRS diagnosis.

Most of the CRS-related mortality is driven by cardiac defects, our study

showed a relatively low CRS mortality rates (i.e. 20%), this is mainly attributed to early identification, timely surgical intervention and rehabilitation services. In addition, 43 (93%) had been linked to governmental or non-governmental community-based rehabilitation programs which are available free of charge to CRS individuals and their families countrywide also contributing to long survival of CRS individuals.

The current study has some limitations: the CRS registry was not established until 2000, after significant rubella outbreaks in Oman. This limited our ability to complete follow-up and evaluation of pre-2000 cases and resulted in clinical assessment of only ~50% of patients. The other limitation is the total number of CRS included may affect the generalizability of our results.

Lesson learnt and challenges

Maintaining the registry at governorate level and the need for vigilant annual follow-up of each case are among the most important lessons learned. Among the challenges, are loss to follow-up and provision of timely assistance to the patient. In addition, information and data generated by the CRS national registry system must be used efficiently in increasing awareness for late CRS-related manifestations, detecting previously missed cases, and linking these patients and their families to support services.

In conclusion, our paper has highlighted the importance of our CRS registry in identifying long-term CRS manifestations that include a wide spectrum of abnormalities ranging from ocular, auditory or neurological deficits to endocrine manifestations. Detection of these late manifestations emphasizes the persistence of rubella virus infection-associated risk, and highlights the importance of maintaining high childhood rubella vaccination coverage and achieving high population immunity. Further, the identification and follow-up of CRS cases provides an opportunity to assess late or unrecognized manifestations of congenital rubella, to understand rubella teratogenesis and to support earlier clinical intervention.

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Conflict of interest

The authors declare no conflict of interest.

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