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Congenital Rubella Syndrome Surveillance in South Africa Using a Sentinel Site Approach: A Cross-sectional Study

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Background. Congenital rubella syndrome (CRS) includes disorders associated with intrauterine rubella infection. Incidence of CRS is higher in countries with no rubella-containing vaccines (RCV) in their immunization schedules. In the World Health Organization African region, RCVs are being introduced as part of the 2012–2020 global measles and rubella strategic plan. This study aimed to describe the epidemiology of confirmed CRS in South Africa prior to introduction of RCVs in the immunization schedule.

Methods. This was a descriptive study with 28 sentinel sites reporting laboratory-confirmed CRS cases in all 9 provinces of South Africa. In the retrospective phase (2010 to 2014), CRS cases were retrieved from medical records, and in the prospective phase (2015 to 2017) clinicians at study sites reported CRS cases monthly.

Results. There were 42 confirmed CRS cases in the retrospective phase and 53 confirmed CRS cases in the prospective phase. Most frequently reported birth defects were congenital heart disease and cataracts. The median age of mothers of CRS cases was 21 years in the retrospective phase (range: 11 to 38 years) and 22 years in the prospective phase (range: 15 to 38 years).

Conclusion. Baseline data on laboratory-confirmed CRS will enable planning and monitoring of RCV implementation in the South African Expanded Programme on Immunization program. Ninety-eight percent of mothers of infants with CRS were young women 14–30 years old, indicating a potential immunity gap in this age group for consideration during introduction of RCV.

Keywords. rubella; congenital rubella syndrome; surveillance; rubella-containing vaccines; birth defects.

Congenital rubella syndrome (CRS) includes a range of disorders associated with congenital rubella infection (CRI) following maternal rubella infection, especially in the first trimester of pregnancy. Birth defects include cataracts, glaucoma, hearing impairment, congenital heart defects, microcephaly, and pigmentary retinopathy. Intra-uterine rubella infection can also result in miscarriage or stillbirth. Although some signs of CRS are apparent during the neonatal period, onset of other disorders after the age of 2 years has been described [1]. Laboratory tests for CRS include rubella immunoglobulin M (IgM) in cord blood or in the serum of the infant, immunoglobulin G (IgG),

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and polymerase chain reaction (PCR). Maternal rubella infection frequently goes unnoticed because there often is no rash [2]. Treatment for CRS is limited to management of symptoms because there is no available antiviral therapy and diagnosis is made in the newborn when tissue damage has already occurred during intrauterine life.

There were about 105 000 (95% confidence interval [CI]: 54 000–158 000) CRS cases globally (based on mathematical modeling) in 2010, decreasing from about 119 000 (95% CI: 72 000–169 000) in 1996 [3]. This decrease was attributed to introduction of rubella-containing vaccines (RCV) in several countries. The World Health Organization (WHO) region of the Americas successfully eliminated indigenous transmission of rubella virus in 2009 [4] by introducing RCV into routine vaccination schedules with high coverage (≥95%), carrying out mass campaigns, and integrating measles surveillance with rubella and CRS surveillance. The WHO European region also implemented a similar strategy with the objective of eliminating rubella and CRS [5]. Elimination of rubella and CRS is achievable in Africa, building on the lessons learned from these experiences.

The main objective of rubella vaccination is to prevent CRS, but if high vaccine coverage is not maintained, there can be a paradoxical increase in CRS incidence [6, 7]. This paradoxical increase is attributed to a decrease in circulating rubella in childhood such that individuals reach adolescence and adulthood while being susceptible to rubella infection. Subsequent infection during the first trimester of pregnancy then leads to CRS. The WHO, in its Global Vaccine Action Plan and Global measles and rubella strategic plan 2012–2020 aims to achieve measles and rubella elimination in at least 5 WHO regions by 2020 [8, 9]. The WHO Africa region has not yet set an elimination target for CRS [8]. Seven sub-Saharan countries had introduced RCV by 2014 [10] and 14 by 2017 [11] through assistance from the Global Alliance for Vaccines and Immunization [12]. The EPI schedule in South Africa does not currently include RCV, but rubella vaccines are administered in private health care facilities [13]. Rubella vaccines have high immunogenicity and confer long-lasting protection [14], while having a favorable safety profile [15]. No CRS cases were reported when RCVs were inadvertently administered around the period of conception [16]. Achieving rubella and CRS elimination requires vaccination of children, as well as females and males of reproductive age [17] with RCVs, a strategy that has been shown to be cost-effective [18].

Introducing RCV into routine immunization schedules requires careful planning. WHO has outlined a number of activities that can lead to CRS elimination over varying periods of time. These include wide age range immunization campaigns, integration of rubella and measles surveillance, vaccination of older populations to fill immunity gaps, and CRS surveillance [19, 20]. Rubella and measles vaccines are often administered in combination so coverage figures for measles vaccine can be used to estimate projected RCV coverage. The WHO recommends a minimum measles vaccine coverage of 80% at district and national levels before RCV introduction [8, 20]. It is imperative to maintain this high coverage in all districts since disparities in vaccination coverage might lead to localized increases in CRS incidence [21, 22].

Data on rubella surveillance in South Africa has been published for 2000–2010 [21], 2016 [23], and submitted for 2017 [24]. Rubella surveillance was discontinued for a period of time during 2013–2014. Males and females were equally affected, and most rubella cases were aged between 1 and 12 years. There is a consistent seasonal pattern throughout all these years with annual increase in cases during the last 3 months of the year.

Previous publications on CRS in South Africa included case reports and mathematical modelling studies [2, 21, 25]. A recent study conducted from 2008 to 2011 reported on CRI in 1 province of South Africa [26] but there has been no national CRS surveillance program.

OBJECTIVES

We aimed to describe the epidemiology of laboratory-confirmed CRS in South Africa from 2010 to 2017. Specific objectives were to enumerate laboratory-confirmed CRS cases in sentinel public health facilities, describe birth defects found in laboratory-confirmed CRS cases and describe characteristics of mothers of laboratory-confirmed CRS cases in terms of age and rubella vaccination history.

METHODS

This was a descriptive cross-sectional study with 2 phases: a retrospective phase and a prospective phase.

We included laboratory-confirmed CRS cases, defined as any infant aged less than 12 months with a positive laboratory test (rubella IgM, 2 serial rubella IgG tests 4 weeks apart with titers that do not drop 2-fold or PCR), and who presented with at least one of the following: cataracts, congenital glaucoma, congenital heart disease, hearing impairment, pigmentary retinopathy, purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease. We adapted the case definition used by US Centers for Disease Control and Prevention [27].

We included 28 clinical sites that were referral hospitals in major cities of each province. In the South African health system cases are referred from primary health care facilities through to tertiary hospitals following a tiered system. Cases reported by more than one hospital were only recorded once. Focal persons were pediatricians, neonatologists, or pediatric infectious disease specialists at study sites (see Supplementary Material 1). Participating laboratories were National Health Laboratory Service (NHLS) virology departments at Groote

Schuur Hospital (GSH), Tygerberg Hospital (TH), Steve Biko Academic Hospital (SBAH), Dr George Mukhari Academic Hospital (DGMAH), and Inkosi Albert Luthuli Central Hospital (IALCH). The South African NHLS has a network of laboratories that perform testing for all health facilities in the public health sector. The selected laboratories carry out rubella testing for patients at sentinel sites. In addition to these laboratories, some samples were sent to the National Institute for Communicable Diseases (NICD) for testing.

All participating laboratories are accredited by the South African National Accreditation System according to the standard ISO15189. Infants with compatible clinical syndromes were tested either by serology, or rubella PCR on urine, or both according to clinical request. Different commercial assays were used for serology testing at the different laboratories: automated platforms, either the Architect (Abbott, Germany) or Elecsys (Roche, Germany) were used at DGMAH, IALCH, SBAH and GSH. Commercial m-capture enzyme-linked immunosorbent assays, either Vitek (BioMerieux, France) or Enzygnost (Siemens, Germany), were used to detect rubella IgM at GSH, TH, and NICD laboratories.

Rubella PCR was performed at GSH, TH, and NICD using in house assays, based on primers from Bothma et al [28].

In the retrospective phase, we extracted positive rubella serology or molecular test results between 2010 and 2014 in patients aged ≥12 months from the laboratory information system of the NHLS. We retrieved data from the medical records in the hospital archives and completed the case investigation form (CIF) (see Supplementary Material 2). Medical records were searched electronically at three sites (Tygerberg, Universitas and Peolnomi hospitals) and manually at all other sites.

In the prospective phase (2015–2017), each focal person received a monthly e-mail (see Supplementary Material 3) for reporting of confirmed CRS cases (including zero reporting) and completion of the CIF if applicable. Although not part of the initial plan for monthly reporting, clinicians who did not respond for a number of months received a phone call to check that no CRS cases were missed. Participant information was captured and stored in a Microsoft Excel 2010 database that was accessible only to the epidemiologists at the Centre for Vaccines and Immunology. The database was updated monthly and imported into Stata (Stata Statistical Software: Release 14. StataCorp LP, College Station, TX, USA) for descriptive analysis. Continuous variables were reported using medians and ranges while categorical variables were reported using absolute numbers and percentages.

ETHICAL CONSIDERATIONS

All 9 provincial ethics committees as well as the management of participating hospitals and university research ethics committees that cover the tertiary hospitals approved the study.

RESULTS

We identified 95 laboratory-confirmed CRS cases (Table 1), 77 diagnosed by IgM serology, 17 by PCR, and 1 by serial IgG serology. There were 42 cases in the retrospective phase and 53 in the prospective phase. Participant characteristics are summarized in Table 2.

Maternal Characteristics

Maternal age ranged from 14 to 38 years in the retrospective phase with a median of 21 years. In the prospective phase, maternal age ranged from 15 to 38 years with a median of 22 years (see Supplementary Material 4). None of the mothers reported ever having received RCV. In the retrospective phase none of the mothers had laboratory-confirmed rubella, although 2 (4%) in the prospective phase had laboratory confirmed rubella infection during the index pregnancy. Six (14%) mothers in the retrospective phase and 6 (11%) in the prospective phase reported having a rash during pregnancy. Data on maternal rash was unavailable for 34 (81%) mothers in the retrospective phase and 34 (64%) in the prospective phase.

Distribution of Reported CRS Cases Across Provinces in South Africa

The Western Cape Province reported the highest number of cases in both study phases with 19 cases in the prospective

Table 1. Congenital Rubella Syndrome Cases Reported at Sentinel Surveillance Sites, South Africa, 2010–2017

	Retrospective Phase (N = 42)					Prospective Phase (N = 53)			
Province and Study Site	2010	2011	2012	2013	2014	2015	2016	2017	Province Total
Eastern Cape Province	0	0	0	0	0	4	0	0	**4**
Free State Province	0	2	0	1	1	6	0	2	**12**
Gauteng Province	0	0	0	1	2	0	7	4	**14**
KwaZulu-Natal Province	0	1	1	2	5	3	0	0	**12**
Limpopo Province	0	0	0	0	3	3	0	2	**8**
Mpumalanga Province	0	0	0	0	1	2	0	0	**3**
Northern Cape Province	0	0	0	0	0	1	0	0	**1**
North West Province	0	0	0	0	0	0	0	0	**0**
Western Cape Province	5	6	3	2	6	18	1	0	**41**
Total per year	**5**	**9**	**4**	**6**	**18**	**37**	**8**	**8**	**95**

Table 2. Infant and Maternal Characteristics of Congenital Rubella Syndrome Cases Identified at Sentinel Surveillance Sites, South Africa, 2010–2017

	Retrospective Phase: 2010–2014 (N = 42)	Prospective Phase: 2015–2017 (N = 53)
Infant		
Age group, n (%)		
0 to 1 month	14 (33%)	27 (51%)
2 to ≤3 months	18 (43%)	18 (34%)
4 to ≤6 months	9 (22%)	6 (11%)
6 to 11 months	1 (2%)	2 (4%)
Unknown	0 (0%)	0 (0%)
Sex, n (%)		
Females	16 (38%)	28 (53%)
Males	26 (62%)	25 (47%)
Gestational age, n (%)		
Preterm	13 (31%)	18 (34%)
Term	17 (40%)	29 (55%)
Unknown	12 (29%)	6 (11%)
Mortality		
Alive	20 (48%)	39 (74%)
Died	3 (7%)	8 (15%)
Unknown	19 (45%)	6 (11%)
Maternal		
Age (median(range))	21 years (14–38)	22 years (15–38)
Reported, n (%)	23 (55%)	40 (75%)
Unknown, n (%)	19 (45%)	13 (25%)
Parity, n (%)		
1	18 (43%)	20 (38%)
2–7	14(33%)	18 (34%)
Unknown	10 (24%)	15 (28%)
Rubella vaccination, n (%)		
Yes	0 (0%)	0 (0%)
No	0 (18%)	11 (21%)
Unknown	42 (82%)	42 (79%)
Rash during pregnancy		
Yes	6 (14%)	6 (11%)
No	2 (5%)	13 (25%)
Unknown	34 (81%)	34 (64%)

Unknown refers to cases that had no information available in the medical records.

phase and 22 in the retrospective phase. No CRS cases were reported in North West province (see Supplementary Material 5).

Birth Defects in CRS Cases

The most common birth defect was congenital heart disease, and the least common were pigmentary retinopathy and radiolucent bone diseases (Table 3). There were 18 CRS cases with 1 or more abnormalities not included in the case definition with the most frequent being bicytopenia (4 cases) and microphthalmos (3 cases). Each of the following defects were found in only single cases: bicuspid aortic valve, hydrops fetalis, hypospadias with single umbilical artery, cerebral atrophy with cortical blindness and cerebral palsy, hydrocoele, supra-umbilical hernia with dilated renal pelvis, myxomatous tricuspid and mitral valves, cleft palate, coloboma of iris, colpocephaly, rubella keratitis, and Williams syndrome.

Age at CRS Diagnosis

The age at diagnosis in the retrospective phase ranged from 0 to 11 months with 14 (33%) cases diagnosed within 4 weeks of delivery. In the prospective phase, age at diagnosis ranged from 0 to 11 months with 27 (51%) cases diagnosed within 4 weeks of birth (see Supplementary Material 6).

Mortality Among CRS Cases

At the time data was captured on the CIFs, 3 (7%) cases in the retrospective phase were reported to have died, and 20 (48 %) were still alive. In the prospective phase, 8 (15%) cases were reported to have died, and 39 (74%) were alive. The proportion of cases with no data on mortality was 45% in retrospective phase and 11% in the prospective phase.

Surveillance Adequacy Indicator

Monthly e-mails to focal persons in the prospective phase were used as a surveillance indicator. Five sites had a 0% response rate for all 3 years of the prospective phase. Eight sites had a 100% response rate for at least 1 year of the prospective phase (see Supplementary Material 7). For clinicians in KwaZulu-Natal province, monthly reporting started in 2016 due to delayed ethics approvals.

DISCUSSION

The number of laboratory-confirmed CRS cases varied from 4 in 2012 to 37 in 2015, and a total of 95 laboratory-confirmed CRS cases were detected between January 2010 and December 2017. The Western Cape Province reported the highest number of CRS cases when compared to other provinces. The most frequent anomalies, according to our case definition, in both phases of the study were congenital heart disease and cataracts, whereas the least common were hearing impairment and radiolucent bone disease. Most mothers of CRS cases were between 14 and 30 years of age.

The higher number of reported cases in the prospective phase compared to the retrospective phase could be explained by increased awareness following discussions with clinicians at the start of the study. Because laboratory testing of CRS cases was initiated by the clinician's suspicion, increased awareness of the study might have led to a higher index of suspicion among clinicians. The drop in reported cases between 2015 and 2017, however, suggests limited influence of clinician awareness on detection of CRS cases. The fewer number of cases in the retrospective phase of the study could be explained by challenges in record keeping because medical records of many patients could not be retrieved.

The higher number of reported CRS cases in the Western Cape does not imply a higher CRS burden in that province.

Table 3. Clinical Signs per Case Definition of Congenital Rubella Syndrome Cases Identified at Sentinel Surveillance Sites, South Africa, 2010–2017

Clinical Characteristic n (%)	2010–2014 (N = 42)	2015–2017 (N = 53)
Congenital heart disease		
Yes	30 (71%)	43 (81%)
No	3 (7%)	3 (6%)
Unknown	9 (22%)	7 (13%)
Cataract		
Yes	22 (52%)	28 (53%)
No	8 (19%)	15 (28%)
Unknown	12 (29%)	10 (19%)
Glaucoma		
Yes	1 (2%)	2 (4%)
No	15 (36%)	20 (38%)
Unknown	26 (62%)	31 (58%)
Hearing impairment		
Yes	5 (12%)	3 (6%)
No	6 (14%)	2 (4%)
Unknown	31 (74%)	48 (90%)
Hepatosplenomegaly		
Yes	16 (38%)	26 (49%)
No	6 (14%)	17 (32%)
Unknown	20 (48%)	10 (19%)
Jaundice		
Yes	3 (7%)	10 (19%)
No	7 (17%)	26 (49%)
Unknown	32 (76%)	17 (32%)
Meningoencephalitis		
Yes	2 (5%)	7 (13%)
No	11 (26%)	24 (45%)
Unknown	29 (69%)	22 (42%)
Mental Retardation		
Yes	9 (21%)	2 (4%)
No	4 (10%)	4 (8%)
Unknown	29 (69%)	47 (88%)
Microcephaly		
Yes	10 (24%)	23 (43%)
No	11 (26%)	14 (27%)
Unknown	21 (50%)	16 (30%)
Pigmentary retinopathy		
Yes	0 (0%)	2 (4%)
No	14 (33%)	14 (26%)
Unknown	28 (67%)	37 (70%)
Purpura		
Yes	3 (7%)	13 (24%)
No	8 (19%)	28 (53%)
Unknown	31 (74%)	12 (23%)
Radiolucent bone disease		
Yes	0 (0%)	5 (9%)
No	6 (14%)	16 (30%)
Unknown	36 (86%)	32 (61%)

Differences in the diagnosis and referral processes as well as the presence of a highly specialized referral pediatric hospital in Cape Town could explain this finding.

Several studies reported varying frequencies of congenital abnormalities in CRS case [7, 29], usually occurring in combinations [30]. However, in the individual case, it is not possible attribute every anomaly observed to rubella virus [31]. Birth defects such as cataracts and congenital heart disease are frequently observed early after birth, whereas hearing impairment and developmental delay are usually diagnosed in late infancy. Many cases may therefore be diagnosed in specialist clinics when the children are over the age limit for our case definition (12 months). As infants approach 1 year of age, laboratory confirmation becomes challenging because a negative rubella test result does not exclude CRS [32], but the infant would be excluded from our study. Interestingly, some identified CRS cases had additional symptoms that are not part of standard case definitions.

The number of deaths reported among CRS cases differed between study phases. Differences in in-hospital CRS mortality between study phases could be explained by challenges in follow-up of cases and obtaining data from medical records. Infants with CRS are at higher risk of severe morbidity and mortality [2, 7, 33], and following these cases prospectively would enable more accurate estimates of survival.

None of the mothers of CRS cases reported having received rubella vaccine. A rash during pregnancy was reported by mothers in the prospective and retrospective phases. History of rash was not available in most cases in the prospective and retrospective phases. Rubella infection frequently presents without a rash [34], and in many cases, the mother may have forgotten a rash in early pregnancy. The presence of rash is often a key element that raises suspicion and leads to identification of rubella in pregnancy.

Most mothers in our study were aged between 14 and 30 years. About 27% of the general female population of South Africa is in this age range [35], whereas 70.7% of pregnant women included in the antenatal human immunodeficiency virus survey are within 15 to 30 years of age [36]. The age distribution of mothers of CRS cases is an indication of the susceptible adult female population of child-bearing age in public health facilities in South Africa. Immunity testing among adolescents and adults of both sexes could complement data on susceptibility to rubella.

This study had a number of strengths: All cases were laboratory confirmed and sentinel sites were dispersed nationally in all provinces. Both the clinicians and virology laboratories that test for rubella were involved in case finding. This 2-way flow of information on potential CRS cases ensured a high probability of identifying cases from the study sites. Finally, active communication was maintained with the clinicians at study sites to ensure regular reporting and document zero reporting. The absence of responses to e-mails sent to a number of clinicians prompted phone calls that served as an alternative method of communication. The main limitation of the study is that we excluded CRS cases at health facilities that were not sentinel sites. Another limitation relates to difficulties in obtaining patient data, especially in the retrospective phase of the study. We could not calculate CRS incidence because

there was no suitable denominator for an incidence estimate. Some of the CRS cases reported by the sentinel sites were referred from other health facilities, often situated in different health districts or provinces. Given that some CRS cases were diagnosed at health facilities that were not sentinel sites, using the birth cohort at sentinel sites would overestimate incidence, whereas using the national birth cohort in South Africa would underestimate CRS incidence. Finally, there likely was underreporting because our case definition was limited to infants <12 months of age.

CONCLUSION

The number of laboratory-confirmed CRS cases in South Africa ranges from 4 cases in 2012 to 37 cases in 2015 in the absence of public rubella vaccination. The identified CRS cases predominantly presented with severe signs and symptoms that could be diagnosed early by clinicians. The ages of 98% of mothers of the CRS cases ranged from 14 to 30 years. An immunity gap exists among women in this age group that should be considered when identifying target age groups for RCV introduction. Continuous CRS surveillance will enable monitoring of the impact of rubella vaccination once introduced into the South African EPI schedule.

Our findings highlight the need for a rubella control program in South Africa. Optimal timing for implementation depends on ability to exceed 80% vaccine coverage, using measles vaccination coverage at 1 year of age as a proxy. South Africa should strengthen routine immunization coverage in preparation for RCV implementation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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