Manual for the Laboratory-based Surveillance of Measles, Rubella, and Congenital Rubella Syndrome

Chapter 12  Quality assurance, quality control, and assessment of laboratory capacity and performance

Overview
The laboratories in the GMRLN provide test results for measles and rubella that are critical to outbreak control measures and policy decisions related to disease surveillance. The true impact of immunization activities can often be determined only through high quality, laboratory-based surveillance. The importance of laboratory support for disease surveillance has been underscored in the essential criteria for verification of elimination and the role of the laboratory in meeting quality indicators for surveillance. The laboratory must demonstrate that the test results and sequencing data are generated through standard operating procedures that are designed with appropriate quality assurance and quality control elements and that the laboratory has met required accreditation or performance standards.

The laboratories in the global measles and rubella laboratory network (GMRLN) participate in an external quality assessment (EQA) programme administered through WHO and a network accreditation programme, described in sections 12.5 and section 12.6, respectively.

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12.1 The establishment and benefits of a quality management system

Ideally, the implementation of a quality plan or a quality management system (QMS), is recommended to integrate all aspects of laboratory processes and management. A well-functioning QMS not only oversees quality assurance and quality control activities but encompasses all operations within an organization that affect laboratory performance. Setting up a QMS in a laboratory requires an analysis of the organizational structure, responsibilities, procedures, processes and resources to achieve the highest accuracy and reliability possible.

By adopting a QMS model, activities along the path of workflow across departments are systematically analysed and quality policies can be built into all processes in a step-wise and eventual, integrated whole. Coordination of policies across departments with the aim of quality improvement only be achieved with a dedicated QMS.

It is the responsibility of the head of the laboratory to establish, implement and ensure compliance with the requirements of the QMS. However, the success of a QMS is the responsibility of all laboratory personnel. A strong supporting organizational structure with the commitment of management is crucial. In addition, a quality manager is recommended to coordinate all the activities of implementation and documentation.

When all the laboratory procedures and processes are organized into an understandable and workable structure, the opportunity to ensure that all components are appropriately managed is increased. A well-functioning QMS enables standardization to ‘best practices’ in all areas of an organization that influence quality. This comprehensive approach directs and controls the organization with regard to quality.

The implementation of a QMS can be initiated at different starting places, adding on building blocks which are each continually refined and expanded. A set of coordinated activities, or quality system “essentials” are often identified as the building blocks for the establishment of a QMS. The WHO Handbook, Laboratory Quality Management System (2011), describes 12 building blocks for planning and implementing a QMS [1]. An additional web-based resource,
Laboratory Quality Stepwise Implementation (LQSI) tool, provides a practical guide for laboratories to implement a quality management system by following a stepwise plan [2].

There are several international organizations which are involved in the promotion of laboratory quality. The largest of these is the International Standards Organization (ISO) which is the developer and publisher of international standards applicable to many kinds of organizations, including clinical and public health laboratories. Many laboratories in the GMRLN have undergone ISO accreditation to the ISO standard 15189:2012. This standard specifies the requirements for quality and competence in medical laboratories and can be used by network laboratories in developing their quality management systems and assessing their own competence.

Although there are many parallels between the WHO accreditation program and ISO 15189, the ISO standard is considerably more comprehensive, especially in relation to the documentation of quality systems and management. Other international organizations include Clinical and Laboratory Standards Institute (CLSI), a standards-developing organization that promotes the development and use of voluntary consensus standards and guidelines within the healthcare community.

Some countries have also established a certification process for medical laboratories to regulate testing and reporting such as Clinical Laboratory Improvement Amendments (CLIA) in the USA and National Association of Testing Authorities (NATA) in Australia. It is encouraged that all laboratories in the GMRLN consider becoming accredited to ISO and/or any national accreditation authority, as an adjunct to the WHO Measles and Rubella accreditation program.

12.2 Technical elements of QMS

There are a range of activities within QMS that relate directly to the processes that ensure reliable laboratory results and prevention of errors. Process control consists of the technical activities required to produce a test result and includes the preanalytical handling of samples for testing, the steps for testing, and the ascertainment of a valid run. The use of control materials is
a fundamental component for conducting the analytical phase of testing, and both internal (kit) controls and external reagents that serve as positive or negative controls are utilised for validation and to monitor test performance. Quality control (QC) refers to those measures that must be included in each assay to verify that the test is working properly.

Laboratory quality assurance (QA) is the overall programme that encompasses specimen collection, testing processes (including quality control), and the accurate interpretation of results and timely reporting. QA is a systematic approach to define the best practices for all processes associated with the functioning of the laboratory that can affect the reported results. The goal of QA is to prevent errors and assure that procedures are performed consistently. QA establishes procedures to review performance and procedures and directs both proactive and corrective proactive measures to improve laboratory quality. Documentation of QA activities not only leads to improved accuracy but are important to demonstrate the quality of the results generated by the laboratory.

Periodic review of procedures and processes drive continual improvement. By following procedures that have been established to minimize errors and generate the appropriate documentation for subsequent review and critical evaluation of laboratory processes, the laboratory can achieve the highest possible accuracy.

It is becoming more common for risk management principles to be applied to clinical laboratory environments [3,4]. The testing process is mapped as individual steps and any possible weaknesses or hazards are identified and processes are formulated to avoid errors or inconsistencies at each step. This analysis of the process, from pre-analytical to post-analytical phase, is the most important feature and is customized for the particular laboratory test. The potential source of error or hazard at each step is identified and a plan is formulated to mitigate the risks of error.
12.3 **Key objectives of laboratory quality assurance**

All procedures and processes in the laboratory that affect the output of the laboratory must be carried out correctly to assure accuracy and reliability of testing. An error or departure from established protocols within any process can jeopardize the accuracy of laboratory results. Improvement in quality can be achieved by documentation, standard operating protocols (SOPs), proficiency testing, analysis of data, and internal audits designed to reveal weaknesses and ensure adherence to the SOPs. QA is concerned with the prevention of errors by addressing all inputs that are critical to a high functioning laboratory such as qualifications for reagents, maintenance of equipment, and management of human resources so that staff are highly trained and motivated.

Reviews and analysis of the output and performance of the staff are conducted to determine if the SOPs have been followed and to detect any issues that require attention and modification. Each stage of the workflow in the laboratory, therefore, requires careful attention as each is critical to assure quality in the laboratory.

There are 5 key objectives of a quality assurance programme. An overview and guidelines for each of the listed activities are discussed below.

1. Develop standard operating procedures (SOPs)
2. Monitor laboratory output and performance
3. Provide and maintain a highly trained and knowledgeable staff
4. Ensure quality of reagents, sufficient supplies, and maintenance of equipment
5. Maintain appropriate records and establish a document control system

1. **Develop standard operating procedures (SOPs)**

SOPs are documents that contain written step-by-step instructions that laboratory staff should follow when performing a procedure. SOPs should be prepared by experienced, technical staff in the laboratory, revised by their immediate supervisor and approved by the Director of the laboratory. A laboratory will have an SOP for each process (such as accessioning samples) and all laboratory tests that are conducted in the laboratory.
The goal is to write the SOP with sufficient attention to detail (dilution of reagents and precise timing instructions) so that each staff member will perform the test in exactly the same way, ensuring that the same result can be expected from all staff. Staff that does not normally perform the procedure should be able to do so by following the SOP.

All steps in the procedure should be analysed, identifying possible variations or potential “error points”, which could introduce error. If different laboratories develop their SOPs based on the same standardized procedures used throughout the network, direct comparisons of their results can be made. It should be emphasized that all laboratory staff must follow the SOPs exactly. It is important that SOPs are written in a manner that eliminates ambiguity. Flow diagrams may be useful for some activities and processes.

(2) Monitor laboratory output and performance
All laboratories should have regular and thorough processes for monitoring the accuracy and performance of their procedures and the persons performing them. Performance monitoring should be a continuous process in each laboratory. Important indicators of performance include the timeliness of reporting results and summary reports of laboratory data, and the concordance rates for confirmatory testing and annual proficiency tests. See section 12.3 and section 12.4, for more information on confirmatory testing and the annual proficiency tests, respectively.

The process of assessment is a tool for examining laboratory performance and comparing it to standards, benchmarks, or the performance of other laboratories. A combination of internal quality assurance (IQA), performed within the laboratory using its own staff, and external quality assessment (EQA) that is conducted by a group or agency outside the laboratory, is the recommended approach to ensuring quality. Laboratory quality standards are an important part of the assessment process, serving as benchmarks for the laboratory.

Internal assessments or on-site audits should be conducted to identify non-compliance with SOPs or deficiencies in the SOPs that need attention. Reviews of non-conforming events, corrective action taken, and the effectiveness of that corrective action to address the problem are important
(3) **Provide and maintain a highly trained and knowledgeable staff**

A good quality laboratory depends on qualified, motivated staff. Each individual in the laboratory must have a full understanding of QA and the importance of teamwork in successfully implementing QA. An organizational chart should be prepared and distributed that clearly shows the appropriate lines of authority and the functions and responsibilities of each person. Most of the activities in the measles and rubella laboratory such as EIA testing, cell and virus culture, molecular techniques and interpretation of results require staff with a strong scientific and technical training, good technical skills and considerable experience.

Human resources staff and the laboratory manager should regularly review training needs and make arrangements to ensure that technical and scientific staff receive training according to those needs identified and proposed by the heads of department. The training offered to staff should directly contribute to the success of the objectives of the QA. A continuing education programme must be developed which includes on-site as well as external training. The staff training programme should be formalized into records that are maintained as part of the required documentation.

(4) **Ensure quality of reagents, sufficient supplies, and maintenance of equipment**

All reagents should be inspected to ensure that the seals are intact upon receipt in the stockroom or when distributed to the laboratory. These inspections should be recorded with the initials of the person responsible for the inspection and the date on the label. Expiration dates should be recorded and monitored. Reagents that are mixed or diluted in the laboratory should be prepared in conformity with written SOPs.

At least a six months’ reserve stock of reagents should be held in the laboratory at all times. Given the long delivery times and difficulty of transporting supplies to some countries, reagents should be ordered 6 to 12 months ahead of predicted needs. Predicting the utilization of reagents can be challenging due to the epidemiology of measles and rubella disease. An outbreak requiring the immediate testing of hundreds of samples can rapidly consume current stocks of
test kits and require rapid revision of forecasted needs.

Managing stocks of reagents requires regular checks of inventory at scheduled intervals to record stock used and stock remaining. This is especially important when supplies are provided by a third party which may have a timetable for ordering at certain times of the year and the synchronization with their timeline is critical. Some WHO regional offices have the capacity to hold reserve stocks of reagents including test kits should a large outbreak occur. However, the need for regular communication of reagent stock levels to the regional coordinators is vital.

Reference materials and internal controls may be produced by the laboratory for its own use or be provided by reference laboratories in the network or from other organizations. If the laboratory chooses to produce its own reagents, then producing large volumes minimizes the frequency and efforts required to validate these materials. If a third party provides materials, then consideration of transportation conditions becomes important to ensure reagent potency is maintained.

It is recommended that an inventory system is maintained for supplies. A central inventory or logbook of reagents should be kept containing the following:

- Name of the item, supplier and trademark name (origin)
- Lot number, date of receipt, and expiration date (if applicable)
- Location and conditions of storage
- Quantity of material, with dynamic and trigger points for replenishing

The inventory should contain all the information relating to the properties of the items. All staff should be aware of the need to complete an update of the inventory as and when they use or replenish supplies, however, overall responsibility for managing the inventory should be in the hands of the laboratory manager or a designated staff member.

Many kinds of equipment are used in the laboratory, and each piece of equipment must be functioning properly. Choosing the right equipment, installing it correctly, ensuring that new
equipment works properly, and having a system for maintenance are all necessary for quality assurance.

Equipment such as pipettes, incubators, refrigerators, freezers, thermometers, thermocyclers, and sequencers are essential components for generating accurate assay results. Failure or non-compliance of the equipment can be the cause of assay problems and it is essential that regular calibration and preventative maintenance be undertaken. Often the equipment manufacturer will provide a user manual that includes instructions and suggested schedule for equipment maintenance and/or calibration. Following the manufacturer’s recommendations will reduce the chances of failure or non-compliance.

All equipment should have clear and accessible documentation of the processes required for calibration, maintenance and performance recording. Critical equipment such as refrigerators, freezers and incubators should be monitored continually either through once or twice daily manual recording or a continuous electronic monitoring system with out-of-range alarms established. SOPs should be written for each instrument that cover basic operation and maintenance procedures. Detailed logbooks should be maintained with documentation of preventive maintenance, non-routine maintenance and repairs.

(5) Maintain appropriate records and establish a document control system

The product of the laboratory is information, primarily in the form of test reporting. Information (data) needs to be carefully managed to ensure accuracy and confidentiality, as well as accessibility to the laboratory staff and to the health care providers. Records must be meticulously entered and maintained so as to be accurate and accessible. It is important to address both the use and maintenance of documents and records. Information may be managed and conveyed with either paper systems or with computers; both are discussed, along with the use of worksheets, in chapter 11.

Documents, by definition, require updating. A system must be established for managing them so that current versions are always available. Documents such as SOPs will be easier to manage and
update by use of standardized formats and a document numbering system. Even without a QMS in place, a document management system can be developed using the suggestions included in section 16.5 of the WHO Handbook, Laboratory QMS [1].

Each SOP should be signed and dated to ensure that the procedures being used are up-to-date. Modifications should not be made without going through appropriate channels in the laboratory. Protocols should be reviewed on a regular basis. Refer to WHO recommendations as appropriate for assays and protocols that have been adopted for routine testing for measles and rubella. Consistency in the quality control measures incorporated into SOPs allows the surveillance programme to analyse aggregate data and directly compare results from all of the laboratories in the measles and rubella laboratory network.

12.4 Monitoring IgM assay performance

Both measles and rubella infections generate detectable IgM within the first few days of onset of clinical signs and the proportion of cases that can be confirmed through IgM detection by EIA usually peaks at 4-5 days after onset, respectively (see chapter 4). An IgM EIA is the recommended assay to confirm measles and rubella cases in the GMRLN as it can be used on a single blood sample collected from a suspected case at the first contact with the health facility with a high degree of sensitivity and specificity. A trouble-shooting guide is provided in Annex 12.1.

A number of commercial IgM EIAs for measles and rubella have been independently assessed (Annex 4.1) where both capture and indirect format assays were reported to have similar performance. However, EIAs are biological assays and the performance of the assay can be affected by both the quality of the assay at the time the test is carried out and how well the technician performs the test. Locally produced kits must be evaluated for accuracy. The recommendations for conducting an evaluation of EIAs for IgM detection by network laboratories is provided in Annex 12.2.

Several approaches should be taken to monitor the precision and accuracy of the results obtained from EIAs for detection of measles or rubella IgM antibodies. Each of the following methods
listed is discussed in detail below.

1. Quality control programme
2. Confirmatory testing
3. Internal quality assurance
4. Supervisory review and evaluation

(1) Quality control programme

A quality control programme is a systematic process that monitors the validity of an assay by incorporating a method to measure accuracy and precision. While QA includes activities or measures taken to prevent errors, QC activities are designed to detect errors. Steps for QC are completed prior to release of the test result. Ideally, three QC samples or controls should be selected to represent high, normal, and low values. The aim is to include controls that are sufficient to differentiate between normal variation and technical errors.

Guidance for troubleshooting and steps for corrective action must be included in the QC programme. The performance of any assay can be influenced by a multitude of factors including the variability of some lots of microplates, and the performance of the components or reagents in the assay. External factors, such as the operator, incubation time and temperature, and the accuracy of delivery devices must be taken into account. For this reason, it is critical to maintain equipment maintenance records, pipette calibration certifications and logbooks for daily temperature measurements of incubators/refrigerators/freezers to avoid variation due to mechanical problems. In addition, these records provide evidence of adherence to QA procedures that are assessed during WHO evaluations as well as internal audits.

QC materials such as kit controls and in-house controls (IHC) are run to quantify the normal variability of an assay by establishing a normal range. Quality control material should be available in sufficient quantities to minimize the number of times that control ranges must be established. The QC mean should be established by running the QC sample 20 times to quantify normal variation and establish ranges for each QC sample. For more information, refer to the WHO QMS Handbook, section 7-3, Establishing the control range for control materials [1].
For IgM testing, statistical analysis can be used for the daily monitoring of values obtained from IHC samples. Use of a Levey–Jennings chart is recommended to visualize the performance range of an assay and to monitor trends or variation in assay performance. If controls are out of range, corrective action and troubleshooting should be undertaken and the problem should be resolved, and the test repeated before reporting assay results. Westgard rules can be applied to determine whether the results from the IHC sample are valid and sample results can be reported, or if they need to be rerun. Westgard rules are helpful to avoid rejecting runs that may be acceptable for a particular assay and can be used to detect both random and systematic errors. For additional guidance for the use of Levey-Jennings charts and Westgard rules, see Annex 12.3.

The QC protocols include guidelines for addressing any detected errors (troubleshooting) and specifies the corrective action and any remedial action that may be required. Remedial action, or remediation, addresses any consequences that may result from an error. For example, if an erroneous result has been reported, it is essential to immediately notify all persons concerned about this error and to provide the correct result. Corrective actions address the cause of the error.

If a test was done incorrectly, resulting in an incorrect result, corrective actions identify why the test was not performed properly and steps required to prevent a reoccurrence. As an example, the IHC and kit control of an assay may have been giving results that are >3 standard deviations of the mean values, and the corrective actions would be to identify the cause of the problem, rectify and repeat the assay.

(2) Confirmatory testing

Confirmatory testing or retesting and validation of a subset of a national laboratory’s samples by a designated reference laboratory provide an appropriate external measure of a laboratory’s performance over a much longer period of time. Specimens sent for validation should be representative of all results determined by the national laboratory (positive, negative and equivocal) and be chronologically and geographically representative of the country and selected from multiple outbreaks, if applicable.
The proportion of specimens sent to the RRL for confirmatory testing is dependent on the quality of the laboratory and may range from 10-100% with the lower range for a fully accredited laboratory and 100% for a laboratory which has failed accreditation. In general, for fully accredited laboratories, a minimum of 15 samples per shipment should be sent annually, or more frequently if requested by the RLC. The proposed list of selected samples (number and distribution) should be shared with the RLC and Reference Laboratory Director for endorsement before being sent to the RRL.

As with any shipment of samples, the sending laboratory should communicate with the receiving laboratory to determine the optimum time to send and by which means. All samples shipped should be a minimum of 200μl with at least 150μl of the original samples kept back in the national laboratory in case of the need for retesting.

The reference laboratory should ideally use the same commercial EIA as the national laboratory and provide turnaround of results within 14 days of receipt to ensure that any issues detected with the confirmatory testing are resolved as quickly as possible. The optical density values may show considerable variation between the RRL and the NL, but concordance of final results should be high, with the exception of results in the equivocal range or for positive and negative samples with test values close to the cut-offs. For the Siemens assay, a formula to estimate concordance and discordance between two tests of the same sample is provided in Annex 12.4.

Any discordant result should be retested by the RRL and if the discordance remains, the RRL should consult with the RLC and National Laboratory Director to identify a course of action to identify possible causes. The first step for the National laboratory with any discordant sample is to retest it and report the result to the RRL and RLC. Although a score of 90% is a passing score for confirmatory testing, laboratories should carefully review every discordant result and try to resolve any issues detected. Careful documentation of the discordant result and the process to resolve it should be kept and this will be reviewed at the time of the on-site review.
(3) **Internal quality assurance**

Reproducibility of results can be evaluated by re-labelling one or more aliquots (replicates) of a laboratory sample which are then tested as separate samples. This procedure monitors the performance of an assay as well as the person performing the assay. The person responsible for QA or the laboratory director should establish a schedule and identify a sufficient number of samples to be tested as replicates. By testing replicate samples in the same assay and/or in different assays, intra- and inter-assay variation can be determined respectively and coefficient values (CVs) calculated. It is generally accepted that intra-assay CVs should be less than 10% and inter-assay CVs less than 15%.

(4) **Supervisory review and evaluation**

In performing an assay, one of the most common sources of error, and usually among the easiest to address, is the operator. Poor performance may not be due to the operator’s skill level or failure to follow the SOP correctly, but rather may be due to other factors. Among the potential factors that can affect operator performance:

- Time pressure to complete a heavy workload
- Distractions of phone calls or colleagues interrupting workflow
- Incorrectly labelled samples or selection of incorrect samples

It is critical that a supervisor or other highly experienced staff member review the performance of every assay and confirm that all the validity criteria are met and that no transcription errors have occurred before signing the worksheet. Sample results should not be reported without supervisory sign-off that the assay has been performed according to accepted criteria. Errors may also be due to poorly or incorrectly written procedures or SOPs and failed or out of calibration equipment.

12.5 **The WHO external quality assessment programme**

Quality assurance/assessment is a continual process and demonstration of the quality of individual laboratories in the GMRLN is critical to maintain confidence by stakeholders and
colleagues in the surveillance programme that the laboratories are providing results with high sensitivity and specificity. The WHO measles and rubella EQA programme is a coordinated global activity to provide annual proficiency panels, evaluate results, and distribute reports.

Although the annual panels provide only a snapshot for quality assessment, the results provide an assessment tool that has proven to be valuable for individual laboratories and for aggregate evaluation of the laboratory network performance. In addition, the assays and methods that may vary across laboratories can be compared through the distribution and testing of a global proficiency panel.

The proficiency panels for IgM and molecular detection for both measles and rubella require a massive effort to produce and distribute. The details of the proficiency programmes for measles and rubella IgM and for molecular testing available for laboratories in GMRLN laboratories are provided below.

**Measles and rubella IgM proficiency panel**

An annual proficiency programme for measles and rubella IgM has been conducted since 2001 for laboratories within the WHO laboratory network [5]. The RRL in Australia, (Victorian Infectious Diseases Reference Laboratory, VIDRL), assembles the panels using serum that has been provided by network laboratories. The annual panels are identical, consisting of 20 serum samples that have been thoroughly evaluated prior to inclusion in the panel. All samples are tested for both measles and rubella IgM. More than 250 laboratories in GMRLN participate in the annual programme. Laboratories are required to test the panels as they would routine samples and report detailed results of the samples as well as assay validation data within the prescribed timelines.

With the global distribution of the proficiency panel, problems with IgM assays used for measles and rubella surveillance in the GMRLN laboratories can be detected. The performance of each laboratory is assessed according to concordance of expected results, completeness of data provided, and timeliness of the results returned to VIDRL. Points are deducted if incorrect sample results are reported, which may be due to an error in interpretation or in the transcription
of results. In addition, deductions to the final score will occur if kit or assay information, validation data, and details of any in-house control sample used are not provided or not complete. A score of <90% is considered a red flag and may have a negative impact on the laboratory’s accreditation status. Scores below 80% require urgent action to resolve any deficiencies in the laboratory or in the performance of their assays.

Measles and rubella proficiency panel for molecular testing

Molecular characterization of measles and rubella viruses is an important component of surveillance and a valuable tool for measuring the effectiveness of measles and rubella control and elimination programmes. Many laboratories in the global network now have the capacity to perform nucleic acid amplification with samples collected from measles and rubella cases, however some laboratories may not have the capacity to perform sequencing.

The WHO programme for molecular external quality assurance (mEQA) for the measles and rubella laboratories in GMRLN was initiated in 2014 by the Global Specialized Laboratory at CDC, Atlanta, USA. The mEQA panels consist of samples for both measles and rubella virus prepared from lysates of infected cells that had been dried onto FTA® Cards. Six mm disks are cut from the FTA cards and shipped to participating laboratories. The disks are stable for shipping at ambient temperature when packaged with a desiccant. The components of the panels have been coordinated between RRLs and INSTAND e.V., a reference testing institute in Berlin.

RNA extracted from the disks can be used for RT-qPCR/RT-PCR and genotype identification. In order to achieve the maximum points, the report should demonstrate:

- Correct identification of measles or rubella RNA from all positive samples
- No false positive results from the negative samples
- Adequate positive and negative controls on PCR reactions
- Correct identification of the measles or rubella genotypes from each positive sample
- Ability to amplify and sequence the complete WHO standard sequencing windows for measles (N-450) and rubella (739nt)

All network laboratories performing molecular techniques for measles and rubella surveillance
must achieve a passing score in the annual mEQA so that molecular results reported to the surveillance programme can be accepted. Evidence of performance issues in individual laboratories will require development of an action plan to address these issues and successful completion of a subsequent mEQA panel before routine molecular testing can proceed.

Laboratories that do not have the capacity for determining genotypes from measles and rubella cases or have not passed the mEQA should send suitable samples from representative outbreaks to the designated reference laboratory, in consultation with the regional lab coordinator.

12.6 Process of WHO assessment and accreditation

The WHO measles and rubella accreditation programme was established in 2002 and consists of an assessment or external audit of laboratories within the network [6]. Accreditation provides documentation of the laboratory’s qualifications and capacity to detect, identify, and promptly report measles and/or rubella positive samples to the national surveillance programme and the regional and global WHO programmes. The accreditation process also provides a learning opportunity and serves as a mechanism to identify resource and training needs.

The WHO Regional Laboratory Coordinator (RLC) is responsible for coordinating the accreditation of National Measles and Rubella Laboratories annually and the Global Laboratory Coordinator (GLC) is responsible for coordinating the reviews of the Regional Reference and Global Specialised Laboratories. The accreditation assessment is based on laboratory’s performance with complete data during the preceding 12 months. A laboratory achieving full accreditation will maintain that status for the forthcoming calendar year. A partial accreditation, or a non-accreditation result, will set in motion a series of activities to build the capacity of the laboratory needed to reach full accreditation status as soon as possible.

Due to the considerable time and workload required for conducting on-site reviews, the on-site accreditation will be reserved for higher priority laboratories. All network laboratories will be required to complete “desk” accreditation checklists annually and submit them to the appropriate laboratory coordinator by correspondence. The checklists will be reviewed, and on-site reviews will be
prioritised for laboratories that failed accreditation, have provisional accreditation status, or those laboratories requiring support to attain full functionality. The next priority for on-site visits will be given to those laboratories that have not undergone an on-site accreditation in the past 3–4 years.

Four major areas of assessment listed here are described in detail below.

1. Review of the laboratory’s QA/QC programme (including the results of the WHO EQA panels)
2. Review of laboratory environment and human resources
   A. Profile of physical space
   B. Biosafety in the laboratory
   C. Profile of human resources
3. Review and verification of documented procedures, results and records of laboratory activities
4. Review of supervisory visits, coordination and interaction with the GMRLN

1) Review of the laboratory’s quality assurance and quality control programme

A QA/QC programme is essential to ensure accuracy and reliability of laboratory testing in the laboratory network. The laboratory should establish a quality programme that monitors the quality of all tests performed. The accreditation review requires demonstration of satisfactory performance in each laboratory’s quality assurance and quality control programmes. The QC data must be adequately recorded and maintained in an easily accessible format. The accreditation reviewer should have access to the raw data generated from testing, assay kit validation information, and evidence that proper QC procedures have been followed from any assay over at least the previous two years.

Accreditation reviewers will be expected to examine SOPs, IHC results, selected equipment maintenance records and especially check validation of equipment that can have a critical impact on results of routine testing such as daily temperature monitoring of incubators, refrigerators and freezers, and six-monthly calibration of pipettes.
2) Review of laboratory environment and human resources

A. Profile of physical space

The work space in the laboratory should be allocated to provide adequate space and separation as required for different activities performed. In addition, attention must be given to elements of the laboratory environment that can be adjusted to allow for safe performance of laboratory work and for cleaning, disinfecting and maintenance. Walls, ceilings and floors should be smooth, easy to clean, impermeable to liquids and resistant to the chemicals and disinfectants normally used in the laboratory. Bench tops should be impervious to water and resistant to disinfectants, acids, alkalis, organic solvents and moderate heat. Illumination should be adequate for all activities. Additional important aspects of laboratory design are provided in Annex 12.5.

Laboratory furniture should be sturdy and under bench storage cabinets and equipment should be accessible for cleaning. Ideally, storage space for supplies in use should be available and adequate to prevent clutter on bench tops and in aisles. Additional long-term storage space, located outside the laboratory working areas, should also be provided. There should a clear separation of infectious and clean areas with designated, separate areas for office work and eating or drinking.

Microbiological containment should be appropriate for the levels of risk of the potential pathogens in the material being worked with. Areas where the risk of contamination of microorganisms or PCR products is high should be isolated from areas that could be adversely impacted. Use of color-coded gowns, pipettes and other mobile equipment or supplies for each specialized area enhances the chances that these are not used inappropriately in clean areas. The accreditation reviewer will expect to have ready access to all areas of the laboratory and will investigate that each area of the laboratory is used appropriately and there is containment of potentially contaminating materials. The means of disinfection and sterilization prior to disposal should be adequate and performed in a safe manner.
B. Biosafety in the laboratory

The publication, *WHO Laboratory Biosafety Manual Third Edition* (2004) describes the essential biosafety, chemical, fire and electrical safety requirements to protect staff, the community and the environment [7]. All new staff should be made aware of the risks involved in working in a measles and rubella laboratory before starting work in the laboratory and adequate safety training should be provided. The director is responsible for implementation of and compliance with the provisions of the manual.

It is recommended that all laboratory staff receive the Hepatitis B vaccine. Measles and rubella vaccination are also strongly recommended for staff, especially in laboratories that are attempting to culture measles or rubella virus from clinical samples. Women of child-bearing age working in the measles and rubella laboratory should have demonstrable immunity to rubella.

The safe handling of blood products and precautions for opening packages of clinical samples is provided in chapter 3, section 3.2.

C. Profile of human resources

Laboratories should develop an organogram clearly showing the names and job titles of all the staff and showing lines of responsibility and accountability and hold records of their education and training achievements. Mechanisms should be in place for regular onsite training and for regular meetings to include periodic updating of staff on technical issues. Arrangements for staff absences, either scheduled leave or due to illness, are required to ensure services are maintained. Contingency plans for increased workload, such as during outbreaks, should be developed with anticipated staff and resource needs determined and possible solutions identified. Opportunities should be provided for staff to acquire skills outside their own discipline or cross training to allow for flexibility in shifting or reassigning personnel if needed.

The profile of human resources includes a training and competency assessment. It is essential that every person working in the laboratory has undergone appropriate orientation and training in the functioning and in the operation of the laboratory. For any assay to be performed correctly,
training is critical to achieve quality practices in the laboratory and in order to produce accurate, reliable and timely test results.

Training can be in several formats: one-on-one or group; hands-on or theoretical; on-site or off-site; institutional tutors or external tutors. The general topics of training should include: health and safety; SOPs and procedures and QA/QC. WHO periodically holds hands-on training workshops for the performance of specific tests and every opportunity should be taken for the persons routinely performing these tests to attend. RRLs and GSLs are also instrumental in providing on-site training and learning opportunities to the national laboratories in their constituencies.

Assessment of an employee’s performance in the laboratory should occur periodically. Refresher courses should be required to ensure technical skills, knowledge of and adherence to safety rules and policies. Positive feedback, as well as suggestions for improvement, should be provided. All identified personnel problems should be addressed with the employee when they occur, so that they can correct any issue before it can have a major impact.

3) **Review and verification of documented procedures, results and records of laboratory activities**

The long-standing essential indicator of quality laboratory surveillance, timeliness of reporting, requires documented totals of samples tested for both measles and rubella, as well as records of dates of sample receipt and corresponding results reported. The total number of samples tested must demonstrate that the minimum testing requirement has been met (50 serum specimens annually).

During an on-site review, the accreditation reviewer will expect to have complete and detailed documentation for all procedures and processes in the laboratory. Documents to be reviewed will be comprehensive and may include: SOPs, reagent/kit inventory lists, staff training records, safety audits, equipment logs, temperature monitoring sheets, pipette calibration details, assay details with raw data, printouts or digital records, in-house control use and graphic analysis, specimen database, confirmatory testing results and follow-up actions, minutes of regular
meetings with surveillance staff, and others documents as the reviewer may think appropriate. Documents should be kept for a minimum of 10 years and the reviewer may request to review documents at least from the time of the previous on-site review.

The QA/QC system in place can illustrate the level of commitment to ensuring that all practical steps and procedures for QA have been addressed. The SOPs for laboratory tests and assays must be sufficient for detection of errors and direct the steps and documentation required for timely correction of detected errors or non-conformance to SOPs. Non-conformance (“non-conforming event report”) and the remedial and corrective action documentation is reviewed to assess adherence to established protocols and whether adequate corrective measures were implemented in time to eliminate the root cause of the errors or deficiencies.

When control samples values are outside the acceptable range, troubleshooting must be undertaken to identify the problem (Annex 12.1). In order to identify the cause of the problem all variables should be checked systematically and preferably only one remedial action at a time should be undertaken before repeating the assay. All tests with controls out of range, inconsistencies or failure of equipment should be documented, with the original problem, the problem resolution, and the remedial action clearly noted and brought to the attention of the QA manager and the Laboratory director.

4) Review of supervisory visits, coordination and interaction with the GMRLN
Due to the tiered structure of the GMRLN, some laboratories in the global network will have responsibility for monitoring the quality of other network laboratories (see chapter 2). It is important that laboratories document all interactions with other laboratories in the network and share at least a summary of the interaction with the relevant Regional Laboratory Coordinator (RLC) or Global Laboratory Coordinator (GLC), as appropriate.

It is important to communicate issues that arise to the RLC. Often, a quick resolution may be possible by an exchange of information since similar issues may have been previously encountered by other national laboratories in the region. In addition, some issues may have consequences for the entire region or even the global network. Notifications regarding important
laboratory issues by e-mail with other laboratories should include a carbon copy (cc) to the appropriate RLC. The RLC will ensure that issues are brought to the attention of those RRLs or NLs that are responsible for sub-national or other non-network laboratories. Any accreditation reviews of network laboratories carried out at the request of the RLC should follow the current checklist. The outcomes and recommendations should be reported within the prescribed timeframe. All conclusions and recommendations from the review should be presented to the relevant laboratory staff, institute director, and the Ministry of Health at the conclusion of the review in the form of a draft document which will be finalized after consultation with the RLC.

Bibliography to chapter 12


