Congenital Rubella in the Western Cape Province of South Africa: a vaccine preventable condition

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Declaration

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Abbreviations

CRS: Congenital Rubella Syndrome
CRI: Congenital Rubella Infection
EPI: Expanded Program on Immunization
PCR: Polymerase Chain Reaction
LBW: Low birth-weight
SGA: Small for gestational age
Prematurity: infants born before 37 completed weeks
PDA: Patent ductus arteriosus
PPS: Peripheral pulmonary stenosis
VSD: Ventricular septal defect
CDC: Centers for Disease Control
WHO: World Health Organization
MMR: Measles mumps rubella

NHLS: National Health Laboratory Services
ICU: Intensive Care Unit

ABSTRACT

Background: Congenital rubella syndrome (CRS) is characterized by multiple defects causing physical, intellectual and developmental retardation, auditory and visual problems, placing a huge burden on health care services in countries where rubella immunization is not routine. The incidence and extent of CRS in South Africa, where rubella vaccine is not included in the expanded program on immunization (EPI), is unknown.

Objective: To determine the minimum prevalence and morbidity of CRS in the public sector of the Western Cape province of South Africa, as well as to describe the clinical presentation and features of all confirmed and probable CRS cases at Tygerberg Children's Hospital.

Methods: A retrospective descriptive study and case series using clinical records. Rubella serology data was retrieved from National Health Laboratory Systems at Tygerberg Academic Hospital between 01 January 2006 and 31 December 2011 and Groote Schuur Hospital between 01 January 2008 and 31 December 2011. For confirmed CRS, detection of rubella by PCR or specific IgM antibodies below 3 months of age was diagnostic. For probable CRS, a PCR or IgM positive at 3 months - 1 year of age with more than two of the following conditions: cataracts, congenital glaucoma, congenital heart disease, hearing impairment or pigmentary retinopathy. Alternatively, one of one of these conditions plus any of the following: purpura, splenomegaly, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease or neonatal jaundice within 24 hours of birth.

Confirmed cases between 01 January 2008 and 31 December 2011 from the two laboratories were used to calculate a minimum prevalence for the Western Cape. Medical records of infants with confirmed and probable CRS under a year of age from Tygerberg between 01 January 2006 and 31 December 2011 were reviewed for inclusion in the case series.

Results: Thirty confirmed cases were identified from 01 January 2008 and 31 December 2011 in the two laboratories for a minimum prevalence of 0.073 cases per 1000 population for the Western Cape (95% confidence interval [CI] 0 – 0.1). Twenty confirmed and probable cases were obtained from Tygerberg Children's Hospital from 01 January 2006 to 31 December 2011. The median gestational age at birth was 37 weeks (interquartile range [IQR] 32 – 38). Fourteen (70%) had low birth weight (LBW), nine (45%) were premature and seven (35%) were small for gestational age (SGA). Six women (30%) gave a history of rubella in pregnancy, five in the first trimester and one in the second trimester. The most common presenting signs were: petechiae in eight (40%), and cataracts in seven (35%) infants. Other presenting signs in the infants included hepatosplenomegaly. Nine (45%) had ophthalmologic involvement, all with cataracts; of these three had pigmentary retinopathy and one had congenital glaucoma. Four of the twelve tested (33%) had hearing impairment and ten

(50%) had microcephaly. Cardiac anomalies were noted in eleven of the infants. One infant presented with bilateral knee arthritis, not previously described in CRS.

Eleven of fourteen LBW infants (79%) and three of six (50%) with birth weights above 2500g had at least one major congenital anomaly (p = 0.3). All three deaths occurred in SGA term infants. Eight of the twenty infants (40%) required more than one hospital admission, with seven (35%) also requiring intensive care. Hospital stay in LBW infants was also significantly longer than those with birth weights above 2500g (median 27 vs 6 days) (p = 0.01). Seven patients (35%) underwent a surgical procedure with three requiring more than one procedure. PDA ligation and cataract removal were most common.

Conclusions: CRS has extensive morbidity and high mortality, requiring a multidisciplinary approach. Rubella immunization should be urgently incorporated into the extended program of immunization in South Africa to prevent this devastating infection.

Introduction

Rubella occurs mainly in children and young adults, usually without serious sequelae. However, infection in pregnancy, especially during the first 18 weeks is teratogenic as first described in 1941 by Sir Norman McAlister Gregg, an Australian ophthalmologist [1]. Swan *et al* expanded this initial description and described low birth weight (LBW), congenital heart disease, cataracts, deafness and central nervous system (CNS) damage as part of the congenital rubella syndrome (CRS). Prior to developing an effective vaccine in 1969, rubella outbreaks occurred episodically. The most recent major pandemic occurred between 1963 and 1965, affecting 10% of pregnant women with thousands of fetal and early neonatal deaths and severe congenital defects [2].

Pathogenesis

Rubella is a single-stranded RNA virus of the genus *Rubivirus* with one serotype. Infection is spread through droplets. Prior to a maternal immune response, rubella virus infects the placenta and spreads hematogenously to the fetus. The fetus relies on maternal IgG to overcome the infection. Placental transfer is inefficient early in pregnancy when the virus is most fetotoxic. Maturation of the placenta, increased transfer of maternal antibodies as well as development of the fetal immune response limit viral activity in the second trimester, with fetal damage rare after this time. Organogenesis appears largely unaffected with damage occurring in established structures such as the eye and inner ear. Rubella causes necrosis in cardiac endothelium, resulting in patent ductus arteriosus (PDA), peripheral pulmonary stenosis (PPS) and ventricular (and atrial septal defects (VSD). Vascular insufficiency may result in growth retardation, deafness and neurodegenerative damage **[2].**

Definitions

The Centers for Disease Control (CDC) definition of congenital rubella infection (CRI) includes all outcomes associated with intrauterine rubella infection. These include miscarriage, stillbirth, abortion, combinations of birth defects and asymptomatic infection.

CRS refers to variable constellations of birth defects. The highest risk of CRS and CRI is in countries with high susceptibility rates among women of childbearing age due to inadequate pre-conceptual vaccination. The risk of CRI varies according to the time of onset of maternal infection during pregnancy, with the highest risk in the first trimester (80 – 100%), 50% in the 13th and 14th weeks, 12% in weeks 24 – 28, 19% after rubella during weeks 28 – 36 and then increases again to 58% when the illness occurs in the last month of pregnancy **[3,4,5].** Embryopathy is not invariable after intrauterine infection. The risk for malformations is 90% in the first 11 weeks of pregnancy, 33% in weeks 11-12, 11% in weeks 13-14 and 24% in weeks 15-16 [6]. No malformations were noted in those infected after week 18 [2]. (Figure 1)

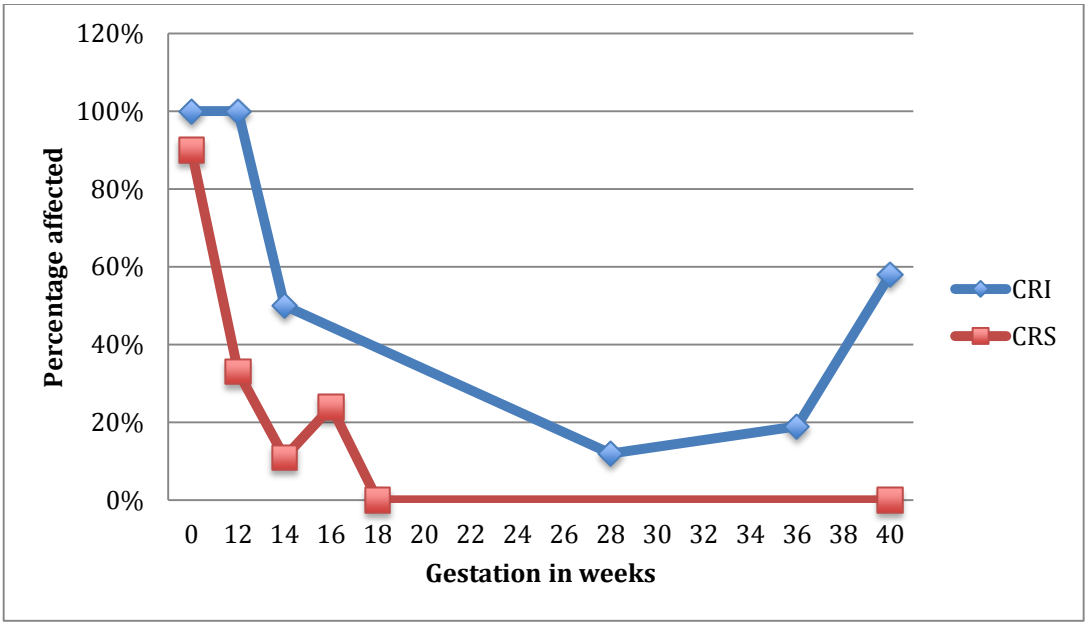

Figure 1: Risk of CRI [5] and CRS [2,6]

CRS comprises a combination of defects, particularly the heart (PDA, PPS or VSD), craniofacial (microcephaly), eyes (cataracts, microphthalmia, glaucoma, chorioretinitis) and ears (sensorineural deafness). Neonatal manifestations of CRI include hepatosplenomegaly, meningoencephalitis, hepatitis, thrombocytopenia and long bone radiolucency. The later sequelae of CRI include thyroiditis, diabetes mellitus and autism, which may not be recognized initially [7]. CRS places a huge burden on health services in countries where rubella infection has not been controlled or eliminated. (Table 1)

Congenital defects	Late manifestations
Ophthalmic defects Cataracts Chorioretinitis Glaucoma Microphthalmia	Diabetes mellitus type 1 Thyroiditis Growth hormone deficit Autism spectrum disorder Pan-encephalitis (rare)
Audiologic defects Sensorineural deafness	
Cardiac defects Patent ductus arteriosus Peripheral pulmonary stenosis Ventricular septal defect	
Central nervous system Microcephaly Meningoencephalitis	
Other Intrauterine growth restriction Thrombocytopenia Hepatosplenomegaly Radiolucent bone disease Prolonged jaundice	

Table 1: Early and late manifestations of CRS [7]

Diagnosis and case definitions of congenital rubella infection

Pregnancy [8]

Early diagnosis of acute rubella infection in pregnancy is imperative. Clinical diagnosis is unreliable as infection is often subclinical with non-specific symptoms.

The diagnosis of acute rubella infection is made by any of the following:

- Four-fold rise in rubella IgG antibody titer between acute and convalescent serum specimens
- Positive rubella-specific IgM antibody
- Positive rubella culture (on nasal, blood, urine or cerebrospinal fluid)

Antenatal rubella screening is seldom done in all countries due to its cost.

Infant

Antibody in the fetus may be transplacentally acquired, produced by the fetus or both. Passively acquired maternal antibody is found up to 15 months after delivery and is entirely IgG. In contrast, the antibodies produced by the infant may comprise of IgG (indistinguishable from the transplacentally acquired IgG) and IgM. Thus IgM is used diagnostically [9].

The detection of rubella specific IgM using a μ-capture ELISA in cord blood or infant serum is the method of choice. However, false negative rubella IgM results can occur [10]. Specific IgM has been demonstrated in all confirmed cases up to 3

months of age, in 86% between 3 and 6 months, 62% between 6 and 12 months and in 42% between 12 and 18 months **[11].** Since rubella is uncommon below the age of 2 years due to the passively acquired maternal IgG, IgM detected below a year likely indicates CRI **[11].** Reverse transcriptase polymerase chain reaction assays (PCR) can also be used to detect rubella virus after growth in tissue culture or directly from clinical specimens. Appropriate specimens include nasal and throat swabs, cerebrospinal fluid, cataracts, blood and urine.

Epidemiology of congenital rubella infection

The global incidence of CRS is estimated between 0.1 and 0.2/1000 live births in endemic periods and up to 1 – 4/1000 live births following epidemics [12]. Reliable statistics are unavailable for many developing countries, but the estimated worldwide caseload exceeds 100 000 cases [13]. However, in 1995 only 37 cases were reported to the World Health Organization (WHO) with none from South Africa. Many remain undiagnosed, as clinical manifestations may not be apparent at birth. Some manifestations of CRS, such as auditory impairment and developmental retardation become apparent later in childhood and may then be difficult to ascribe to CRS. (Table 1)

In South Africa, an incidence of 0.06 cases of acute rubella per 1000 population can be extrapolated from the case-based measles surveillance program initiated by the South African National Institute for Communicable Diseases in 1998. From 1 January 2011 to 31 December 2011 38% of suspected measles cases (3268 cases) were rubella IgM positive, females accounting for 49%, of whom 12% were in women of childbearing age [14]. The estimated population in 2011 used as the denominator was 51,770,560.

As CRS is neither notifiable nor monitored, its incidence in South Africa is unknown. Schoub *et al* estimated 654 CRS cases in South Africa annually, translated into 0.5/1000 live births – above the WHO estimate of 0.1 – 0.2 / 1000 in endemic periods [12]. Corcoran and Hardie documented that 4.7% of women of childbearing age were susceptible to rubella in the Western Cape. Also, immunity was higher in the age group of 35-45 years than 15 – 24 years, suggesting that primary infection occurs also in the childbearing age **[15].** The serological immunity gap defined as the number of women susceptible to rubella differs in the private and public sectors in South Africa, estimated as 10% and 5% respectively. **[12].** Although better living conditions and less crowding are largely responsible for decreased immunity in the upper socio-economic group, a low uptake (59%) of the Measles Mumps Rubella (MMR) vaccine is contributory **[12].** Such partial coverage causes a paradoxical increase in young females susceptible to wild-type virus in their childbearing years. This scenario was documented in Greece in the 1990's **[16].**

Rubella vaccine based on the live, attenuated RA27/3 strain is safe and effective and available either as a single component, combined with measles vaccine (MR) or MMR. Seroconversion after vaccination exceeds 95%. Vaccine-induced immunity is assumed to be life-long. Since its use from the early 1970s, the

incidence of CRS in the developed world has dramatically declined. For example, in the United States of America (USA) between 1962 and 1965 about 20 000 newborns had CRS, but after vaccine licensure in 1969, CRS decreased dramatically, with only 18 cases reported in 2002 [13]. By 1997, 78 countries (92% industrialized, 36% in economic transition and only 28% of developing countries) included rubella vaccine in their national immunization programs. In 1999 Cutts and Vynnycky modeled rubella serosurvey data to estimate the number of new CRS cases for 1996 in developing countries as follows (See Table 2): [17]

WHO REGION	NEW CASES
South East Asia	46 621
Africa	22 471
Americas	15 994
Western Pacific	12 634
Eastern Mediterranean	12 080

Table 2: Estimate of new CRS cases in developing countries for 1996

STUDY

Aims

The aims of this study were to 1) establish a minimum prevalence of confirmed CRI in the Western Cape public sector and to 2) describe the clinical presentation and features of all confirmed and probable CRS cases at Tygerberg Children's Hospital.

Methods

Study design

This was a retrospective descriptive study and case series using laboratory and clinical records.

Laboratory identification of CRS

Rubella serology and PCR data were retrieved from National Health Laboratory Systems (NHLS) virology databases at Tygerberg Academic and Groote Schuur Hospitals between 1 January 2006 and 31 December 2011. Data from GSH were unavailable prior to 2008 and therefore only cases from 1 January 2008 to 31 December 2011 from GSH were identified. Both laboratories use the same diagnostic assays and quality assurance programs.
We applied the following case definitions:

- *Confirmed case*: Rubella PCR or IgM positive below 3 months of age
- *Probable case:* an infant 3 months to 1 year of age with positive rubella PCR or IgM and at least 2 of the following features from
  - A: cataracts, congenital glaucoma, congenital heart disease, hearing impairment, pigmentary retinopathy OR one feature from A and one or more from
  - B: purpura, splenomegaly, microcephaly, mental retardation, meningo-encephalitis, radiolucent bone disease or jaundice with onset within 24hr of birth with no alternative etiology

Population study

All confirmed cases from the two NHLS laboratories between January 1, 2008 and December 31, 2011 were used to calculate a minimum prevalence for the Western Cape. We obtained data for registered births in the Western Cape from the Department of Health. The estimated birth population (408252) was the number of registered births in the Western Cape from 2008 – 2011.

Case series

We reviewed the files of all children younger than 12 months with positive rubella IgM or PCR from Tygerberg Academic Hospital between 01 January 2006 and 31 December 2011 to determine whether the children met the case definition for a confirmed or a probable case using the above definitions. Only probable and confirmed cases from Tygerberg Academic Hospital were included in our case series.

Statistics

Data was collected in Excel and analyzed using Statistica (version 12 of 2014) and SAS version 9.1.3. Incidence/prevalence was presented using proportions with corresponding exact 95% confidence intervals (CI). Non-parametric methods were used for comparisons between groups.

The minimum prevalence was calculated by taking the cases of CRS with the total number of registered births in the Western Cape over the same time period as denominator.

Ethics

Ethics approval was obtained from the Health Research Ethics Committee of Stellenbosch University (reference number S13/02/033). The Tygerberg Children's Hospital management approved the retrieval of data from medical records.

Results

Population study

Thirty confirmed cases of CRI were identified between 01 January 2008 and 31 December 2011 – sixteen from Tygerberg and fourteen from Groote Schuur NHLS databases. No data were available for the preceding 2 years from Groote Schuur. The minimum prevalence for CRS was 0.073 cases per 1000 live births for the Western Cape (95% CI 0-0.1). The diagnosis was made by PCR in twelve cases and by IgM in eighteen.

Case series

Twenty confirmed and probable cases were obtained from Tygerberg Children's Hospital from 01 January 2006 to 31 December 2011 for the case series. Patients from Groote Schuur database were excluded due to the inability to access medical records from affiliated hospitals.

Diagnosis-:

The diagnosis was made by PCR in four cases and by positive IgM in sixteen infants. In sixteen infants (80%) the diagnosis was in the first 3 months of life.

Gender -:

There was no significant difference in the gender with nine (45%) infants being female and eleven (55%) male.

Race -:

Fourteen (70%) infants were of mixed race, with one (5%) Caucasian and five (25%) Black infants.

Birth data -:

The median gestational age was 37 weeks (IQR 32 – 38) with nine babies being premature, and the median birth weight was 2040 grams (IQR 1550 – 2800). Fourteen (70%) were low birth weight of which five (35%) were term infants. Six

(30%) of all the infants were small for gestational age. Eleven of the fourteen LBW infants (80%) had at least one major congenital anomaly. These included ophthalmological disease, cardiac defects and hearing impairment. Major anomalies were confirmed in three (50%) of the six infants above 2500g. (P = 0.3)

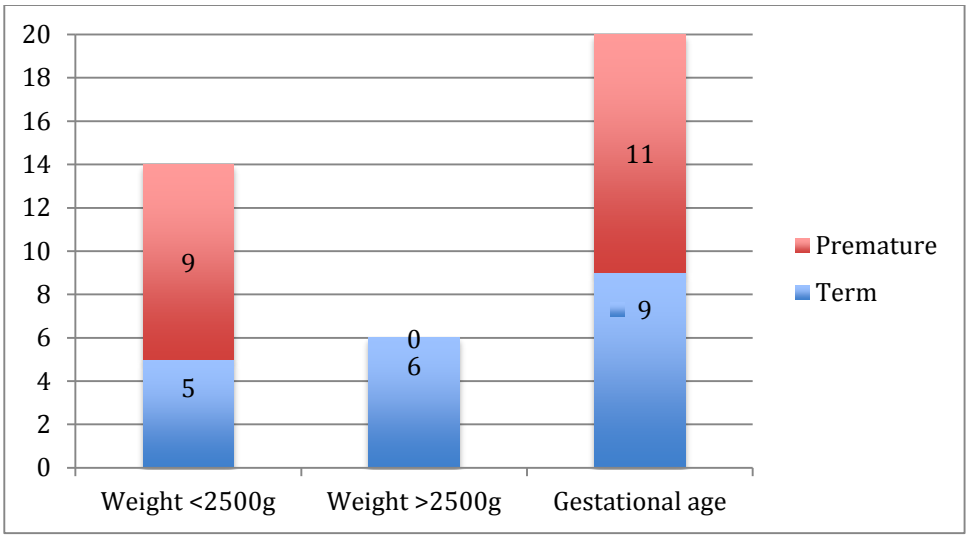

Figure 2: Birth data

Clinical features:

The most common presenting sign was purpura in thirteen (65%), followed closely by cataracts in seven (35%). Hepatosplenomegaly was the presenting sign in four (20%) infants. Nine infants (45%) had eye involvement. All had cataracts, three also had pigmentary retinopathy and one had congenital glaucoma. Cataracts were never an isolated finding. Four (33,3%) of twelve patients tested had hearing impairment. Seventeen (85%) had hepatomegaly and ten (50%) had splenomegaly. Ten (50%) had microcephaly. Eleven (55%) had cardiac anomalies – nine (45%) with a PDA, of whom five also had PPS, one a VSD and another had total anomalous pulmonary venous drainage (TAPVD). The remaining two patients with cardiac anomalies had PPS (1 also had a VSD). Cataracts were significantly associated with cardiac disease (P = 0.008 - Pearson Chi-square).

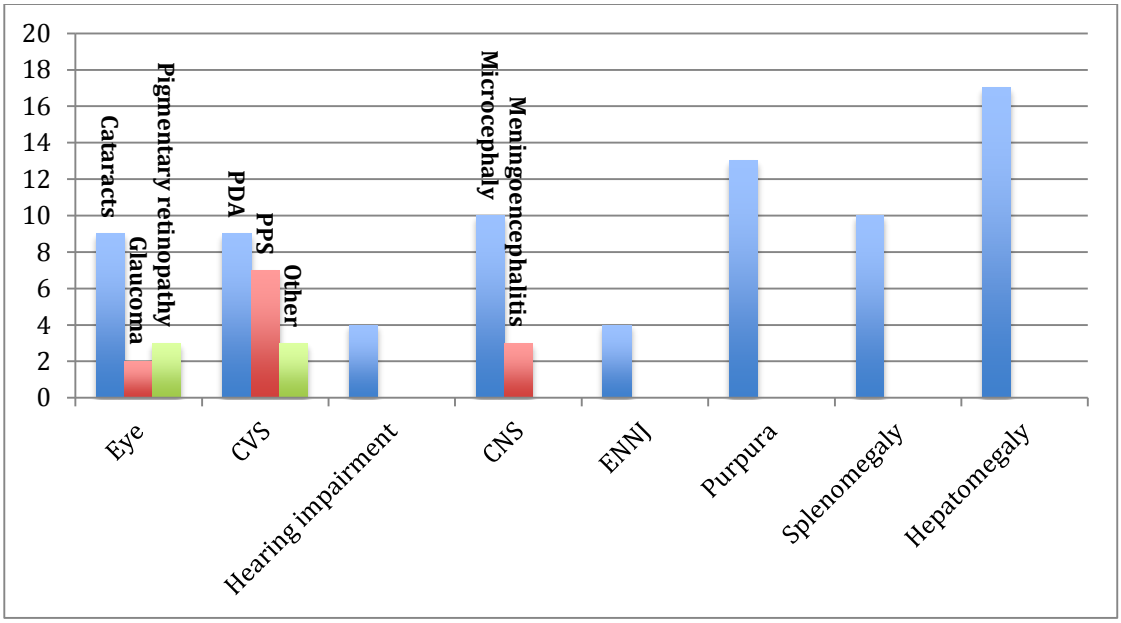

Figure 3: Clinical features of CRS
CVS – cardiology, CNS – central nervous system, PDA – patent ductus arteriosus, PPS – peripheral pulmonary stenosis, ENNJ – early neonatal jaundice

One infant presented with bilateral knee arthritis. (Not previously described in CRS – see case report on page 12).

Hospitalization:

8 (40%) patients had more than one hospital admission. Three (15%) were admitted twice and 5 patients (25%) had three or more admissions. Duration of hospitalization in LBW infants [median 27 (IQR 9 – 49) days] was significantly longer than those with birth weights above 2500g [median 6 (IQR 6 – 11) days (p = 0.01). 7 (35%) infants including 4 premature infants, required intensive care admission. Seven patients (35%) underwent a surgical procedure with 3 requiring more than 1 procedure. PDA ligation and cataract surgery were most common.

Follow-up and outcomes:

The median follow up period was 25,9 (IQR 1 – 40) months. 14 (70%) of infants were referred to cardiology and 13 (65%) to ophthalmology services. 9 (45%) required more than one appointment for cardiology and 9 (45%) for ophthalmologists. Only 12 (60%) infants, of whom 4 (33%) had hearing impairment, were seen by the audiology service. (Figure 4) Of these, 10 (83%) required at least one follow-up appointment. Three deaths were recorded by two years of age, all in term LBW infants. One infant was lost to follow-up.

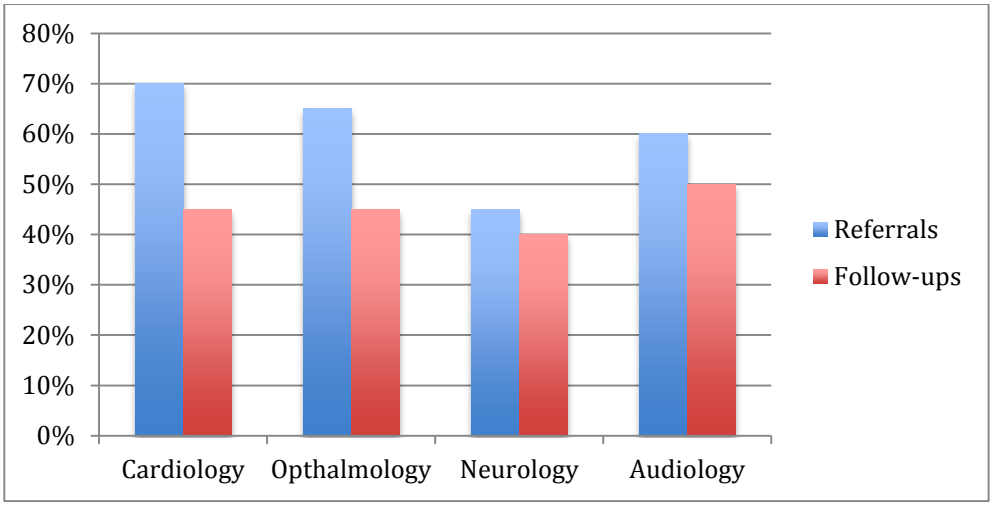

Figure 4: Referrals and follow-up by special services

Maternal information -: Due to the retrospective study design, maternal information was largely incomplete. 16 had antenatal care documented but more than two thirds were unaware of their rubella immune status. Of 6 (30%) with a history of rubella in pregnancy, 5 (83%) occurred in the first trimester and 1 case in the second trimester.

CASE REPORT – RUBELLA PERI-ARTHROPATHY (Tenosynovitis?)

This infant presented at 4 months of age with painful knees for 4 days with decreased movement and fever. Both knees were warm, tender and swollen. An effusion was noted in the right knee. Other manifestations of CRS included bilateral cataracts, PDA, hepatosplenomegaly and microcephaly. The mother had reported rubella-like illness in her pregnancy.
Inflammatory markers were raised: the erythrocyte sedimentation rate was 130 mm/hr (Normal: 0-10 mm/hr). C-reactive protein was 20 mg/l (Normal: 0-10 mg/l), the white cell count was 14 x 10^9 (5.5-18.0 x 10^9) cells/L and neutrophil percentage was 22%, both within normal range.
At arthrotomy done shortly after presentation, no effusion was found. Cultures on synovial biopsies were all negative. PCR for rubella on synovial fluid was also negative. On histology, no inflammation or atypia was seen. Serum IgM for rubella was positive. The infant was treated empirically with antibiotics and 6 months later the arthritis had resolved spontaneously.

Discussion

Our calculated CRS prevalence for the Western Cape is far lower than estimates of both Corcoran *et al* and WHO. Reasons include under-reporting and lack of awareness. The clinical manifestations may not be immediately apparent, but rather present later in childhood, when it may be difficult to ascribe to rubella.

Limitations in our calculation include uncertainty of the population of the Western Cape. The estimated population was calculated using the number of registered births in the Western Cape for 2008 to 2011 according to the Western Cape Department of Health. This however excludes late registrations and immigrants from other provinces that use the maternity services of the Western Cape health system and the private sector.

We have documented CRS-related morbidity and mortality in TBH. Patients from hospitals other than TBH were not included in the case series due to the inability to access these patients' files. The racial demographics of the patients reflect the population attending the public hospitals in the Western Cape. As previously noted [1,18], low birth weight due to prematurity and intrauterine growth restriction was documented in the majority of our case series. The mortality and morbidity was significantly higher in the low birth weight infants, with increased congenital anomalies and all deaths occurring in this group. Hospital stay in the LBW infants was also significantly longer – 35 days in LBW vs 9 days in infants above 2500g – resulting in increased cost and burden on the health care system.

Petechiae and cataracts were the most common findings with cataracts present in almost half the patients. Both are detectable early and should raise suspicion and prompt early investigation of CRS. In our study, cataracts were significantly associated with cardiac disease (p = 0.008). Also, 77% of those with cataracts also had hearing impairment. Eckstein *et al,* in a study from India, found that cataract of nuclear morphology had a 75% positive predictive value for CRS and accounted for 25% of congenital cataracts in their survey [19]. There is wide variability in the incidence of pigmentary retinopathy, reported in 13 – 61% of case series [2] and noted in 15% of our cohort. Multisystem involvement emphasizes the importance of proper screening in infants presenting with cataracts. The cardiac defects noted in our study correlated well with previous reports – just over half of the patients having a cardiac anomaly, most commonly, PDA.

Only one third of those tested had hearing impairment. This may suggest a lower rate of hearing impairment than in other reports, where it is the most common congenital defect. Also, many patients in the study did not have a hearing assessment as they were born in outlying hospitals. Reasons include limited access to equipment and specialist services for newborn infants, available only at tertiary centers. Lack of awareness by inexperienced medical staff may contribute to inadequate referral and parents may not appreciate this risk. Hearing impairment may occur as a single defect, and may therefore not be actively sought [20]. Hearing impairment does not appear to be progressive [21] but early intervention is essential to preserve language development.

Arthralgia is a recognized complication of acute rubella, occurring predominantly in adult females. We documented arthritis or tenosynovitis most likely as a new manifestation of CRS. Ogra *et al* hypothesized that arthritis following rubella vaccination was due to continued replication of the rubella virus in the affected joint, despite viral isolation from the joint being rare. Other investigators have

been unable to prove this, suggesting that the pathogenesis of post vaccination arthritis was due to an immunologic component **[22].**

Maternal information was largely incomplete. Over half of the women denied or gave no history of having rubella during their pregnancy. This may be due to the subclinical nature of the infection or a decreased awareness of rubella symptoms. Of the women who reported rubella infection in pregnancy, the majority occurred in the first trimester.

Caring for CRS cases is costly in all countries. All cost-benefit studies of rubella vaccination, regardless of setting, show that benefits outweigh costs, particularly when combined with the measles vaccine (all these studies were conducted in countries with coverage >80%) **[7].**

In South Africa, mandatory measles vaccination is given at 9 and 18 months of age since April 2009 as part of the WHO Expanded Program on Immunization (EPI). A combination vaccine against measles, mumps and rubella is available in the private sector since 1975.

High measles vaccine coverage presents an opportunity for effective rubella vaccination and although the average national coverage with the first measles vaccine dose in South Africa is about 88%, there are districts that fall well below 90% [23]. This requires improvement prior to introducing MMR vaccine. There are two approaches for incorporating this into the EPI. The first is selective immunization of adolescent girls aiming to protect the population at risk but not altering the circulation of the wild type virus. The second is universal vaccination of all young children, aiming to eliminate rubella. Inadequate universal vaccination may cause an upward shift in the age of rubella infection, thereby increasing CRS and is not recommended unless the national program can sustain high levels of coverage (>80%) [24]. The choice of approach should be based on the level of susceptibility in women of childbearing age, the burden of disease due to CRS and the strength of the immunization program as indicated by the routine measles coverage. A combined strategy in South Africa may be the most effective, immediately eliminating CRS and avoiding a situation similar to the Greek tragedy in 1993. An additional benefit would be the inclusion of mumps vaccine where substantial benefits have been seen post immunization [30].

Conclusion

We have documented devastating consequences of CRS. These include severe congenital anomalies requiring life-long interventions. Short term consequences include prolonged hospitalization, surgical intervention and ICU care. CRS, a vaccine-preventable condition thus imposes a huge burden on the health care system

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