Chapter 2. The Global Measles and Rubella Laboratory Network

Overview

The WHO Global Measles and Rubella Laboratory network (GMRLN) was established in 2000 when international efforts were aimed at measles mortality reduction. The national measles and rubella laboratories that comprise the global laboratory network developed and expanded in conjunction with regional control and elimination programmes. For example, in the Region of the Americas (AMR), national laboratories conducting measles and rubella laboratory confirmation were strengthened following the 1994 resolution for the elimination of endemic measles in the Americas. The organization and coordination of the GMRLN was modelled after the WHO Global Polio Laboratory Network. Within the framework of the GMRLN, the collective experience of all laboratories provides essential input for development of improved methodologies, testing strategies, and establishment of quality assurance programmes.

In the elimination phase, it is well established that surveillance based on clinical recognition of cases is unreliable and the laboratory confirmation of suspected cases is critical for effective surveillance. Therefore, the laboratories in the GMRLN have an increasingly important role in confirming suspected measles, rubella, and CRS cases and to monitor viral genotypes when cases occur. With international efforts focused on accelerating the elimination of measles and rubella in all WHO Regions, many laboratories will experience higher workloads. The requirements for the verification of elimination will involve greater scrutiny of laboratory data to ensure that the laboratory meets the indicators for high quality laboratory-based surveillance.

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2.1 Objectives and organization of the global laboratory network

There are several key objectives for maintaining a unified network of laboratories to support measles and rubella programme goals:

- to develop and improve standardized protocols for the laboratory confirmation of measles and rubella
- to establish standards for quality assurance and quality control
- to administer and implement standardized global proficiency testing
- to monitor the performance of network laboratories through annual accreditation
- to provide training resources and facilities for staff of network laboratories
- to facilitate inter-laboratory cooperation for expanding national and regional capacity
- to maximize the efficient use of limited reagents and validated reference materials
- to share expertise and data to track transmission of measles and rubella viruses
- to provide support including WHO funding to enhance and maintain laboratories in limited resource settings

The laboratories in the GMRLN are organized into four levels: global, regional, national and sub-national laboratories. The global and regional laboratories have been established as centres of excellence and act as reference facilities for national and subnational labs. National and sub-national laboratories are nominated by the Ministry of Health of each Member State. The sub-national laboratories may be organized according to governing administrative levels and/or geographic areas (e.g., province/state, district/prefecture) [1].

Some of the laboratories may have more than one designation. For example, those RRLs that are responsible for first-line testing of samples by IgM and/or RNA detection fulfil the responsibility of a national laboratory. A description of general areas of responsibilities for the four levels of network laboratories is given below.

- **Global Specialized Laboratory (GSL)**
  The responsibilities of the GSL extend to measles and rubella laboratories in all regions and countries.
  **Technical support/Training:** Provides technical advice, consultation and specialized training to regional and national laboratories. Assists in preparation of global reports and
summaries of network activities. Develops periodic proficiency testing for regional laboratories.

**Research:** Contributes to the development and validation of novel methods and the standardization of procedures and protocols. Evaluates diagnostic kits and develops and improves methods.

**Quality Assurance:** Prepares standards, proficiency panels (IgM/serum and virus strains) and training materials.

**Virologic surveillance:** Develops and maintains standard protocols and databases for molecular epidemiology.

- **Regional Reference Laboratory (RRL)**

  Laboratories designated as an RRL have demonstrated the capacity to undertake international responsibilities and collaborate closely with the GSLs. Each WHO region may have up to 4 RRLs.

  **Reference Testing:** Samples referred by National and Sub-National Laboratories are tested to provide case classification using standard and specialized methods. The RRL provides support for genetic characterization for samples referred for virologic surveillance.

  **Quality Assurance:** Performs validation of their own and national laboratory results using a validated assay and internal controls. Coordinates proficiency testing, provides confirmatory testing for National Laboratories.

  **Technical support/Training:** Provides training and consultation to national laboratory staff in collaboration with WHO.

  **Research:** Collaborates with GSLs in the development and evaluation of new or improved methods.

  **Reports to:** Country programme manager, National Laboratories and WHO.

- **National Laboratory (NL)**

  The NLs communicate directly with immunization programme managers.

  **Testing:** Provides case classification for clinically suspected measles and rubella using IgM detection by EIA. Performs virus isolation or direct RT-PCR or both with samples collected for virologic surveillance. If facilities and capacity do not support molecular testing, the NL forwards clinical samples, virus isolates, or RT-PCR positive samples to the designated RRL. Performs epidemiologically essential serological surveys.

  **Quality assurance:** Participates in annual proficiency programme. A proportion of specimens are sent to the RRL for confirmatory testing. Monitors the quality of Sub-National Laboratories under its responsibility.

  **Reports to:** Country programme manager, Sub-National Laboratories and WHO.

- **Sub-National Laboratory (SNL)**

  In many countries, the responsibility of first-line testing of specimens for case classification is shared by laboratories at the sub-national level. This may be necessary because of population size and/or logistical challenges.
**Testing:** Provides case classification for clinically suspected measles and rubella using IgM detection by EIA. Samples collected for virologic surveillance are processed and packaged for shipment to the National or Regional Reference Laboratory for molecular testing and genetic characterization.

**Quality assurance:** Participates in annual proficiency programme. A proportion of specimens are sent to the NL for confirmatory testing.

**Reports to:** Country programme manager, National Laboratories.

In May 2018, there were 713 laboratories in the GMRLN conducting measles and rubella surveillance for 191 countries. These laboratories were based in 165 countries and included 506 sub-national, 180 national, 14 regional reference and 3 global specialized laboratories [2].

### 2.2 Coordination of the global laboratory network

Coordination of the GMRLN is carried out by WHO, based on the experience gained in establishing the Global Polio Laboratory Network. Each of the six WHO regions has a Regional Laboratory Coordinator (RLC) responsible for the laboratories within their region. The RLC works closely with the GSLs, RRLs and WHO HQ to coordinate training activities. Each of the regions works in partnership with the Global Laboratory Coordinator (GLC) based at WHO headquarters, Geneva, Switzerland. The GLC and RLCs share comments, requests and queries, and provide ongoing communication through summaries and regional meetings. Procurement and distribution of essential standardized laboratory equipment and reagents for selected countries is also coordinated through WHO.

An established system for monitoring indicators of laboratory performance, including external quality assurance for IgM detection, molecular detection and characterization, and laboratory accreditation has proven beneficial for the participating laboratories. The analysis of quality assessment activities helps to guide training needs and the data is valuable for tailoring recommendations intended to improve testing methods as well as to respond to changes in technology. For example, external quality assessment activities for molecular testing was established in 2014 following a comprehensive training programme to expand the number of laboratories routinely performing molecular techniques for measles and rubella surveillance.
Laboratory virologists and epidemiologists at all levels must establish mechanisms to exchange information on a regular basis to monitor and evaluate performance indicators of the surveillance system and to link laboratory and epidemiology data. Therefore, while responsibilities for measles and rubella testing (along with documentation and reporting requirements) increase the workload for laboratories in the GMRLN, the technical collaborations and collegial relationships are important benefits that member laboratories enjoy. The network laboratories interact closely with national immunization programmes and timely information exchange is critical for the integrated surveillance required to meet measles and rubella elimination goals and provide necessary data for verification of elimination [3].

The advantages of providing updates and reviewing aggregate data in a scheduled meeting format are now well established. Representatives of the GSLs and RRLs hold meetings on an annual basis and many participate more frequently through membership in one or more research working groups. Representatives from the NLs should hold meetings with their immunization programme counterparts at least once a month and participate in regional meetings every year.

An effective and efficient laboratory network depends on collaboration and information exchange within the network, with the disease control field staff, and colleagues in the immunization programme. Standard referral and reporting forms have been developed to ensure that all essential patient information is transmitted (see chapter 11 and Annex 11.1 for example). Collection and dissemination of relevant information that guides both control activities and testing strategies is the cornerstone of effective surveillance.

### 2.3 Role and major activities of network laboratories

The primary role of the laboratories in the GMRLN is to provide reliable laboratory testing to support the goals of the national, regional, and global measles and rubella immunization programmes. There are 4 broad areas of activities that network laboratories carry out in support of these immunization programmes. These are listed and discussed in detail below.

1. **Laboratory testing for case classification and serosurveys**
2. **Virologic surveillance for measles and rubella**
2.3.3 Communication and documentation of laboratory results and data
2.3.4 Participation in WHO quality assessment and accreditation programmes

2.3.1 Laboratory testing for case classification and serosurveys

The rapid implementation of activities to control transmission is most effective when cases and outbreaks are notified early. Therefore, laboratory testing of clinical samples and results reported for clinically suspected cases must be timely and accurate. The detection of virus-specific IgM is the standard method for case confirmation. However, the use of RT-PCR for direct detection of measles- or rubella-specific RNA is being adopted by many laboratories in the network to complement IgM antibody detection (chapter 6).

The GMRLN is dedicated to full integration of measles and rubella surveillance. A testing strategy or algorithm that is aligned with the epidemiologic situation in the country should be applied to rule out the possibility of either disease. In addition, laboratories are strengthening, or transitioning to, case-based surveillance to support elimination goals and meet laboratory indicators. Additional and specialized testing methods may be required for case classification in elimination settings (chapter 8).

Immunization programmes will need to identify susceptible populations and age groups to target for vaccination campaigns to meet the elimination goals. The laboratories in the GMRLN should be involved at an early stage in planning seroepidemiology studies. Considerations for planning successful seroepidemiology studies and methodologies for measuring population immunity are provided in chapter 9.

2.3.2 Virologic surveillance for measles and rubella

Virologic surveillance is a critical element for measles and rubella immunization programmes and the verification of elimination. The molecular epidemiology of measles has proven useful to support evidence for progress in controlling measles. In near-elimination settings, reduced numbers of lineages within a genotype are typically observed. Additional efforts are needed to fill in gaps in molecular surveillance, particularly for rubella virus [4].
Communication with field immunization staff is important to ensure that adequate samples are collected for genetic characterization. All laboratories that perform genetic analysis to determine genotypes of circulating measles and rubella viruses must report the genotype, relevant sequence data and epidemiological information to WHO measles or rubella sequence databases, MeaNS or RubeNS (chapter 7).

The sub-national and national labs that do not perform molecular testing must promptly notify the appropriate NL or RRL regarding samples that need to be referred for such testing. It is essential that samples are properly processed and stored to preserve the integrity of the samples.

2.3.3 Communication and documentation of laboratory results and data

The format and timing of result reporting at the local, national level, and regional levels will be based on global standards, but operational procedures will be drafted in consultation with appropriate surveillance and immunization programme staff. These operational procedures for conducting surveillance should be clearly assigned and understood. All pertinent information must be transmitted rapidly and reliably from the local units to higher levels of the surveillance or health centre offices.

Zero reporting (reporting even if no cases are confirmed) may be required on either a weekly or monthly basis, depending on the recent history of measles or rubella activity. This is an especially important activity in near-elimination and elimination settings.

Regional laboratory coordinators and national laboratories must ensure that the activities completed by the laboratory in support of programme goals are documented. Calculation of the laboratory indicators requires careful management of data. All national laboratories are requested to provide a weekly or monthly report of results to WHO. Laboratories that have been accredited for molecular analysis of measles and rubella viruses should transmit data for wild type virus sequences according to the timeframe specified for genetic data (chapter 7) to the WHO nucleotide surveillance databases MeaNS and RubeNS. For more information on data management and reporting, refer to chapter 11.
2.3.4 Participation in WHO quality assessment and accreditation programmes

Laboratories in the network are required to participate in annual proficiency testing in selected techniques and are evaluated on an annual basis through the WHO accreditation programme. In addition, all laboratories are required to refer samples for confirmatory testing for quality assurance. Usually this is accomplished by forwarding a percentage of samples to a designated network laboratory at the next higher administrative level. Records of samples referred for confirmatory testing, and other necessary elements that demonstrate quality control and quality assurance must be maintained. Chapter 12 covers the requirements for all aspects of quality assurance and quality control, including the WHO-sponsored proficiency programmes and accreditation.

Bibliography to Chapter 2


