NIGERIA CENTRE FOR DISEASE CONTROL

NATIONAL GUIDELINES FOR CONGENITAL RUBELLA SYNDROME SURVEILLANCE

World Health Organization Nigeria

CDC Centers for Disease Control and Prevention

AFENET African Field Epidemiology Network. A healthier Africa

National Surveillance Guidelines for Congenital Rubella Syndrome Surveillance

August, 2019

<u>These surveillance guidelines were developed based upon two documents:</u>
WHO African Regional Guidelines (WHO African Regional Office, "African Regional Guidelines for Measles and Rubella Surveillance" 2015:1-82.)

Vaccine Preventable Diseases Surveillance Standards: Congenital Rubella Syndrome Surveillance (September 5, 2018 update) (WHO, "Vaccine Preventable Diseases Surveillance Standards: Congenital Rubella Syndrome Surveillance", Geneva, 2018:1-16.

Foreword

The Nigeria Centre for Disease Control as the country's national public health institute has prioritised the surveillance of congenital rubella syndrome (CRS) in Nigeria. This is in recognition of the critical role of several stakeholders.

Our goal is to provide data and information for public health action, especially for the planning, implementation and evaluation of relevant public health interventions. Critically, we want to ensure that CRS surveillance data can drive the uptake of vaccines for this disease that is vaccine preventable.

In developing this guideline, we want to ensure that the surveillance system for CRS in Nigeria is sensitive, specific and capable of determining whether cases can be linked with sustained transmission.

This national guideline will also support our goal of establishing the burden of CRS in Nigeria. We are keen to work with stakeholders including clinical health workers, surveillance officers at the state and Local Government level, academia and our partners to better understand the epidemiology of this disease in Nigeria.

Finally, this document provides clear recommendations for CRS surveillance and is intended for surveillance officers and clinicians. The document provides guidance on defining and responding to cases and outbreaks of CRS in Nigeria. Together, we can ensure no child in Nigeria is affected by CRS by implementing measures to effectively prevent its occurrence.

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Acknowledgments

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A full list of contributors is provided after the annexes.

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Acronyms

AFENET	African Field Epidemiology Network
CDC	Centers for Disease Control and Prevention
CRS	Congenital Rubella Syndrome
CPHL	Central Public Health Laboratory
DSNO	Disease Surveillance Notification Officers
EPID	Epidemiology
HSFP	Health Facility Surveillance Focal person
IPC	Infection, Prevention and Control
NCDC	Nigeria Centre for Disease Control
NSTOP	National Stop Transmission of Polio
NIP	National Immunization Programs
NREC	National Rubella Expert Committee
PDA	Patent ductus arteriosus
PPS	Peripheral pulmonary stenosis
SORMAS	Surveillance Outbreak Response Management and Analysis System
UMB	University of Maryland Baltimore
WHO	World Health Organization

Background

Rubella disease presents with a mild rash and fever. Rubella disease usually occurs during childhood resulting in life-long immunity; but when infection occurs early in pregnancy, it can lead to miscarriage, still birth, premature delivery and/or birth defects. A child born with such defects following maternal rubella infection is said to have congenital rubella syndrome (CRS). The risk of congenital infection and birth defects is highest if maternal infection occurs during the first 12 weeks of gestation and decreases thereafter, with defects rarely occurring after the 20th week of gestation of the mother.

In more than 80% of CRS cases, at least one of three main defects is present: hearing impairment, congenital heart disease, and/or eye defects. Hearing impairment, including deafness is the most common defect, followed by a congenital heart defect. The most common heart defects observed in CRS cases are patent ductus arteriosus (PDA) or peripheral pulmonary stenosis (PPS). Eye defects include cataract, glaucoma, and pigmentary retinopathy. Other signs include microcephaly, meningoencephalitis, developmental delay, purpura, hepatosplenomegaly, jaundice, thrombocytopenia, and radiolucency in the long bones[1].

In the absence of vaccination, rubella is generally endemic, with epidemics occurring every six to nine years. In non-epidemic periods the incidence of CRS typically ranges from 0.1–0.2 cases per 1,000 births while during epidemics incidence can increase to 1–4 cases per 1,000 births[(1)(2).] In 2010, an estimated 103,000 children were born with CRS worldwide.[(3)] Disease burden of rubella in Nigeria has been assessed through mathematical modelling and chart reviews. In 2010, a modelling study estimated that approximately 9,000 infants were born with CRS in Nigeria; this would account for 9% of the 103,000 global CRS infants born annually (Nigeria data is from an unpublished, global analysis[2]). The estimated mortality of CRS is 25-40% of CRS cases, amounting to an estimated 2,500 to 3,600 childhood deaths each year in Nigeria. It is estimated that in a low-income country, each case of CRS has an economic cost of $11,255 for care[3], including costs to address medical and special educational needs.
In August 2012, the WHO African Region (AFRO) proposed a regional strategy option for

[1]World Health Organization, "Rubella Position Paper," 2011; *Weekly Epidemiological Report* 86:301-316.
[2]Vynnycky E, Adams EJ, Cutts FT, Reef SE, Navar AM, et al." Using Seroprevalence and Immunization Coverage Data to Estimate the Global Burden of Congenital Rubella Syndrome, 1996-2010: A Systematic Review," 2016; *PLoS ONE* 11(3): e0149160.
[3]Thompson KM, Odahowski CL, "The Costs and Valuation of Health Impacts and Rubella Risk Management Policies" *Risk Analysis* **36**:1357-82.

rubella/CRS elimination, although rubella elimination goal has not been recommended.[4] By the end of 2018, rubella vaccination was in the process of being introduced into the national immunization programs (NIP) of 26 of 47 (55%) countries within the WHO AFRO region. A measles-rubella (MR) campaign targeting all children less than 15 years is recommended at the time the vaccine is included in the NIP. Nigeria has not yet begun the rubella vaccine introduction process as at August, 2019.

Surveillance for congenital rubella syndrome (CRS)

Surveillance for CRS is being adopted for several reasons. First, it can demonstrate the burden of CRS in a country, which will serve as evidence to support the introduction of rubella vaccine into the country's immunization programme. Like most sentinel-site surveillance systems, the data is often not representative of Nigeria as a whole; however, as CRS is often unrecognized, demonstration of cases is necessary for the decision-making process. In addition, to monitor the impact of the introduction of rubella vaccine, surveillance for CRS identifies disease trends, and burden to provide primary basis to introduce rubella vaccine. Surveillance is especially useful when established prior to provide baseline data prior to introduction of vaccine. Surveillance also rapidly detects CRS cases in the hospital setting, which mitigates the risk of rubella outbreaks resulting from CRS infants, who shed virus for up to one year of life, as well as mitigate consequences of the defects associated with CRS through early treatment. In the long run, surveillance for CRS will provide supportive evidence for determining the elimination of rubella virus transmission in a country.

Recommended surveillance for CRS

WHO minimal recommended approach for surveillance for CRS is sentinel-site surveillance with case-based data and laboratory confirmation. CRS sentinel surveillance is done through identifying new-borns and infants (children less than 12 months of age). This is crucial for capturing of all infants with suspected CRS. High level of specificity and laboratory confirmation is critical because CRS is a combination of congenital defects that may have several other causes.

Tertiary or specialist hospitals should be prioritised as sentinel sites as most infants with birth defects associated with CRS are likely to present at such health facilities. The sentinel surveillance system can be based on a single

[4] World Health Organization: Regional Office for Africa Region. Africa Regional Strategic Plan for Immunization Challenges and Opportunities Recommendations in Brief Conclusion Recommended Actions Members of the Mid-Term Review panel Acknowledgements. [accessed 2019 Jan 21] athttps://www.afro.who.int/sites/default/files/2018-09/MTR_RSPI_English_Final.pdf

reporting site, or on a network of selected sites that can be monitored closely, with needed clinical skills for evaluation of suspected CRS cases. At selected sites, specialists should be provided with written guidelines and trained in order to report all identified cases of suspected congenital rubella syndrome to the surveillance officer.

Congenital Rubella Syndrome may be diagnosed by its classic triad of clinical signs: cataract, heart disease, and deafness. Many infants only have one of these manifestations, or may present earlier with neonatal signs; thus, laboratory confirmation of the diagnosis is recommended. Rubella-specific IgM is readily detected in the first 6 months of life, and among a decreasing proportion of cases as affected children approach the first year of life. Its detection usually indicates prenatal rather than postnatal infection.

The manifestations exhibited by neonates (e.g. purpura, splenomegaly, low birth weight) or during early infancy (e.g. cataract, congenital heart disease) can usually be detected during investigations that follow rubella outbreaks. Affected neonates can also be identified through routine toxoplasmosis, rubella, cytomegalovirus, rubella, herpes simplex, and syphilis (TORCHES) screening programs.

Rationale

To evaluate the benefits of introducing rubella vaccine, the Nigeria Centre for Disease Control (NCDC) made the decision to begin prospective CRS surveillance by establishing sentinel sites across geopolitical zones in the country.

In general, CRS surveillance will provide standardised data that will allow comparisons over time and will serve as the basis for documentation and verification of rubella virus elimination. Identifying infants with CRS is important due to the following reasons:

1. Demonstrate the burden of CRS in Nigeria, to provide data to decision-makers regarding introduction of rubella vaccine in the country.
2. Monitor the impact of the potential introduction of rubella vaccine. This will enhance the measles surveillance system, as it is less sensitive to rubella disease than measles. Approximately 50% of rubella cases, including mothers giving birth to infants with CRS, had asymptomatic rubella infection, and therefore not detected through the measles surveillance system.
3. Efforts can be taken to prevent rubella transmission and outbreaks resulting from infants with CRS, who may shed virus for up to 1 year.
4. Early interventions to treat CRS manifestations reduce long-term health consequences for the infant.

Objective of Surveillance for CRS in Nigeria

Given the above rationale, the objectives of establishing CRS surveillance in Nigeria are as follow:

- To provide data on the contribution of CRS to the disease burden of vaccine-preventable diseases in order to help prioritise resources and plan public health interventions
- To provide a baseline level of CRS, which will eventually serve as evidence for introduction of rubella vaccine into the Nigeria's immunisation schedule
- To provide a platform that will enable monitoring and evaluation of rubella vaccine introduction and inform further public health actions needed in CRS control and elimination
- To detect and monitor affected infants closely to mitigate the consequences of CRS through early intervention and limit rubella transmission.
- To provide data for the effective planning on CRS elimination in the country.

Establishing CRS surveillance in Nigeria

Process of establishing surveillance for CRS

Prospective sentinel-site surveillance for CRS cases among children <12 months with laboratory testing will occur as outlined below and described in detail in subsequent sections. The steps for establishing CRS surveillance are:

1. Selection of surveillance sites for identification and notification of suspected cases
    a. Use of standard case definition
2. Case investigation
    a. Case investigation form should be filled for each suspected case
    b. Venous blood, and throat swabs should be collected from every suspected case
3. Storage of specimens
    a. All specimens should be stored under appropriate conditions and sent to designated national reference laboratories
4. Laboratory testing and confirmation
    a. Serum testing for rubella IgM
    b. Freeze throat swab for future rubella virus detection
5. Final case classification
    a. Review clinical and laboratory data
    b. Classify cases based on standard clinical and laboratory criteria

6. Feedback on results and follow-up of CRS cases
    a. Provide report of results to patient's doctor and parents/caretakers
    b. Follow-up testing, minimizes transmission through infection prevention and control (IPC), and medical referral of confirmed CRS cases

Selection of surveillance sites

As mentioned above, sentinel surveillance for CRS utilizes sites that have the highest likelihood of identifying suspect CRS cases. Identification of a case requires affected persons to present to the facility as well as availability of skilled staff who are enthusiastic to identify and investigate the case. Due to the nature of the congenital defects, suspect CRS cases are few and far between.

To focus resources, sentinel-sites selection prioritises referral centres where diagnosis of congenital defects commonly associated with CRS is available. These sites generally utilise neonatal and paediatric units and clinics with specialties in paediatric ophthalmology, ENT, paediatric cardiology. These sites are not usually engaged in disease surveillance; therefore, they require enthusiastic key persons to champion surveillance activities as these sites are established, and to maintain participation.

In Nigeria, the establishment of sentinel-sites across the various geopolitical zones in the country will address the diversity of the population. Selected sites will be appropriately equipped at establishment and provided with necessary resources for ongoing activities. The sites will be identified after proper evaluation using a standardized site assessment tool by a national team, to ensure that selected sentinel-sites meet all criteria including the capacity of the laboratory to handle specimens and capacity to identify, investigate and report cases. This assessment is primarily qualitative. Individuals at the sites and at LGAs will each have specific responsibilities as outlined in Annex 4.

Establishing expert committee

A National Rubella Expert Committee (NREC) shall be established to support the CRS surveillance system. The committee will function three-fold: first, to review the CRS surveillance data and case classification, assist with its interpretation; second, to promote the use of surveillance data in Nigeria; third, to make recommendations to CRS sites to ensure that they are functioning at their best.

The NREC will consist of 5-7 members including a chairperson and secretary. NCDC will serve as the secretariat for the NREC. The committee will meet twice per year and plan for the annual review meeting. The suggested experts are as follows:

- Paediatric Cardiologist/Neonatologist
- Paediatric Ophthalmologist
- ENT Surgeon
- Epidemiologist
- Obstetrician and Gynaecologist

Case identification and investigation

Selected surveillance sites should be able to identify, investigate, report and respond (clinical management and public health response) to identified cases. The process for case identification and investigation is outlined (Figure 1). Suspected cases are identified in appropriate clinics at the site where cases are likely to occur. The clinics that are most likely to see CRS cases are those that see infants in the following subspecialties:

- Ophthalmology (usually paediatric ophthalmology)
- ENT Clinic
- Special Care Baby Unit/ Neonatal Intensive care unit
- Paediatric Cardiology
- Post-natal Clinics
- Laboratory (review laboratory testing for rubella)

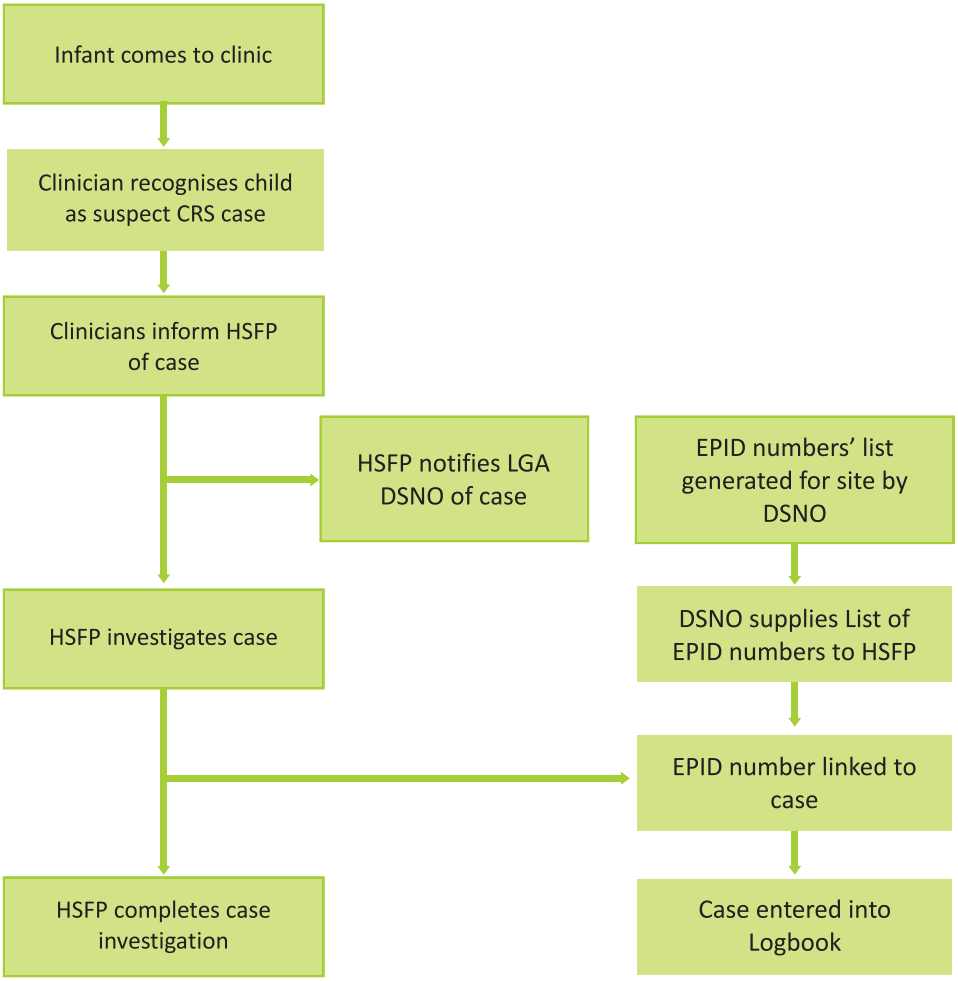


Figure 1 - Case investigation and reporting, including how case identification number (EPID) are generated and assigned. The health facility surveillance focal person (HSFP) is responsible for majority of the case investigations

Identification and notification of suspected cases

Suspected cases of CRS are detected by clinicians working at the sites; therefore, clinic staff should be sensitised on the suspect case definition and taught to notify the health facility surveillance focal person (HSFP) by phone calls or text messages when a case is detected. The HSFP will thereafter begin the case investigation process.

Cases are also identified by the HSFP through a review of in-patient and out-patient registers weekly to identify possible missed cases that may have medical conditions related to CRS. Each possible case that is identified should be noted in a surveillance logbook (defined in Annex 4). At the end of every weekly review, 'Chart checked for CRS' should be initialled in the margin of the register. This marking will avoid duplication of efforts, enable supervisory visits and retrospective reviews to quantify the quality of the surveillance. The charts of cases identified in the register will be pulled for

further review to evaluate if the condition is related to CRS, and key information placed in the CRS surveillance logbook.

When the HSFP is notified of a possible suspected case, he/she will notify the Disease Surveillance and Notification Officer (DSNO) immediately (within 24hours). The DSNO would have provided a list of EPID numbers to the HSFP and the next sequential number will be assigned to that case. The EPID number is facility-based and assigned originally from a list provided by the DSNO. The EPID number will follow a uniform format of location code, specific number, and label all specimens from that case, including follow-up samples with the EPID stickers corresponding to that number, rather than names and personal identifiers. The HSFP is responsible for the case investigation of all suspected cases, once they are notified or identify a case themselves.

Suspected Case Definition for case finding

The Suspected CRS case is:

- Any child less than one year of age that presents with any of the following:
    - Congenital heart disease
    - Suspicion of hearing impairment
    - One or more of the following eye signs: cataract (white pupil), congenital glaucoma (large eyeball) or pigmentary retinopathy.

OR

- Any child < 12 months of age in whom a health worker suspects CRS, even without apparent signs of CRS, including infants born to mother with a history of suspected or confirmed rubella during pregnancy.

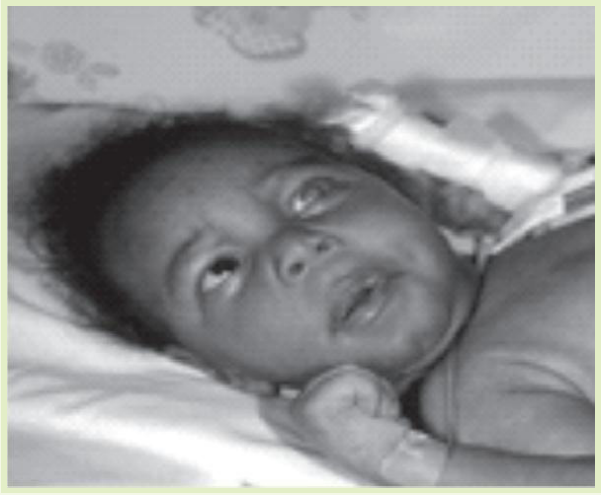


Figure 2 - Congenital cataract is one of the conditions used to identify an infant with congenital rubella syndrome

Case investigation

The HSFP is responsible for ensuring completion of the case investigation form, and collection of two specimens, a blood/serum specimen and a throat swab, within 48 hours of notification. The case investigation form should be completed and a clinical evaluation for at least eye and cardiac defects, in addition to completing the patient name, address, date of birth, symptoms, date of notification, date of investigation, date of specimen collection, maternal age, and any possible prenatal maternal rubella exposure. If a hearing impairment, heart murmur or eye defect is suspected, further evaluation is required and should be documented on the case investigation form including entering results of any subsequent studies (e.g. echocardiogram) as results become available.

Before collecting the specimens, the purpose of collecting the sample, what to expect during the procedure, the minimal risks involved and that subsequent samples may be required should be explained to the parents or caregiver. Specimens should be labelled with a sticker printed with the EPID number, which is the unique surveillance identification number that is specific to the case. The HSFP will enter the specimen data into the database and attach a paper form with the specimen.

The clinical specimens to be collected are:

1. 3-5ml of venous blood and
2. Throat (oropharyngeal) swab.

Protocols for collection of throat swabs are in Annex 2. Depending on the age of infant, a second blood specimen may be required for laboratory confirmation of the CRS case, as described below.

Processing and storage of specimens

Laboratory staff will ensure that each specimen arriving at the laboratory is associated with an appropriate EPID. Number. Laboratory staff should ensure that the laboratory portions of the specimen form are complete and labelled with stickers with the EPID and specimen number. Laboratory protocols are described in Annexes 1 and 2.

Blood samples from infants with suspected CRS will be separated into serum at the site hospital laboratory. Sera obtained will be stored at -20°C at the site laboratory prior to shipment to the national reference laboratory. Throat swabs will be submersed in the tubes with viral transport media (VTM) and stored at -20°C at the site laboratory. Throat swabs should be promptly stored at -70°C when they arrive at CPHL.

Laboratory testing and confirmation

Initially, all specimens will be sent to the Central Public Health Laboratory (CPHL), Lagos for laboratory testing, according to the measles-rubella surveillance protocol. At a future date, additional laboratories may also be utilized for testing. Throat swabs should be stored for possible future testing for rubella virus detection and genotyping. The laboratory should use the same rubella IgM kits utilised for measles/rubella surveillance, according to the manufacturer's instructions. Data to be recorded by the laboratory includes specimen ID, EPID number, date specimen collected, date specimen received, date specimen tested, date specimen results shared, tests performed, laboratory test results. For throat swab specimen, additional information should include the date it was shipped, date received at the confirmatory testing laboratory and date result was sent back.

All sera are tested using ELISA for rubella IgM.

If the IgM test is negative within the first month of life, and the clinician has high suspicion of CRS, the IgM test should be repeated on a new serum sample after 1 month. Laboratory criteria for confirmation of CRS is achieved with a positive rubella IgM test, this is linked to clinical criteria for final classification. In addition, all laboratory confirmed cases should have the throat swabs tested to determine rubella virus genotype, through the standard WHO protocols for rubella genotyping, this would be performed at the regional reference laboratory, until capacity is available at the national level.

Cases are considered discarded cases if they have a negative test result from an adequate sample. An adequate sample is as follows: at least 1ml serum is obtained (from a minimum of ~3-5ml of blood); serum sample is stored in the refrigerator and transported in cold chain to the laboratory.

Recording and reporting laboratory findings

Laboratory results are recorded in a laboratory logbook and returned within seven days of receipt. Once results are available, they are to be sent to the HSFP of the reporting site and shared with the clinician treating the child. The laboratory is also responsible for entering the laboratory results into SORMAS (see below).

Final case classification criteria

After case investigation and laboratory testing, adequate information should have been collected to classify cases. Cases are classified according to criteria from the two aspects of the case

investigation, the clinical information (signs and conditions) as well as laboratory findings. Final classification of CRS cases depends, in part, on identifying Group A or Group B clinical signs of CRS, defined as follows:

Group A: Cataract(s), congenital glaucoma, pigmentary retinopathy, congenital heart disease (most commonly peripheral pulmonary artery stenosis, patent ductus arteriosus or ventricular septal defects), hearing impairment.

Group B: Purpura, splenomegaly, microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease, jaundice that begins within the first 24 hours after birth.

The Laboratory classification criteria for this surveillance system is based upon rubella IgM antibody detection, defined by the global laboratory protocols. In addition, an adequate sample needs to be collected, with adequate cold chain and transport. An adequate sample is as follows: at least 1ml serum is obtained (from a minimum of ~3-5ml of blood); serum sample is stored in the refrigerator and transported in cold chain to the laboratory.

Final case classifications definitions

- ***Laboratory-confirmed CRS case:*** A suspected CRS case with at least one sign from group A and meets the laboratory criteria for confirmation of CRS.

- ***Clinically confirmed CRS case:*** A suspected CRS case without an adequate specimen in whom a qualified clinician detects at least two of the complications from group A OR one from group A and one from group B.

- ***Congenital rubella infection (CRI):*** An infant who has none of the clinical signs of CRS from group A, but who meets the laboratory criteria for CRS.

- ***Discard Case:*** A suspected CRS case with an adequate specimen not meeting the laboratory confirmed case definition, or a suspected case without an adequate laboratory specimen and not meeting the clinically compatible case definition.

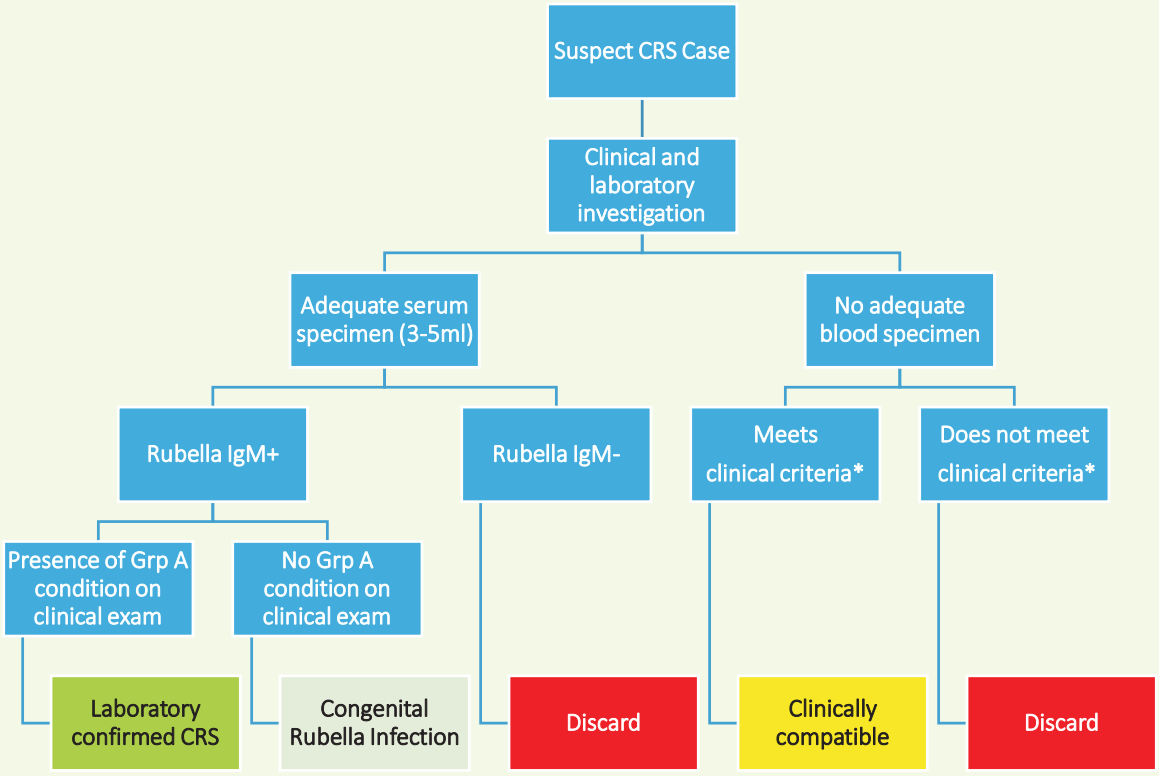


Figure 3 - Diagram that outlines the process of case classification of suspected congenital rubella syndrome (CRS) cases. Cases which are not easily classified maybe referred to the expert committee for further consultation

- *Clinical criteria refer to the clinically compatible case definition, based upon Group A and Group B symptoms. Criteria are met if the infant has 2+ Group A conditions; OR 1+ Group A and 1+ Group B conditions.

The NREC will be responsible for reviewing the CRS data, including the case classifications, and making recommendations for sites to improve the quality of their work. For cases with questionable classification, the NREC and the NCDC surveillance focal person can call upon the expertise of US CDC, and WHO for additional consultations.

Case follow-up

Laboratory result shall be noted on the case investigation form, scanned and sent to the site coordinator and the HSFP who will convey the result to the managing clinicians. Doctors shall in turn notify the parents/caretakers of the infant. In the case of confirmed CRS cases, the following are recommended:

- Implement hospital infection control precautions (specifically, contact isolation for CRS cases) to limit contact of rubella non-immune individuals with CRS case during any

admission until 1 year of age (or sooner if infant is determined to be non-infective[5]).

- Ensure all healthcare workers taking care of the infant are rubella-immune through IgG testing; assign immune persons for care. If vaccine is available, vaccinate healthcare workers that are not immune. If testing and vaccination is not possible, it is critical to ensure that pregnant women or women who might become pregnant in the next month do not care for the CRS-infant.[6]
- Educate and ensure parents/caretakers of the CRS infant have appropriate IPC implemented outside the hospital, specifically contact isolation of the infant from the community for the first 12 months of life, especially other children and pregnant women. This will prevent further rubella infection transmission and reduce CRS incidence during the presumed period of infectivity of the infant with CRS.
- Refer infants with confirmed CRS, as appropriate, for audiology, ophthalmologic, cardiologic evaluation; medical intervention, such as heart or eye surgery; and support services (e.g. hearing aids; occupational, speech or physiotherapy; community-based rehabilitation or home visits; schools for the deaf or developmentally disabled).
- Sites should consider provision of free or subsidized treatment for infants with CRS, and/or develop a list of resources to support families to care for their child (e.g. educational support)

Data management

A flow chart of CRS case reporting, feedback of results, and follow-up (Fig 4). Data will be entered electronically into a password protected Surveillance Outbreak Response Management and Analysis System (SORMAS) database by the HSFP; data should be entered for each suspect case (notified cases that meet the suspect case definition). Each case will be entered with the assigned EPID number and data from the case investigation form. The HSFP will confirm medical history with the clinician and update the electronic case investigation form as additional data are available (e.g. echocardiography results). Laboratory data is entered electronically at the CPHL, in addition to informing appropriate individuals as defined above. The data entered from the case investigation form will be uploaded, and available to the LGA and State, as well as be forwarded to the NCDC. Laboratory results will be entered by the laboratory staff into SORMAS, as well as notifying DSNO and state epidemiologists of results. The SORMAS database is backed up

[5] An infant can be considered non-infectious at 12 months of age or earlier if there are two sequential negative tests for virus.

[6] Infants with CRS have virus titers 100–1000 times higher than cases infected after birth, making them much more contagious. One study showed a 75% rate of infection of rubella-susceptible nurses caring for an infant with CRS. Rubella outbreaks among health care workers in contact with CRS infants have been documented. Infection of rubella-susceptible female medical professionals through contact with the CRS infant or other infected health care workers during a hospital-outbreak could result in subsequent CRS cases.

weekly to a separate storage device.

The NCDC data manager will be responsible for linking the laboratory and epidemiological data, as well as compiling data from all the surveillance sites into a single database.

The classification of cases will be done by the HSFP with the support of the site coordinator. The case classification will be reviewed and finalized by the NCDC Measles/Rubella focal person. Access to information regarding cases should be restricted to health workers involved in patient care and necessary CRS surveillance staff to ensure patient confidentiality.

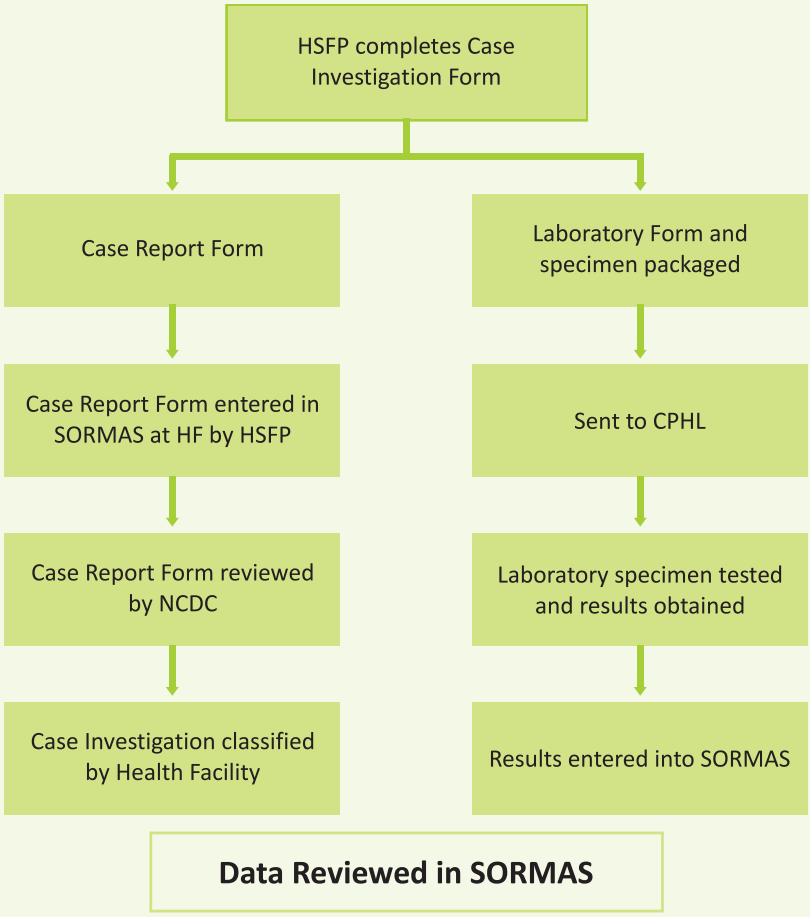


Figure 4-Case reporting following the case investigation occurs as in the diagram. Cases are reported and entered into the electronic database, steps that occur through the Surveillance, Outbreak, Response Management, and Analysis System (SORMAS)

Evaluation of CRS surveillance and use of data

The short-term goal of the CRS surveillance system is to document the burden of CRS in Nigeria. True incidence measures cannot be calculated for several reasons 1) the catchment population will be poorly defined, 2) not all cases will present to a selected surveillance site, 3) high mortality, and/or 4) hearing impairment, the most frequent CRS manifestation often presents after infancy. In the long-term, the data collected will assist local and national decision-makers to monitor the impact of vaccine introduction and track progress towards elimination of CRS in Nigeria.

Surveillance site updated reports will be generated and shared quarterly as part of the supervision process. These reports will report the status of different aspects of the surveillance system, including detection, reporting, laboratory findings, and final case classification of suspected CRS cases, in the current quarter and year. There will also be a short section regarding indicators of system capacity. The NREC will review the data and request additional data to monitor the progress of the surveillance system.

An annual review meeting should be conducted presenting in-depth analysis of the surveillance data, and as a forum to share experiences of the surveillance system. The NREC can provide recommendations to NCDC on strengthening of the surveillance system.

Monitoring of the surveillance system will be performed on an ongoing basis by NCDC, with assistance from partners. An evaluation will be performed at the end of the first year where data is reviewed and analysed, and feedback is solicited from staff involved in the surveillance system. A report from the evaluation will be generated and shared with all stakeholders.

CRS surveillance systems would be valuated quarterly and annually to assess completeness of CRS reporting at surveillance sites. This will include hospital record review to identify any missed cases. Missed cases can be identified by comparing the list of reported CRS cases with the list of all cases that meet the suspected CRS case definition. Review the indicators below at least annually. Data gathered from CRS surveillance system evaluations will be included in National Verification Committee (NVC) reports for CRS.

Table 1: Surveillance performance Indicators and Targets for CRS

Indicator	Description	Target	Frequency
Number of CRS cases reported	Total number of CRS cases reported from all sentinel sites /month	-	Monthly/Quarterly/Annually
Timeliness of reporting	The number of congenital rubella cases detected and reported within 24hrs, divided by the number of cases reported monthly × 100%	⩾80% of cases detected and reported within 24hrs	Monthly /Annually
Completeness of reporting	• The number of forms filled divided by total number of forms submitted x 100% • Number of sites reporting cases divided by the expected sites × 100%	⩾80% of reports received	Monthly/Annually
Laboratory investigation (testing) rate	The number of cases with specimens adequate for detecting rubella collected and tested divided by the total number of specimens received × 100%.	⩾80% of specimens adequate for detecting rubella infection. Any suspected cases that are not tested by the laboratory and are • a) confirmed by epidemiologic linkage or • b) discarded as non-rubella by epidemiological-linkage to a laboratory-confirmed case of another communicable disease or epidemiological-linkage to a rubella IgM-negative case, should be excluded from the denominator.	Weekly

Rate of discarded cases	The rate of suspected rubella cases that have been investigated and discarded as non-rubella cases using laboratory testing and/or epidemiological linkage to another confirmed disease	At least 2 discarded rubella cases should be reported annually per 100,000 population/year	Quarterly/Annually
Laboratory turnaround time	• The proportion of results reaching the health facility within seven days following receipt of specimen	⩾80% of specimens tested, and results received in health facility within 7days following receipt of specimen	Quarterly/Annual
	• The completeness of laboratory samples proportion of samples tested and Sent out of the laboratory within two days		

Annex 1- Handling, transport storage and shipment of specimens

Handling and transport of blood sample

Collect 3-5ml of blood by venepuncture into a plain tube/EDTA labelled with patient identification, EPID number and collection date.

Separate the serum from red cells:

1. Allow the blood to stand for 30-60 minutes,
2. Then centrifuge at 2000 RPM for 10-20 minutes
3. Transfer the serum is transferred into a clean cryovial.

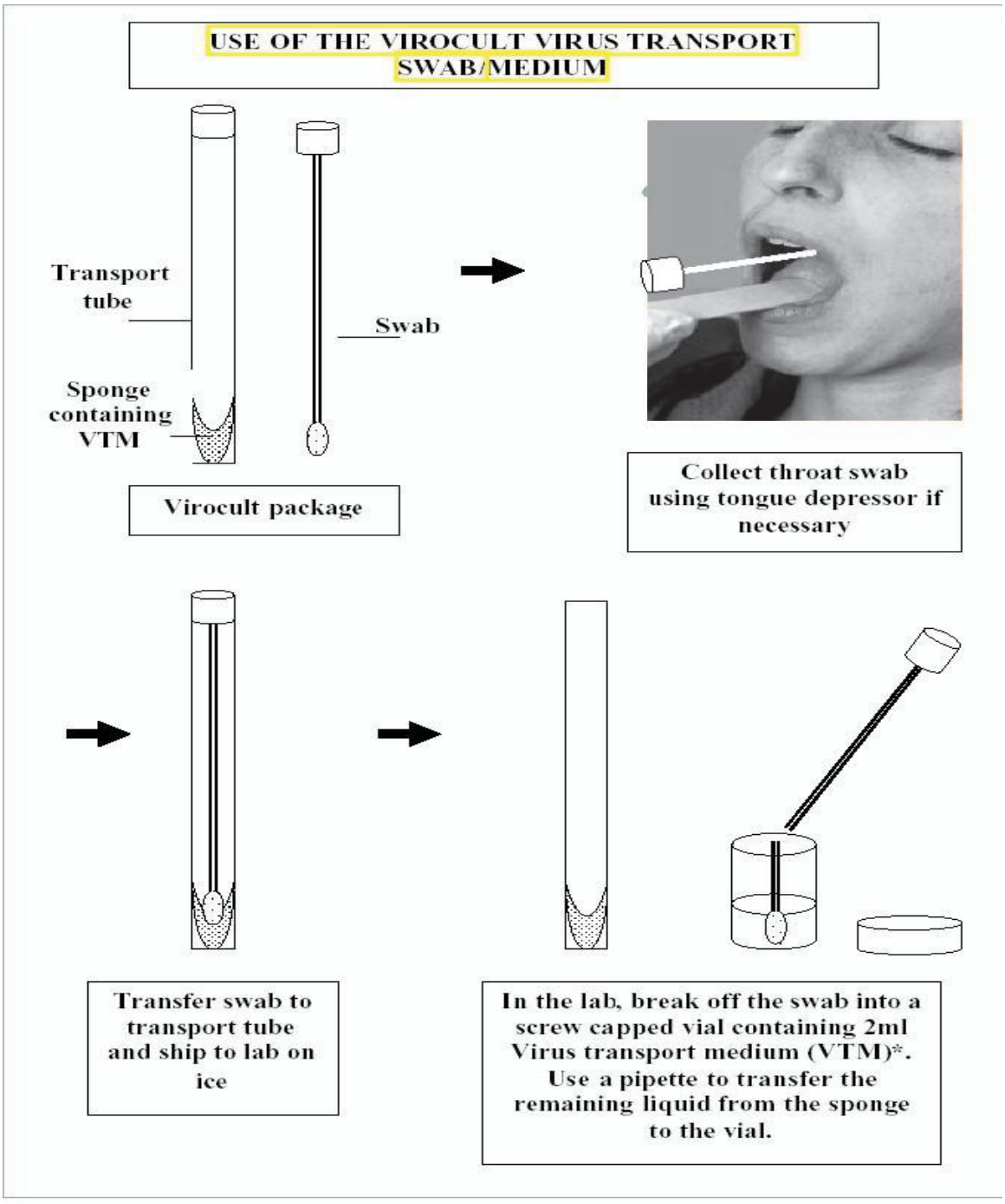
DO NOT FREEZE WHOLE BLOOD

Storage and shipment of serum specimens:

- Store serum at -20°C until it is ready for shipment. The serum can be stored for a maximum of seven days. Ensure that the lab form accompanying the specimen is appropriately filled. Three dates are very important
    - Date of birth
    - Date of collection of the sample
    - Date of presentation
- Ensure specimens are triple packaged and shipped to the reference laboratory as soon as possible.
- Specimens from different patients should never be sealed in the same Ziploc bag.
- Place specimen form and case investigation form in another plastic bag and tape to outer top of the specimen transport box.
- If using ice packs (these should be frozen), place ice packs at the bottom of the box and along the sides, place samples in the centre, then place more ice packs on top.
- When shipping arrangements are finalized, inform receiver of time and manner of transport.

Annex 2: Collection and handling throat swabs for viral culture.

NB: Ideally, throat swab samples for virus isolation should be collected simultaneously with the blood samples for serological confirmation. Collection of specimens for virus isolation should not be delayed until laboratory confirmation of a suspected case of CRS is obtained.



* VTM = HBSS plus 0.5% BSA plus Pen/Strep **OR** Cell culture medium with 2% FCS

Handling and transport of throat swabs

Oropharyngeal specimens for virus isolation must be collected as soon as possible, when the virus is present in high concentration. The tongue should be depressed with a spatula, and a throat swab obtained by firmly rubbing the pharyngeal passage and throat with sterile cotton swabs to dislodge epithelial cells.

The swab is then placed in a labelled viral transport tube ensuring that the swab is immersed in the specimen tube containing the viral transport medium. The tube is transported to the laboratory on cold chain using ice packs and appropriately insulated shipping container.

Annex 3- CRS surveillance logbook

A CRS surveillance logbook should be kept at each site. All cases reported to the health facility surveillance focal person (HSFP) should be logged into the logbook, regardless if it met the definition or not. The logbook should contain the following columns.

- Name of patient
- Medical Record number
- Clinic where case identified
- Date of birth
- Age (months) when notified to surveillance system
- Sex
- Town and LGA of residence
- Parent contact number
- Identifying clinician
- Clinician contact number
- Chart reviewed (yes/no)
- Presenting symptoms
- Case met suspect case definition (yes/no)
- Case reported (yes/no)
- EPID number
- Serum specimen collected (date or 'not done')
- Throat swab specimen collected (date or 'note done')
- Final classification

Annex 4- Roles and responsibilities

National Rubella Expert Committee (NREC):

- This will consist of 5-7 members that will provide a supervisory oversight of the congenital rubella syndrome surveillance activities in Nigeria.
- The committee will be chaired by Chairman with a secretary and three other members.
- NCDC will be the secretariat.

NCDC Measles/Rubella Focal Person

- Oversight and supervision of CRS surveillance implementation
- Liaising with hospitals and other partners concerning CRS surveillance activities and findings
- Sharing findings from CRS surveillance with partners
- Provide supportive supervision to sites
- Ensure case investigation forms are complete and entered electronically
- Support the functioning of NREC

NCDC Data Manager

- Ensure data entered into surveillance database is complete
- Cleaning of surveillance database data (e.g. removing duplicates)
- Ensure laboratory data is linked with the case investigation form data
- Generate quarterly reports

LGA Disease Surveillance and Notification Officer (DSNO)

- Provide EPID numbers to sites in lists of 5-10
- Receive notification for awareness of suspect CRS cases from HSFP
- Review results from sentinel-site the LGA
- Receipt of case investigation forms
- Ensure forms are completed
- Forward data on CRS cases diagnosed within the LGA to State epidemiologist

State Epidemiologist/DSNO

- Collation of data from all LGA surveillance officers
- Review sentinel site surveillance data

CPHL Laboratory Focal Person

- Responsible for maintaining stocks of laboratory reagents
- Responsible for receiving and processing samples within 3 days of specimen receipt

- Responsible for sharing laboratory results with 1) Health facility surveillance focal person (HSFP), 2) CRS Data Manager, 3) District Surveillance Medical Officer

Clinicians/Nurses at site

- Awareness of CRS symptoms and how they relate to cases admitted to ward
- Notification of all infants meeting suspect case definition to health facility surveillance focal person
- Collection of serum and throat swabs

Health facility surveillance focal person (HSFP)

- Should be public health or other specialty health officer
- Maybe focal person for another sentinel-site surveillance
- Attendance at annual review meetings
- Sensitizing hospital staff for CRS surveillance
- Investigating cases, completing case report forms
- Entering case investigation data into electronic database
- Collecting specimens (or ensuring collected) and sending them to lab for processing
- Informing treating clinician of laboratory results
- Review clinic registers to ensure all cases reported
- Maintain CRS surveillance case logbook

Hospital CRS Surveillance Coordinator

- Responsible for ensuring clinicians are sensitized
- Attendance at annual review meetings
- Sharing progress of surveillance with hospital leadership
- Support trouble shooting with HSFP to ensure cases identified and investigated

Hospital laboratory, departmental head or designated focal person

- Receiving and preparing specimens for transport, same as measles surveillance protocol
- Maintain CRS surveillance specimen register

WHO Measles/Rubella Focal Person

- Support CPHL to receive and maintain stock of CRS surveillance reagents
- Provide supportive supervision
- Participate in regular review meetings

Annex 5-Case investigation form

Reporting site: _____EPID Number_____
Name of person reporting:_____Designation:_____Telephone:_____
Clinician:_____Designation:_____Telephone:_____
Date of notification: _____/_____/_____ Date of Investigation:_____/_____/_____

1. Patient Details

Patient's Name: _____
Father's Name: _____
Mother's Name: _____
Ward/LGA/State : _____
Contact mobile number: _____

Sex: Male / Female
Date of birth:____/____/____
Age: months _____ days _____
Only report children less than 12 months at investigation
Patient hospital ID # _____

2. Clinical Signs and Symptoms ***[NOTE: Y=Yes, N=No, U=Unknown]***

Place of birth (Ward/LGA/State): _____ ☐ Home ☐ Health facility ☐ Unknown
Gestation age at birth: weeks _____ ☐ Unknown Birth weight: grams _____ ☐ Unknown

Group A Defects (please complete all)		**Group B Defects** (please complete all)	
Cataracts	**Bilateral / Unilateral N U**	Purpuric rash	**Y N U**
Congenital glaucoma	**Y N U**	Microcephaly	**Y N U**
Pigmentary retinopathy	**Y N U**	Developmental delay	**Y N U**
Hearing impairment or deafness	**Y N U**	Splenomegaly	**Y N U**
Congenital heart disease (specify type)	**Y N U**	Meningoencephalitis	**Y N U**
☐ Patent ductus arteriosus (PDA)		Radiolucent bone disease	**Y N U**
☐ Peripheral pulmonary stenosis (PPS)		Jaundice, within 24 hours of birth	**Y N U**
☐ Ventricular septal defect (VSD)			
☐ Other heart defect (specify): _____			

Other symptoms:
Other diagnosed syndromes: ☐ Down's Syndrome ☐ HIV+ ☐ Congenital Syphilis ☐ Other_____
Outcome: Alive Died: date ____/____/____ Unknown
Notifying clinic: Pediatric -Inpatient / Nursery / EPU / CHER / OPD / Eye / ENT / Cardiology / Other :_____

3. Maternal History

Total number children: _____ Mother's age at birth of infant patient: _____years

Illness during pregnancy

Conjunctivitis	**Y N U**	If yes, date of onset: ____/____/____	Month of pregnancy:
Maculopapular rash	**Y N U**	If yes, date of onset: ____/____/____	Month of pregnancy:
Lymph nodes swollen	**Y N U**	If yes, date of onset: ____/____/____	Month of pregnancy:
Arthralgia/arthritis	**Y N U**	If yes, date of onset: ____/____/____	Month of pregnancy:
Other complications	**Y N U**	If yes, date of onset: ____/____/____	Month of pregnancy:

Laboratory -confirmed rubella in the mother: **Y N U** If yes, date: ____/____/
Known exposure during pregnancy to any person with maculopapular rash (not vesicular) illness with fever? **Y N U**

If yes, date: ____/____/____ Month of pregnancy: _____ Ward/LGA/State :_____

EPID Number: _____

4. Laboratory specimen collection

Specimen(s) collected:	**Y N U [Note: infants 6 to <12 months old, likely need 2nd blood to confirm]**		
Serology	1st Blood	Date taken: ___/___/___	Date sent: ___/___/___
	2nd Blood	Date taken: ___/___/___	Date sent: ___/___/___
Viral detection	Throat swab	Date taken: ___/___/___	Date sent: ___/___/___

5. Results and Final Classification [To be completed by CPHL]

Serology

Date 1st serum received at CPHL: ___/___/___ Date tested: ___/___/___ ☐ Adequate ☐ Not adequate

Date 2nd serum received at CPHL: ___/___/___ Date tested: ___/___/___ ☐ Adequate ☐ Not adequate

Rubella IgM: **1. Positive 2. Negative 3. Equivocal 4. Pending 8. Not done 9. Unknown**

Date of results sent to site: ___/___/___

Viral Detection

Date received at CPHL: ___/___/___ Date sent to RRL: ___/___/___ Date received result: ___/___/___

Date received at CPHL: ___/___/___ Date sent to RRL: ___/___/___ Date received result: ___/___/___

Date received at CPHL: ___/___/___ Date sent to RRL: ___/___/___ Date received result: ___/___/___

Rubella virus detected: 1. Detected 2. Not detected ☐ Not done

Rubella PCR: **Genotype __ ☐ No Result ☐ Pending ☐ Not done ☐ Unknown**

Date of conclusive lab result: ___/___/___

6. Final Classification [To be completed by National Department of Health Surveillance Unit]

Date form received at NCDC: ___/___/___ Date result returned to reporting institution: ___/___/___

Final Out come: Alive Died: date ___/___/___ Unknown

Final Classification: **1. Lab-confirmed CRS 2. Clinically-compatible CRS 3. Congenital rubella infection**

4. Discarded (specify): _____ **5. Pending 6. Unknown**

Definitions

Suspected CRS case: Infant <12 months with cataract(s), or congenital glaucoma, or hearing impairment, or congenital heart disease, or purpura, or suspected TORCH infection, or mother with suspected/confirmed rubella in pregnancy

Clinical criteria for a CRS case: Presence of ≥2 clinical features from (A), or 1 feature from (A) and ≥1 from (B), as follows:

A) Cataract(s)/congenital glaucoma,* pigmentary retinopathy, sensorineural hearing impairment, congenital heart disease (most commonly patent ductus arteriosus or peripheral pulmonary stenosis).

B) Purpura, hepatosplenomegaly, jaundice (within 24 hours of birth), microcephaly, developmental delay, meningoencephalitis, radiolucent bone disease.

* For clinically-confirmed cases, cataracts and congenital glaucoma count as single clinical feature from (A).

Laboratory criteria for a CRS case

- Detection of rubella IgM antibodies in serum
- Sustained rubella IgG antibody level on ≥2 occasions between 6 and 12 months of age in the absence of rubella vaccination
- Detection of rubella virus by culture or RT-PCR

Annex 6: Copy of CRS surveillance logbook

S/No	Name	Medical Record Number	Clinic where case identified	Date of birth	Age (months) when notified to surveillance system	Sex	Town of residence	Parent contact number	Identifying clinician	Clinician contact number	Chart reviewed (yes/No)	Case met suspect case definition (yes/no)	Case reported (yes/no)	EPID number	Serum specimen collected (date or 'not done')	Throat swab specimen collected (date or 'not done')	Final classification
1																	
2																	
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Table 2: List of Contributors

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