

Framework for Verifying Elimination of Measles and Rubella

SAGE Working Group on Measles and Rubella

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Preamble

The Global Vaccine Action Plan 2012-2020, established the target of eliminating measles and rubella in at least 5 WHO Regions by 2020. The SAGE Working Group on Measles and Rubella has prepared revised guidance on how to monitor progress towards and verify elimination of measles and rubella to ensure alignment between the activities of different regions. This guidance, or framework, builds on the experience gained so far in regions and countries, and provides an approach to integrating rubella surveillance into measles and rubella elimination activities.

This framework is developed for settings where the aim is to interrupt transmission of both measles and rubella, and the revisions to all the elements are tailored for that context. Modified definitions and indicators may be appropriate in settings where measles and/or rubella are still endemic.

It is also recognized that not all countries will be able to measure all the indicators laid out below, and alternative and complementary lines of evidence may be used to verify elimination of measles and rubella. The aim is to balance standardization against the need for flexibility to accommodate differences in national health systems.

This document does not cover definitions and surveillance indicators for determining the elimination of congenital rubella syndrome (CRS). An approach to verifying the elimination of CRS in the Region of the Americas has been published by Castillo et al (2011)¹ and fieldwork is ongoing to evaluate approaches to CRS surveillance in other regions.

Principles and process

The achievement of measles and/or rubella elimination should be verified for individual countries and areas and eventually for each of the WHO Regions as a whole following a standard process. While each region may adapt the process to its specific situation, the basic principles and process should be common to all regions.

At country level, a national verification committee should be established to conduct an annual review of progress towards elimination. This committee does not have authority to verify elimination; rather it's role is to help countries document progress towards elimination by gathering, analyzing and validating the national data and submitting the necessary documentation to the regional verification commission. The national committees should be multi-disciplinary including laboratory, epidemiological, public

¹ Castillo-Solorzano C, Reef SE, Morice A, et al. Guidelines for the Documentation and Verification of Measles, Rubella, and Congenital Rubella Syndrome elimination in the Region of the Americas. *Journal of Infectious Diseases* 2011;204:S683–S689.

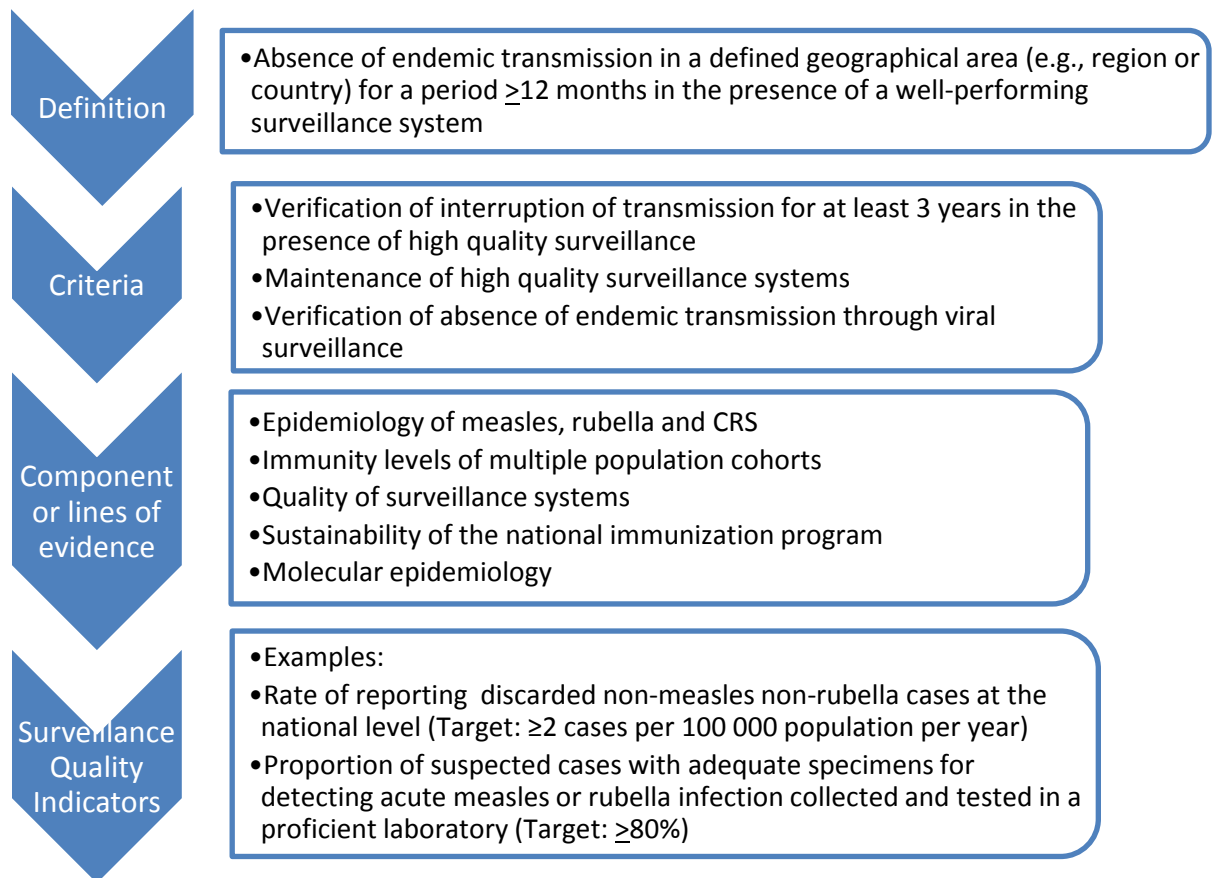
health, and clinical expertise. As far as possible the members should not be involved in the day-to-day management of the national immunization or surveillance activities. In addition to national-level data, disaggregated data should be assessed at the 3rd administrative level (i.e., district, municipality, county, or equivalent administrative unit with a population size of no more than 500,000). Also, information should be analysed on populations served by the private sector and underserved subpopulations (e.g., minorities, migrants, or marginalized communities) who may fall outside the national health and surveillance systems because these groups have been shown to be important for sustaining measles and rubella transmission.

At regional level, a regional verification commission should conduct an annual review to determine progress towards and accomplishment by individual countries of measles and/or rubella elimination. Verification of elimination for the region as a whole is possible when all countries are able to document interruption of endemic virus transmission for a period of 36 months or more. Members of the regional verification commission should be recognized leaders with expertise in the fields of public health, epidemiology, laboratory science, clinical medicine, and social sciences. They should be independent of the day-to-day management of national immunization programmes and conflicts of interest should be sought and declared.

Conceptual Framework

A framework for thinking about the evidence to be assembled to monitor progress towards and eventual elimination of measles and rubella includes explicit definitions, criteria for elimination, lines of evidence, and indicators of the quality of field and laboratory surveillance (Figure 1).

Figure 1. Hierarchy of evidence for verification of elimination



Definitions

Table 1. Definitions for verifying measles and rubella elimination

Word or Phrase	Definition
Measles or rubella eradication	worldwide interruption of measles or rubella virus transmission in the presence of a surveillance system that has been verified to be performing well
Measles elimination	<p>the absence of endemic measles transmission in a defined geographical area (e.g., region or country) for ≥ 12 months in the presence of a well performing surveillance system</p> <p>Note: <u>verification</u> of measles elimination takes place after 36 months of interrupted measles virus transmission</p>

Rubella elimination	<p>the absence of endemic rubella virus transmission in a defined geographical area (e.g., region or country) for ≥ 12 months and the absence of CRS cases associated with endemic transmission in the presence of a well performing surveillance system</p> <p>Note: There may be a lag (up to 9 months) in occurrence of CRS cases after interruption of rubella virus transmission has occurred. Evidence of the absence of rubella transmission from CRS cases is needed because CRS cases excrete rubella virus for up to 12 months after birth.</p> <p>Note: <u>verification</u> of rubella elimination takes place after 36 months of interrupted rubella virus transmission.</p>
Endemic measles or rubella virus transmission	the existence of continuous transmission of indigenous or imported measles virus or rubella virus that persists for ≥ 12 months in any defined geographical area
Endemic measles or rubella case	laboratory or epidemiologically-linked confirmed cases of measles or rubella resulting from endemic transmission of measles or rubella virus.
Re-establishment of endemic transmission	<p>occurs when epidemiological and laboratory evidence indicates the presence of a chain of transmission of a virus strain that continues uninterrupted for ≥ 12 months in a defined geographical area (region or country) where measles or rubella had been previously eliminated</p> <p>Note: a measles or rubella virus strain is determined by sequencing the WHO standard 450nt region of the N gene for measles and the 739nt of the E1 gene for rubella.</p>
Measles or rubella outbreak in an elimination setting	a single laboratory confirmed case
Suspected case of measles or rubella	a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular (non-vesicular) rash
Laboratory confirmed measles case or rubella case	<p>a clinically-compatible case of measles or rubella that has been confirmed by a proficient laboratory</p> <p>Note: a <u>proficient</u> laboratory is one that is WHO accredited and/or has an established quality assurance programme</p>
Epidemiologically-linked confirmed	a clinically-compatible case of measles that has not been confirmed by a laboratory but that was geographically and temporally related (with dates of rash onset occurring between 7 and 21 days apart) to a laboratory-

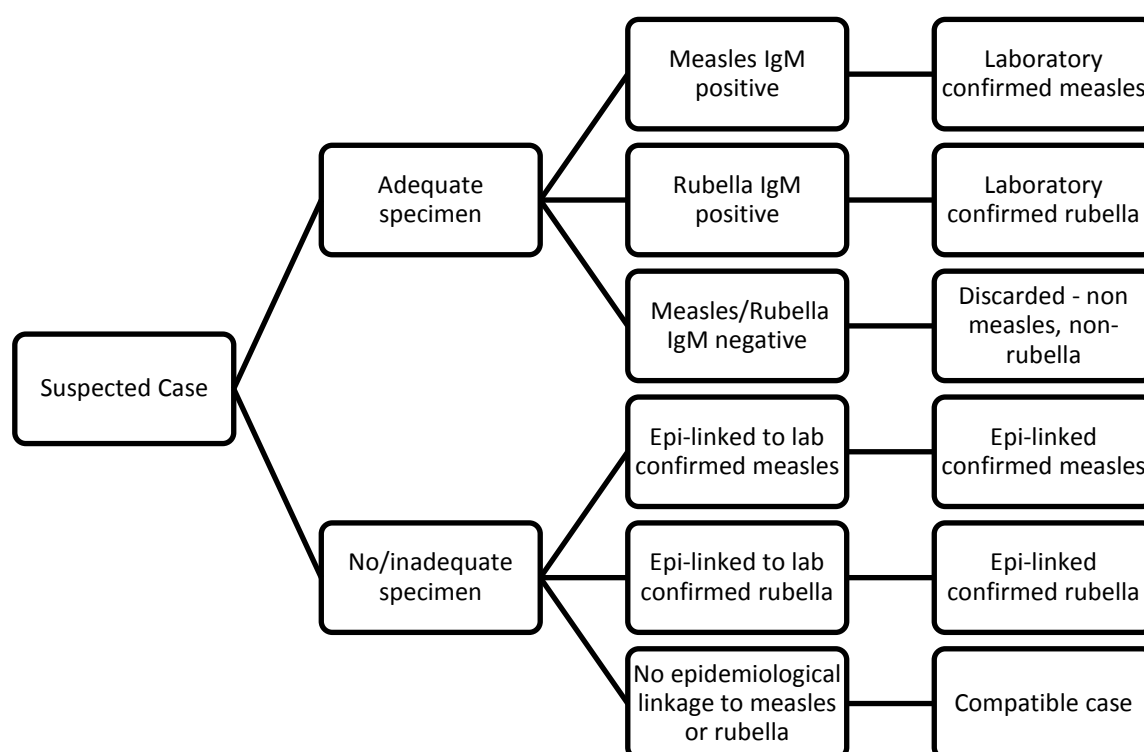
measles case	confirmed case or (in the event of a chain of transmission) to another epidemiologically confirmed measles case
Clinically-compatible measles case	a case with fever and maculopapular (non-vesicular) rash and one of cough, coryza, or conjunctivitis but for which no adequate clinical specimen was taken and which has not been linked epidemiologically to a laboratory confirmed case of measles or another laboratory-confirmed communicable disease
Clinically-compatible rubella case	a case with maculopapular (non-vesicular) rash and fever (if measured) and one of arthritis/arthralgia or lymphadenopathy but for which no adequate clinical specimen was taken and which has not been linked epidemiologically to a laboratory confirmed case of rubella or another laboratory-confirmed communicable disease
Non-measles non-rubella discarded case	a suspected case that has been investigated and discarded as a non-measles and non-rubella case using (a) laboratory testing in a proficient laboratory or (b) epidemiological linkage to a laboratory-confirmed outbreak of another communicable disease that is neither measles nor rubella
Measles vaccine-associated illness	a suspected case that meets all 5 of the following criteria: (i) the patient had a rash illness, with or without fever, but did not have cough or other respiratory symptoms related to the rash; (ii) the rash began 7–14 days after vaccination with a measles-containing vaccine; (iii) the blood specimen, which was positive for measles IgM, was collected 8–56 days after vaccination; (iv) thorough field investigation did not identify any secondary cases; and (v) field and laboratory investigations failed to identify other causes. Alternatively, a suspected case from whom virus was isolated and found on genotyping to be a vaccine strain.
Imported measles or rubella case	<p>a case exposed outside the region or country during the 7–21 days (12-23 days for rubella) prior to rash onset and supported by epidemiological or virological evidence, or both.</p> <p>Note: for cases that were outside the region or country for <u>only a part</u> of the 7-21 day interval (12-23 day interval for rubella) prior to rash onset, additional evidence including a thorough investigation of contacts of the case, is needed to exclude a local source of infection.</p>
Importation-related measles or rubella case	<p>a locally acquired infection occurring as part of a chain of transmission originating from an imported case as supported by epidemiological or virological evidence, or both.</p> <p>Note: if transmission of measles or rubella cases related to importation</p>

	persists for ≥ 12 months, cases are no longer considered to be import-related, they are endemic.
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Case classification

Countries nearing elimination of measles and/or rubella, should immediately investigate all suspected cases and obtain a clinical specimen for laboratory testing. Once the case investigation form has been completed and laboratory test results are available, suspected cases should be classified according to the algorithm below.

Figure 1. Flow chart for classification of suspected cases



Criteria for verifying elimination

Three criteria for verifying elimination are recommended based on experience with assessing measles and rubella elimination in the Region of the Americas. They are:

- documenting the interruption of endemic measles, or rubella, virus transmission for a period of at least 36 months from the last known endemic case
- the presence of a high-quality surveillance system that is sensitive and specific enough to detect imported and import-related cases, and
- genotyping evidence supporting interruption of endemic transmission.

All 3 criteria are necessary to verify elimination at the regional level. As some small countries may not have genotyping information prior to interruption of endemic transmission, this criterion is not an absolute requirement for determining if elimination has been achieved at the country level.

Lines of evidence

Five lines of evidence, or components, should be considered by the regional verification commission when determining whether a country or the region as a whole has achieved elimination:

1. Epidemiology of measles and rubella over at least the past 60 months and description of the epidemiology including programmatic changes. Where available, summary information since the introduction of measles and rubella vaccine should also be reviewed.

Analyses of the epidemiological data from high-quality surveillance systems provide the critical information on whether and when endemic virus transmission has been interrupted. Standard case definitions and case classification systems should be used (see Definitions and Figure 1). The analyses should include the pre-interruption and post-interruption epidemiological periods to support the identification of a time-point at which endemic virus interruption was achieved. Analyses to be conducted should include annual disease incidence rates and case numbers by case classification; temporal and spatial characteristics; seasonality; and demographic characteristics of the cases. For outbreaks, a description of the epidemiology (e.g., by person, time and place) as well as any results from case-control or cohort studies should be included. Countries and regions that have eliminated either measles or rubella will characteristically have low rates of or no disease, absence of seasonality, imported cases with little or no disease spread, and few outbreaks of which most will be of small size.

2. Population immunity presented as a birth cohort analysis with the addition of evidence related to any marginalized and migrant groups per birth cohort

To achieve and maintain elimination of measles and rubella high levels of population immunity are required. Assuming nearly all persons born before vaccine introduction have natural immunity against measles, it is sufficient to document measles immunity for each annual cohort born since the introduction of measles vaccine in the national immunization schedule. For rubella, countries need to assess the epidemiology of rubella stratified by age groups to identify any susceptibility in the older age groups. A seroprevalence study may be needed to document the immunity in the older age groups. To assess coverage, countries should review and analyze data from administrative reports for routine delivery and supplementary immunization activities, as well as coverage surveys where available. This analysis should be available at the district/municipality, department/state, and national levels. This information will allow for the estimation of population immunity (= vaccination coverage x vaccine effectiveness) against measles and rubella. Countries may want to include other sources of immunity data such as well conducted seroprevalence studies.

3. Quality of laboratory and epidemiological surveillance systems for measles and rubella (see indicators)

Interpretation of the epidemiological data is dependent on the quality of the surveillance system for detecting and confirming measles and rubella. The performance of the surveillance system can be assessed by core indicators such as timeliness of reporting, the reporting rate, adequacy of case investigation, laboratory confirmation of sporadic cases and chains of transmission, and viral detection (see table below). Active case finding and use of retrospective case searches provide additional evidence of system performance and are particularly useful in outbreak situations to identify the primary case, secondary cases, and contacts that may occur within the corresponding incubation period. Active searches should also be considered in high-risk areas, which include silent areas or areas that do not achieve weekly reporting standards and areas with low vaccination coverage.

4. Sustainability of the National Immunization Program including resources for mass campaigns, where appropriate, in order to sustain elimination

The elimination of measles and rubella must be sustained, so assessing the sustainability of national immunization programs is necessary to ensure that these programs will be able to maintain the goal. Political commitment at all levels, efficient programme management, and a favorable economic and legal environment are fundamental requirements to ensure that national immunization programs are successful. Components that may be used to assess sustainability of the programme include:

- a. A current national plan for the elimination of measles and rubella
- b. Standard operating procedures at each level of the programme (e.g., a check list for conducting an immunization session)
- c. Evidence of vaccine demand forecasting and vaccine stock management
- d. Secured funding for vaccine procurement (e.g., a line item in the national budget for vaccine procurement and programme implementation).

5. Genotyping evidence that measles and rubella virus transmission is interrupted

Molecular epidemiologic data are used to verify that elimination has been achieved by documenting the interruption of transmission of endemic viruses. Prior to elimination, the genetic information obtained provides a baseline of the circulating strains including predominantly endemic strains and some imported strains. After elimination has been achieved, the molecular epidemiological information from the new cases can be compared with the pre-elimination endemic viral strains. The absence of previously endemic strains for ≥ 12 months with or without sporadic imported strains is consistent with elimination. For example, the rubella virus genotype 1C was identified as endemic in the Americas because it was frequently found in the region and had 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 rubella outbreaks reported in Brazil, Chile, and Argentina. However, 2B appears to be no longer present in the Americas with the last endemic case identified in Argentina in February 2009.

The individual lines of evidence should not be considered alone but rather should be evaluated together to establish the case for elimination. 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. The work of the Regional Verification Commission is to correlate and integrate the information from each line of evidence and make an overall determination as to whether elimination has been achieved and maintained or not.

Surveillance indicators

High quality epidemiological and laboratory data are required to allow a meaningful assessment of progress towards elimination. The routine surveillance system should provide sufficient and timely data based on pre-established performance indicators. Supplementary approaches to determine the quality of surveillance data include active and retrospective case searches and detailed field investigations conducted during outbreaks.

The set of core indicators that should be used to monitor the quality of field and laboratory surveillance are summarized below (Table 2). These include timeliness of reporting to the national level, the reporting rate of suspected cases, proportion of sporadic cases or chains of transmission laboratory confirmed, proportion of chains of transmission with genotyping information, adequacy of case investigations, time for specimens to reach the laboratory, and the turnaround time for laboratory results. For countries without systems in place to collect data on some of the core indicators, alternative analyses or additional indicators may be provided to allow assessment of surveillance system performance. For countries where substantial numbers of measles cases present to the private sector, additional evidence should be submitted to demonstrate that cases identified by the private sector are being adequately reflected in national surveillance data.

Table 2. Indicators of the quality of field and laboratory surveillance

Indicator	Description
Timeliness of reporting	Proportion of surveillance units reporting to the national level on time (Target: $\geq 80\%$) Proportion of countries reporting to their WHO Regional Office on time (Target: 100%) Proportion of Regions reporting to WHO Headquarters on time (Target: 100%) Note: At each level reports should be received <u>on or before the requested date</u>
Reporting rate of discarded non-measles non-rubella cases	Reporting rate of discarded non-measles non-rubella cases at the national level (Target: ≥ 2 cases per 100 000 population per year)

Representativeness of reporting	<p>Proportion of subnational administrative units (e.g., at the province level or its administrative equivalent) reporting at least 2 discarded non-measles non-rubella cases per 100,000 population (Target: $\geq 80\%$)</p> <p>Note: if the administrative unit has a population $< 100\,000$, then the rate should be calculated by combining administrative units to achieve a population of $\geq 100\,000$.</p>
Laboratory confirmation	<p>Proportion of suspected cases with adequate specimens for detecting acute measles or rubella infection collected and tested in a proficient laboratory (Target: $\geq 80\%$). Any suspected cases of measles that are not tested by a laboratory and are (a) confirmed as measles by epidemiological linkage or (b) discarded as non-measles by epidemiological linkage to another laboratory-confirmed communicable disease case should be excluded from the denominator of suspected cases.</p> <p>Note: <u>Adequate</u> specimens are: blood sample, minimum of 0.5 ml; dried blood sample, at least 3 fully filled circles on filter paper collection device; oral fluid, sponge collection device should be rubbed along the gum until the device is thoroughly wet (this usually takes one minute). Adequate samples <u>for serology</u> are those collected within 28 days after rash onset.</p> <p>Note: a <u>proficient</u> laboratory is one that is WHO accredited and/or has an established quality assurance programme</p>
Viral detection	<p>Proportion of laboratory-confirmed chains of transmission with samples adequate for detecting measles or rubella virus collected and tested in an accredited laboratory (Target: $\geq 80\%$). The numerator is the number of chains of transmission for which adequate samples have been submitted for viral detection and the denominator is the number of chains of transmission identified.</p> <p>Note: Where possible, samples should be collected from 5–10 cases early in a chain of transmission and every 2–3 months thereafter if transmission continues. For virus isolation, adequate throat or urine samples are those collected within 5 days after rash onset. For virus detection using molecular techniques, adequate throat samples are those collected up to 14 days after rash onset, and adequate oral fluid samples are those collected up to 21 days after rash onset.</p>

Adequacy of investigation	<p>Proportion of all suspected measles and rubella cases that have had an adequate investigation initiated within 48 hours of notification (Target: aim for 80%). The numerator is the number of suspected cases of measles or rubella for which an adequate investigation was initiated within 48 hours of notification and the denominator is the total number of suspected measles and rubella cases.</p> <p>Note: An <u>adequate</u> investigation includes collection of all the following data elements from each suspected measles and rubella case; name or identifiers, place of residence, place of infection (at least to district level), age (or date of birth), sex, date of rash onset, date of specimen collection, measles-rubella vaccination status, date of last MR vaccination, date of notification and date of investigation and travel history.</p> <p>Note: Some variables may not be required for cases that are either confirmed as measles by epidemiologic linkage (e.g., date of specimen collection)</p>
Timeliness of specimen transport	Proportion of specimens received at the laboratory within 5 days (Target: $\geq 80\%$)
Timeliness of reporting laboratory results	Proportion of results reported by the laboratory within 4 days of receiving the specimen (Target: $\geq 80\%$)

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