Guidelines for the Documentation and Verification of Measles, Rubella, and Congenital Rubella Syndrome Elimination in the Region of the Americas

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In the region of the Americas, goals for the elimination of endemic measles and rubella/congenital rubella syndrome (CRS) by the year 2000 and 2010, respectively were established. The successful implementation of measles elimination strategies in the region of the Americas resulted in the interruption of endemic measles transmission in 2002 and tremendous progress toward rubella and CRS elimination. In October 2007, the 27th Pan American Sanitary Conference adopted Resolution CSP27.R2 urging member states to begin documenting and verifying the interruption of endemic transmission of the measles and rubella viruses in the Americas. To ensure a standardized approach for the process of documentation and verification, the Pan American Health Organization/World Health Organization (PAHO/WHO) developed a regional plan of action to guide countries and their national commissions as they prepare and consolidate evidence of the interruption of endemic measles and rubella transmission. This article summarizes the plan of action including the essential criteria and components of the guidelines.

In 1994, polio elimination was certified in the region of the Americas of the World Health Organization (WHO) [1, 2] along with the adoption of a goal of measles elimination by 2000 [3]. The success of the measles elimination activities documented the widespread rubella circulation; in 1999 the Pan American Health Organization (PAHO) Technical Advisory Group (TAG) recommended a regional initiative to accelerate rubella control and congenital rubella syndrome (CRS) prevention. In 2002, endemic measles virus transmission had been interrupted. In 2003, with the successes of measles elimination in the region and accelerated rubella control and CRS prevention, the Directing Council of PAHO adopted Resolution CD44.R1 to eliminate rubella and CRS by 2010 [4]. In 2009, endemic rubella virus transmission appears to have been interrupted.

In 2007, with this tremendous progress toward the rubella/CRS elimination goals, the 27th Pan American Sanitary Conference, during its 59th Session of the Regional Committee, adopted Resolution CSP27.R2 [5]. The resolution requested member states to begin documenting and verifying the interruption of endemic measles and rubella virus transmission in the Americas and to develop a plan of action as a guide. This resolution also authorized the formation of an International Expert Committee responsible for documenting and verifying the interruption of endemic measles and rubella virus in the region of the Americas and urged member states to establish national commissions to document and verify measles and rubella elimination in each country.
The 2007 resolution set in motion the process for the documentation and verification of the interruption of endemic measles and rubella transmission in the Americas. To ensure a standardized approach for documentation and verification, PAHO has developed a regional plan of action (POA) to guide countries and their national commissions as they prepare and consolidate evidence that endemic measles and rubella transmission has been interrupted. This article summarizes the components of the POA that will help to guide countries in documenting the elimination of measles, rubella, and CRS.

DEVELOPMENT OF THE REGIONAL PLAN OF ACTION

In early 2007, a multidisciplinary technical committee was formed to draft the plan of action and by May 2007, the draft plan was pilot-tested in Costa Rica and countries of the English-speaking Caribbean and territories. In August 2008, PAHO held a meeting of measles, rubella, and CRS experts to review and discuss the essential elements, including elimination indicators, to be incorporated into the regional POA. Some of the highlights of the meeting included incorporating the lessons learned from the global eradication of smallpox, the regional eradication of polio, and pilot testing of the draft plan of action [6]. With additional comments from experts in the field and members of the Technical Advisory Group (TAG) [7] and the International Expert Committee, the POA was finalized.

COMPONENTS OF THE PLAN OF ACTION

The POA is a standardized approach to guide countries in the documentation of the elimination of rubella and measles by providing the case definitions, basic principles, essential criteria, methodology, and data elements.

DEFINITION OF MEASLES AND RUBELLA ELIMINATION IN THE REGION OF THE AMERICAS

Measles Elimination in the Americas
Measles elimination is defined as interruption of endemic measles virus transmission in all the countries of the Americas for a period ≥12 months, in the presence of high-quality surveillance.

Rubella and CRS Elimination in the Americas
Rubella and CRS elimination is defined as interruption of endemic rubella virus transmission in all the countries of the Americas for a period ≥12 months without the occurrence of CRS cases associated with endemic transmission, in the presence of high-quality surveillance.

BASIC PRINCIPLES

Basic principles established include (1) the area for documentation is the region of the Americas and NOT individual countries or subregions; (2) an independent expert committee will provide guidance to the countries and will verify the achievement of elimination; and (3) each country will establish a national commission, with the exception of the Caribbean countries, where a sub-regional commission will be established.

ESSENTIAL CRITERIA

Three essential criteria were developed based on experiences with regional polio elimination and establishing the global measles elimination criteria and ongoing measles and rubella experiences with countries in the region of the Americas. Each one of these criteria cannot stand alone but should be evaluated and interrelated to support the argument for elimination.

- Verify the interruption of endemic measles, rubella, and CRS in all countries of the Americas for a period of at least 3 years from the last known endemic case, in the presence of high-quality surveillance.
- Maintain a high-quality surveillance system sensitive enough to detect imported and import-related cases.
- Verify the absence of endemic measles and rubella virus strains through viral surveillance in the region of the Americas.

GUIDELINES FOR DATA COLLECTION AND ANALYSIS OF THE EVIDENCE FOR DOCUMENTATION AND VERIFICATION

The following 6 components (Figure 1) will serve as lines of evidence to support the claim that measles and/or rubella/CRS elimination has been achieved. These lines of evidence will provide support that measles and/or rubella/CRS has been eliminated. Each of the components will be summarized below; a detailed description is provided in the POA [8].

Epidemiology of Measles, Rubella, and CRS
Epidemiological data analyses, in the presence of high-quality surveillance systems, provide the critical information on whether and when endemic transmission was interrupted. Using the measles/rubella (Table 1) and CRS (Table 2) case definitions, the analyses should include pre-interruption and post-interruption epidemiological periods to support the identification of a “breaking point,” or a point at which endemic virus interruption was achieved. Analyses to be conducted should include annual disease rates and incidence by case classification (eg, laboratory confirmed, import status); temporal and spatial characteristics; seasonality; and demographic characteristics of the cases. For outbreaks, a description of the epidemiology (eg,
number of cases, case classification, demographics) and investigation should be included. If molecular epidemiology is available, this information should be included in this section.

Countries and regions that have eliminated either measles or rubella will characteristically have low rate of or no disease, absence of seasonality, imported cases with little or no disease spread, few and small outbreaks, and few CRS cases.

**Quality of Measles, Rubella, and CRS Surveillance Systems**

Because the interpretation of the epidemiological data is dependent on the data from the surveillance systems, the integrated measles-rubella and CRS surveillance systems must be of high quality. Several approaches can be used to determine the quality of the surveillance systems including use of indicators for routine surveillance, and the use of active and retrospective case searches.

The routine surveillance systems should provide timely and sufficient information based on preestablished quality indicators. One measure of high-quality surveillance is to monitor the following indicators: reporting rate, adequate investigation for both suspected and confirmed cases, laboratory confirmation, and viral detection (Table 3, 4).

Another approach to monitor the adequacy of the surveillance system is active measles and rubella case searches to identify suspected cases, document the absence of cases, and identify strengths and weaknesses in the surveillance system. Active case searches are particularly useful in outbreak situations to identify the primary case, secondary cases, and contacts that may occur within the corresponding incubation period (detect recent circulation within the past month). Active searches should also be considered in high-risk areas, which include silent areas or areas that do not adhere to weekly reporting standards and areas with low vaccination coverage (<95% per municipality).

To document the absence of CRS cases, it is necessary to complement routine reporting systems with the retrospective search for suspected CRS cases using various sources of information for at least the last 3 years. This methodology will assess the quality of reporting by identifying cases that were not reported to the surveillance system, identify reservoirs of viral transmission, evaluate the impact of elimination strategies, and contribute to the documentation of the interruption of endemic rubella virus transmission in the region.

Post elimination, countries are encouraged to coordinate with dengue surveillance to process a percentage of dengue samples with negative laboratory results for measles and rubella from cases presenting fever and rash and identified in high-risk areas (ie, silent municipalities and areas where dengue circulation has been detected).

**Molecular Epidemiology of Measles and Rubella Viruses and Laboratory Activities**

Molecular epidemiologic data are used to verify that elimination has been achieved by documenting the interruption of transmission of endemic viruses. The genetic information obtained provides baseline for the circulating strains including endemic and imported strains. After elimination has been achieved, the molecular epidemiological information from the new cases can be compared with the pre-elimination endemic viral strain baselines.

For measles, between 1995 and 2001, D6 circulated in the region of the Americas but transmission was successfully interrupted in the Dominican Republic and Haiti, effectively ending known endemic transmission of the D6 measles virus genotype.
However, in 2001, a European tourist introduced the D9 measles virus genotype to Venezuela, which spread to additional countries in the region; D9 virus transmission was interrupted in November 2002, finalizing the interruption of endemic measles virus transmission in the Western hemisphere.

Despite limited molecular epidemiological information, the endemic rubella virus genotype 1C has been identified as endemic in the Americas because it has frequently been found in the region and has not been identified in other regions of the world. The last occurrence of 1C virus transmission was identified in 2005 in Chile and Peru. In 2006, the genotype 2B was isolated during the last rubella outbreaks reported in Brazil, Chile, and Argentina; however, 2B is no longer endemic in the Americas with the last endemic case identified in Argentina in February 2009.

With the importance of molecular typing of virus strains, evaluation of different types of specimens (eg, urine, throat, serum) has shown that virus can be isolated from sera. In the initial visit, usually only a serum specimen is obtained but not urine or throat specimens.

Each national laboratory should produce surveillance information of the highest possible quality in order to document that measles and rubella elimination has been achieved. To this end countries should report the following: 1) quality control, 2) case classification and laboratory testing for sporadic cases, 3) molecular epidemiology, 4) laboratory surveillance for CRS, virus detection and virus shedding, and 5) adequate receipt of the samples and resources.

**Vaccinated Population Cohorts**

To achieve and maintain elimination of measles, rubella, and CRS, high levels of population immunity, particularly for measles, are required. For most countries in the region, this was accomplished through the recommended PAHO vaccination strategy. With the recommended strategies, all population cohorts \( \geq 40 \) years of age, as well as those cohorts that correspond to the year of campaign implementation, should be protected against measles and rubella.

To assess the coverage, countries should review and analyze data from administrative reports of vaccinated persons and results from rapid coverage monitoring and coverage surveys (when applicable). The analysis will also allow countries to determine if high coverage has been sustained over time at the municipality, department/state, and

<table>
<thead>
<tr>
<th>Table 1. Operational Case Definition: Measles and Rubella</th>
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<td>Suspected case:</td>
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<tr>
<td>A patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash.</td>
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<tr>
<td>Case confirmed by laboratory testing or by epidemiological link:</td>
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<tr>
<td>A suspected measles or rubella case that has positive laboratory results or is epidemiologically linked to a laboratory-confirmed case.</td>
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<tr>
<td>Clinically confirmed case:</td>
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<tr>
<td>A suspected case with inadequate laboratory investigation and lacking evidence of any other etiology (considered deficiencies in the surveillance system). These cases should be discussed and decided (confirmed or discarded) by the national commission on documentation and verification.</td>
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<tr>
<td>Discarded case:</td>
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<tr>
<td>A suspected case with adequate investigation and with negative laboratory results.</td>
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<td>Endemic case:</td>
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<tr>
<td>A confirmed case that, as supported by epidemiological and virologic evidence, indicates that it is part of a chain of endemic transmission, meaning that the isolated virus has been circulating in the Americas for a period ( \geq 12 ) months.</td>
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<tr>
<td>Imported case:</td>
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<tr>
<td>A confirmed case that, as supported by epidemiological and/or virologic evidence, the patient was exposed outside the Americas during the 7–21 days prior to rash onset for measles, or from 12 to 23 days for rubella.</td>
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<tr>
<td>Import-related case:</td>
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<tr>
<td>A locally acquired infection occurring as part of a chain of transmission originated by an imported case as supported by epidemiological or virological evidence, or both. (Note: if transmission of measles cases related to importation persists for ( \geq 12 ) months, cases are no longer considered to be import-related, they are considered to be endemic.)</td>
</tr>
<tr>
<td>Unknown source case:</td>
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<tr>
<td>A confirmed case for which the source of infection was not identified.</td>
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<td>Re-establishment of endemic transmission:</td>
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<tr>
<td>Occurs when epidemiological and laboratory evidence indicates the presence of a chain of transmission of a virus strain that continues uninterrupted for ( \geq 12 ) months in a defined geographical area.</td>
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* Laboratory results:
  - Positive serologic test for rubella immunoglobulin M (IgM) antibody.
  - Significant rise between acute and convalescent-phase IgG titers for the diagnose of measles and rubella infection. This is not applicable to CRS. Isolation of rubella virus.
  - Detection of virus by reverse-transcription polymerase chain reaction.
  - Genetic sequencing of measles and rubella virus.
Table 2. Operational Case Definition: Congenital Rubella Syndrome

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<tr>
<th>Case Definition</th>
<th>Criteria</th>
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<tr>
<td>Congenital rubella syndrome (CRS) suspected case:</td>
<td>An infant aged ≤1 year in whom a health-care worker suspects CRS due to:</td>
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<td></td>
<td>1. One or more of the following birth outcomes detected:</td>
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<td>congenital cataracts, congenital heart defects, purpura at birth, or hearing impairment, and/or</td>
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<td></td>
<td>2. History of confirmed or suspected maternal rubella infection during pregnancy.</td>
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<td>Laboratory-confirmed case:</td>
<td>A clinically consistent case that has positive laboratory results.a</td>
</tr>
<tr>
<td>Clinically confirmed case:</td>
<td>A suspected case that is not laboratory confirmed and lacks evidence of any other etiology. This usually occurs due to a loss of follow-up or inadequate collection of specimens for laboratory diagnosis. This is considered a failure in the surveillance system.</td>
</tr>
<tr>
<td>Endemic case:</td>
<td>An infant with confirmed CRS whose mother acquired rubella in the Americas and, as supported by epidemiological and virologic evidence, indicates that it is part of a chain of endemic transmission, meaning that the isolated virus has been circulating in the Americas for a period ≥12 months.</td>
</tr>
<tr>
<td>Imported case:</td>
<td>A confirmed case of an infant whose mother acquired the rubella virus infection outside the Americas or, in the absence of documented rubella infection, the mother was outside the Americas during the period when she may have had exposure to rubella that affected her pregnancy (from 23 days prior to conception to week 24 of gestation).</td>
</tr>
<tr>
<td>Import-related case:</td>
<td>A confirmed case of an infant whose mother, as supported by epidemiological and/or virologic evidence, was exposed locally as part of a transmission chain that initiated with an imported case.</td>
</tr>
<tr>
<td>Congenital rubella infection:</td>
<td>An infant with enzyme-linked immunosorbent assay IgM-positive results for rubella at birth who presents with no clinical signs of CRS. Case requires clinical assessment, including the ruling out of deafness by an adequate procedure.</td>
</tr>
</tbody>
</table>

**NOTE:** a Laboratory results:
- Positive serologic test for rubella immunoglobulin M (IgM) antibody.
- Significant rise between acute and convalescent-phase IgG titers for the diagnosis of measles and rubella infection. This is not applicable to CRS. Isolation of rubella virus.
- Detection of virus by reverse-transcription polymerase chain reaction.
- Genetic sequencing of measles and rubella virus.
- For CRS diagnosis: infant rubella antibody level that persists at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titer that does not drop at the expected rate of a 2-fold dilution per month).

national levels, as well as among population cohorts and age groups targeted in routine and supplementary vaccination activities.

The analysis should begin with the year of vaccine introduction in the country, the different vaccination strategies used, and corresponding target age groups. This information will allow for the estimation of population cohorts vaccinated against measles and rubella.

Countries may want to include other sources such as seroprevalence studies (if available). In the United States, using National Health and Nutrition Examination Survey data collected during 1988–1994 and 1999–2004, it was demonstrated...
that the levels of rubella seropositivity were consistent with targeted groups for immunization. This provided additional evidence that rubella virus had not circulated widely during those time periods and therefore elimination had been achieved.

**Sustainability of the National Immunization Program**

Political commitment at all levels, an efficient organization, and a favorable economic and legal environment have been fundamental conditions to ensure that national immunization programs of the Americas are considered successful over time.

The elimination of measles, rubella, and CRS must be sustained, so assessing the sustainability of national immunization programs is necessary in order to evaluate how well these programs will be able to maintain the goal. The analysis of national immunization programs will also highlight how these programs contribute to the essential elements of the elimination process:

- Sustained and homogeneous vaccination coverage, ≥95%, with strategies and tactics in place to assure 2 measles-mumps-rubella vaccine opportunities.
- A sensitive and efficient surveillance system that detects, reports, and investigates all measles and rubella cases in a rapid and timely manner. The participation of the private sector is fundamental and implies continued collaboration with this sector.
- An efficient laboratory with the capacity to conduct serological diagnosis and virus detection and isolation when facing imported and sporadic cases.

**Correlation and Integration of the Evidence for Elimination**

No single component can stand alone; however, comparing and contrasting the different lines of evidence for consistency among the different components provides support needed to document elimination. These components mainly include epidemiology of measles, rubella, and CRS; the quality of surveillance; molecular epidemiology; the analysis of vaccinated population cohorts; and the sustainability of the national immunization program. The process of correlating and integrating the evidence from the various sources of information will allow countries to determine whether the available data are valid, complete, representative, and consistent.

**DISCUSSION**

The region of the Americas has met the elimination goals for both measles in 2002 and rubella/CRS in 2009 [9]. With these successes, countries in the region are embarking on the next phase of documenting those achievements. There has been much progress to date: the International Expert Committee has been established, almost all countries and overseas departments have established national commissions, and the rest of the countries are in the process of establishing their commissions.

As part of the process of developing the plan of action, several decisions were made, including: (1) the area for documenting the interruption of endemic transmission is the Region of the Americas, and (2) the waiting period would be 3 years after the last endemic case. As with the polio experience, even though each country must go through the documentation process, all the countries in the region will be considered as one area that will be verified for elimination of endemic rubella and measles virus transmission. Even though the assessment will be done on a regional basis, if any one country has not documented elimination, then the elimination within the region cannot be verified.

For the region to be verified, the region will need to provide evidence that no endemic measles and rubella virus was circulating in the presence of high-quality surveillance for a period of at least 3 years. The reason for the 3 years is to provide enough time to have certainty in the presence of high-quality surveillance and high population immunity that the rubella virus has been interrupted. Even with the initial evidence for documentation of interruption of measles and rubella virus transmission, countries will still need to provide evidence for maintaining elimination in their countries.

In the POA, principles, essential criteria, and components are provided to assist in documentation of elimination. In collaboration with the countries’ national immunization programs, each national commission will prepare a report to present evidence that endemic circulation has been interrupted, and proving a negative is more challenging to do. Using the lines of evidence to support elimination has been achieved, and
countries provide support; however, none of these components can alone provide the absolute proof of elimination. Through interrelating the various lines of evidence, the support for interruption of endemic transmission will be achieved.

As other WHO regions make progress toward achieving elimination of measles and rubella, this plan of action and lessons learned from the region of the Americas will help to provide guidance [10].

References