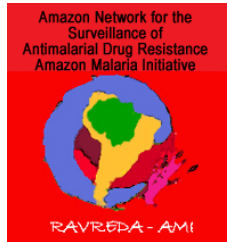




**Pan American
Health
Organization**

Regional Office of the
World Health Organization



USAID
FROM THE AMERICAN PEOPLE

OPS/DPC/CD/M/393/06
Original: English

Guidelines

for

Implementation of a Quality-Management System in Microscopic Diagnosis of Malaria:

Standardization of Procedures and Tools for Quality Control and External Performance Evaluation in Laboratory Networks

**(Proposal of the Technical Advisory Group,
Caracas, Venezuela, July 2004)**

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Introduction

The first component of the overall strategy for malaria control is access to diagnosis and timely, adequate treatment. This strategic component has been emphasized in the efforts made in the Region under the Roll Back Malaria Initiative in the Americas.

The implementation of policies that guarantee access to adequate treatment is necessarily based on the existence of a health care system that offers the opportunity for access to reliable diagnosis. The quality of the preparation and reading of thick blood film in malaria requires the existence of procedures and tools that allow for promotion and monitoring of the quality of the diagnosis based on the structure of the laboratory network.

The countries of the Region have been decentralizing. Malaria diagnosis has moved away from a vertical structure and now involves a variety of actors, both public and private, in the network of health services. The multiplicity of actors, the instability of human resources, and the greater complexity of the network service structure impose ever-growing challenges on malaria control programs and heads of laboratory networks in the countries to guarantee the quality of the diagnosis.

The systems of quality control in the diagnosis of malaria that currently function in the Amazon countries are, in general, inefficient and expensive. The existing structure and available resources in the laboratory network can be optimized to set up quality management systems that better respond to the advances in the health services, including the expansion of access to treatment, and that furnish reliable information to the health authorities. In adopting the ISO framework 15189¹ and NCCLS (National Committee for Clinical Laboratory Standards),² the intention is to obtain greater efficiency in the system. Better management will make it possible for public health laboratories to train staff and carry out supervision and monitoring, operations research, reporting, and publication of the information for policy-making, and to participate in the design of interventions to improve malaria treatment.

Current Situation

Quality control in malaria diagnosis in the countries of the Region is characterized by a predominance of indirect evaluation activities (periodic shipment of material from the local laboratories to intermediate laboratories and in some cases, from this level to a national reference laboratory). This system works partially in some countries but the predominant methodology permits the introduction of biases in the evaluations. In some countries a national laboratory that exercises reference functions has not been identified. The prevailing view is that in most cases, the system uses up significant amounts of time and human resources without necessarily meeting the objectives for quality.

Strengths of the Current System

- Trained human resources available at the different levels that exercise quality control.
- Established routines for the shipment of material and information flow.
- Established network system.
- Functioning analytical plan.

- Adequate national coverage in some countries.
- Existence of protocols, standards, and procedures (not harmonized among the countries).
- Involvement of the reference laboratory in research applied to program control in some countries (resistance to antimalarials, new diagnostic tools).

Weaknesses and Difficulties in the Current System

- Incomplete coverage.
- It allows the introduction of biases by evaluators and the selection of material by those evaluated.
- Noncompliance in the shipment of slides for indirect evaluation by local or intermediate laboratories.
- In some countries, there is no evaluation between the national and intermediate levels.
- Delay in presentation of the results of the indirect evaluation.
- Constraints to implementation of corrective measures.
- Difficulties in the maintenance and replacement of equipment.
- Inadequate budgets.
- Insufficient resources to conduct direct supervision.
- Insufficient numbers of trained human resources.
- Low cost/effectiveness ratio.
- Constraints to the development of applied research on malaria diagnosis and treatment.

OBJECTIVE

General Objective

Implementation and maintenance of a quality management system in the laboratory networks for microscopic diagnosis of malaria.

Specific Objectives

- Proposal and promotion of a conceptual framework that makes it possible to improve the current quality management systems in microscopic diagnosis of malaria in the Region.
- Standardization of processes and tools to optimize the quality management systems.

CONCEPTUAL FRAMEWORK

Manual of Procedures

Procedure is defined as the *precise, concise, clear description of the material, equipment, conditions, activities, and requirements for obtaining a product or a service of a specific quality.*^{3,4}

The manual of procedures is not only a set of procedures (from sampling to release and filing of the results), but individualizes institutional practices through technical-administrative organizational processes; description of the mission, minimum level of training, and competency required; infrastructure; equipment; supplies; quality control; external evaluation of performance; information management; safety measures; cleaning; and waste disposal (the who, what, where,

when, how, and why). The manual establishes the coherence, validity, and continuity of the operating system. It can be defined as an instrument in the service of quality and training that involves the entire laboratory staff and whose purpose is a shift from an oral tradition to a written one.

Operationalizing standards, guaranteeing the duplicability of processes, training personnel, harmonizing techniques in the network, speaking the same language, preventing deviations, reducing costs and errors, facilitating audits, and "selling" an image of offering quality service are the essential functions of the manual of procedures or guide to proper execution of the analyses.

Internal Quality Control

A series of corrective actions applied during the execution of each process to ensure that the results, products, or services can be delivered.^{1,4}

This is a continuous systematic process, with attention to the following characteristics:

- Accuracy and precision of the tests.
- Quality of the equipment, instruments, and reagents.
- Staff performance.
- Control of the results issued.
- Corrective measures.

External Performance Evaluation

External performance evaluation (EPE) is a retrospective, periodic, objective comparison of the different laboratory results through the use of surveys mounted by an independent external entity.

External control of the results released is carried out.⁴

Characteristic Functions of the EPE

- Identification of the laboratory's capacities.
- Ensuring its integration into the network.
- Standardization of the methodology.
- Promotion of training.
- Implementation of corrective measures

Advantages of the EPE

- Periodic.
- Easily executable.
- Standardizable.
- Allows interlaboratory comparison.
- Analyzes the results.
- Permits programmable corrective measures.
- *Complies with ISO*

Disadvantages of the EPE

- Does not explore all the processing stages.
- Does not evaluate the quality of staff training.
- Contains methodological biases (the maximum capacity of the laboratory, not of the staff, is evaluated).
- Does not evaluate local conditions.

Indirect Quality Control

Retrospective monitoring in the reference laboratory of a certain percentage of samples from the network.

Advantages

- Evaluates the technique for preparation of the slide.

- Identifies errors in the diagnosis (result, species, and stage).
- Possible correction of the diagnosis and report.
- More continuous evaluation.
- Reduces biases introduced by giving special attention to the processing of coded samples sent from the reference laboratory within the framework of the EPE.

Disadvantages

- Partial (10% of negatives).
- Does not identify all causes of error.
- Doubling of the work and unit cost.
- Onerous unsanitary logistics.
- Long wait for delivery of results.
- Biases in interpretation through lack of respect for blind reading.
- Excessive workload for the supervisory laboratory. *Not considered in ISO standards.1*

Audit

Systematic independent examination to determine whether the standards and procedures in effect are being applied according to preestablished requirements in all stages on which the reliability of the released results depends.⁴

= Control of conformity and coherence.

= Agreement between theory and practice **Direct Supervision**

Formalized evaluation conducted by the higher level. This type of evaluation permits measurement of the adaptation of the quality system to the quality policy of the institution and its objectives in the network. It is a form of direct observation of performance. The direct supervision modalities stand at an intermediate level between the field EPE and the audit.

Basic Principles of the System

- **Efficient.**
- **Accepted, feasible, and suitable.**
- **Educational in nature.**
- **Confidential.**
- **Equitable and egalitarian.**
- **Legitimately established.**
- **Representative** of the performance of the diagnostic network.
- **Critical, reactive, and proactive** for decision-making and design of interventions.
- **Integrated** into the epidemiological surveillance system and service delivery.
- **Financed and sustainable.**

Essential Elements of the System

Qualification of Human Resources

Personnel in the malaria diagnostic network should be properly trained and certified according to national directives and the structure and standardization of the service delivery network.

Certification of personnel will be established by the national reference laboratories and be based on training and evaluation. In the future it is hoped to have internationally recognized certification.

Manual of Procedures

The national reference laboratory will prepare the standardized manual of procedures for microscopic diagnosis of malaria^{5,6,7} adapted to each operating level (see Item 4.1)

Each procedure should meet the following requirements:

- Performed by experienced responsible personnel.
- Directed by trained staff.
- Consistent with the standards in effect in the country or institution.
- Suitable and consensus-based.
- Detailed, clear, and precise.
- Exhaustive.
- Unequivocal instructions.
- Accessible and eye-catching.

The content of the procedures should include:

- Name.
- Implementation date.
- Principles and fundamentals.
- Drawing, identifying, and transporting the sample.
- Equipment, instruments, and reagents.
- Calibration, internal audits, and processes for indirect control and the EPE.
- Detailed procedures.
- Interpretation of results.
- Limitations of the technique.
- Differential diagnosis.
- Complementary examinations.
- Validation, release, and delivery of the results.
- File.
- Bibliographic references.
- Glossary of terms.
- Specific processes for biosafety and maintenance for each intervention.

Internal Quality Control

Malaria laboratories at all levels should complete and record the following stages as specified in the manual of procedures:

- | | |
|------------------------|---|
| Pre-analytical | Identification and recording of the case, taking and labeling of the sample, transportation and conservation of the material, and working conditions. |
| Analytical | Environment, equipment, reagents, and procedures for preparation, reading, and interpretation. |
| Post-analytical | Validation, recording, issuance, and notification of results. |

The person in charge of each malaria diagnostic laboratory will see to it that there is systematic compliance with the established guidelines for internal quality control. In local laboratories (health posts and/or centers, hospitals) the microscopist should assume this responsibility.

In laboratories at the intermediate and national levels, intralaboratory evaluations (self- evaluations by technical personnel) are recommended.

Visitors, volunteer workers, or other health workers that take, prepare, and ship samples should also meet the requirements laid out in the respective manual of procedures.

External Performance Evaluation

Competencies by Level

The EPE will be conducted at all levels of the laboratory network. Essentially, the national laboratory will be responsible for the preparation of the panels, shipment, and analysis of results. The NRL, in turn, will be subject to external quality control performed by an international laboratory.

Laboratories with public health functions at the next level of complexity in the network will support the NRL in the distribution of material to the other levels and in the flow of information to the national level.

Preparation of Slide Panels

The national reference laboratory will be responsible for preparing the panels of slides of thick blood film according to the following criteria:

- Slides of the species present in the Region and differential diagnoses.
- Slides with different parasite densities.
- Slides with mixed infections.
- Negative slides.
- All slides should be of optimal quality.
- Slides with cover slip.
- Include clinical and epidemiological information and patient history (brief description).
- There should be no fewer than five slides in a panel.
- Groups of uniform panels with respect to the characteristics of the slides (species, parasitemia) should be prepared for use in evaluating different laboratories, so that they can be compared.
- The preparation of uniform panels can be achieved by using blood from a single patient to prepare slides for several panels.
- The slides in the panels should be labeled according to a coding system differentiated by laboratory.

The national reference laboratory can receive assistance from laboratories at other levels in the endemic areas for preparation of panels, for which the NRL will establish a rigorous methodology to be followed to guarantee the quality of the material.

Shipment of Material

- It is recommended that slide panels be sent from the national reference laboratory to the network laboratories at least twice per year.
- Each laboratory will be given an identification code.
- The shipment will conform to the prevailing biosafety standards in the country.

Instruments and Information Flow

- Each slide panel should include the following instruments:
 - Letter of remission that includes methodological details, the objective of the evaluation, and the deadline for the response.
 - Description of the corresponding clinical cases.
 - Response form.
- The deadline for the response should be no longer than one month after receipt of the material.

Analysis and Feedback

- The NRL will analyze the evaluation results on the basis of the following criteria (see Annex 2):
 - Agreement on the result.
 - Agreement on the species.
 - Agreement on the stage.

Evaluation of the agreement on parasitemia will be decided at the national level according to national standards and internationally established methodologies.

- Analysis of the EPE will take into account the overall situation of the laboratories evaluated, the severity of the errors (result, species), repetition of errors, the degree of complexity of the panel, and the number of slides. Aspects to take into account in prioritizing corrective interventions include the following:
 - Errors in identifying the presence or absence of infection.
 - Errors in identifying infection with *P. falciparum*.
 - Errors in identifying *P. vivax* and *P. malariae*.
 - Errors in the differentiation of sexual and asexual forms.
- The NRL will prepare a database to automate information processing.
- The NRL should prepare a report for each laboratory with the results of the individual and global evaluations and recommendations.

Corrective Measures

- Based on the individual report sent by the NRL, the discrepancies identified will be analyzed and reviewed *in situ* by the same microscopist, with the evaluation panel in hand.
- The laboratory in question will document the corresponding corrective measure.
- In coordination with the intermediate laboratories, the NRL will design a plan for direct supervision and training, which will include the laboratories with deficiencies and be based on the following:
 - Magnitude of the error (see Item 6.4.5).
 - Cross-analysis of the results of the EPE with those from indirect control.
- *The NRL will evaluate the determinants of performance, such as supplies, material, equipment, and educational material, using information from other evaluation tools.*

Indirect Quality Control

Characteristics

- Indirect control will be performed by the laboratory at the next level up in the network. The national level is not subject to this type of evaluation.

Shipment of material

- The evaluated laboratories will send 100% of the diagnostic slides processed during the established evaluation period to the higher level (for example, one month per year, which will vary from year to year).
- In the evaluating laboratory a person will randomly select 50 negative slides and 50 positive slides from the evaluated month. If fewer than 100 slides were produced in the designated month, 100% of them will be evaluated.

Analysis of Results and Reporting

- The reading of the slides will be performed by an individual with no knowledge of the initial diagnosis.
- In addition to the criteria for evaluation of diagnostic agreement contemplated for the EPE (see Item 6.4.5), indirect control will include analysis of the technical quality of the preparation, based on the following criteria:
 - Quality of the sample: size, placement, and thickness (thick and thin blood smears).
 - Quality of the preparation: dehemoglobinization, tonality, and precipitates.
- The evaluation of the technical quality of the preparation will be made on the basis of national criteria. A methodology for scoring and qualification (for example, percentage of conformity) should be standardized at the network level.
- In case of a disagreement with the supervised laboratory concerning the diagnosis and identification of the species, there will be a reading by a third party.
- The supervisory laboratory will prepare a report containing the individual and overall evaluations of the area of influence.
- The report on the results will be sent to the NRL and the supervised laboratory.

Corrective Measures

- The supervisory laboratory will design a plan for direct supervision and training that includes the laboratories with deficiencies (see *Corrective Measures*, p. 9).

Direct Supervision

Based on the results of the EPE and indirect control, the laboratories at the higher level will directly supervise the laboratories in their area of influence. These activities are characterized as follows:

- Consistent with the current regulations on competencies and conformities of the different network levels.
- Necessary resources should be programmed.
- At the level of the supervisory laboratory, interventions and timetables for three to six-month periods should be designed.
- Based on preestablished criteria (see Annex 1).
- Supervisors will be trained to standardize the supervision.
- Standard formats will be designed for recording information.

- Adoption of corrective measures will be supported.
- The process of improving management will be consolidated.
- A report should be generated in a preestablished format; it should include the strengths, weaknesses, and recommendations to improve the performance of the laboratory.
- The supervision reports will be sent to the supervised laboratory and the higher level.

Implementation at the Country Level

Implementation of the quality management system in the national networks for microscopic diagnosis of malaria will be a gradual consensus-based process adapted to the structure and development of the laboratory network and network of services in the country. Implementation will be based on the demonstrated strengths of the countries. For this purpose, the formulation of a plan that includes the following steps is recommended:

- Situational diagnosis.
- Preparation of a normative proposal.
- Definition of the structure.
- Preparation of a work plan and a budget.
- Preparation of a manual of procedures.
- Standardization and systematization of external evaluation, indirect control, and direct supervision.
- Systematization of internal quality control.
- Training of human resources involved in the network.
- Implementation and evaluation of pilot experiences.
- Review of the national regulation.
- Gradual implementation at the national level.
- Impact assessment.

The implementation of the system for management of the quality of microscopic diagnosis of malaria coincides with lines of work contained in regional initiatives promoted by the Pan American Health Organization/World Health Organization and developed in the countries:

- *Roll Back Malaria* Initiative ⁸
- RAVREDA/AMI Project (*Amazon Network for the Surveillance of Antimalarial Drug Resistance*)

The *Amazon Network for the Surveillance of Antimalarial Drug Resistance* is functioning in eight countries of the Amazon region (Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, Suriname and Venezuela), with the objective of orienting drug policies on the basis of evidence to guarantee access to safe, effective treatment.

The success of the implementation and the sustainability of the systems for managing the quality of the diagnosis will depend on the political commitment of the Ministries of Health and technical strengthening of the laboratory networks.

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8. PAHO. 42nd *Directing Council. CD42.R15*. 2000.

Annexes

Annex 1: Plan for the Questionnaire for the Audit and Direct Supervision of Laboratories for Malaria Diagnosis

| | |
|--|--|
| <ul style="list-style-type: none">• General organization<ul style="list-style-type: none">- Mission- Organization chart- Work plan | <ul style="list-style-type: none">• Analytical phase<ul style="list-style-type: none">- Validation of techniques- Procedures- Calibration- Internal audits- Interpretation of results |
| <ul style="list-style-type: none">• Quality strategy<ul style="list-style-type: none">- Manual of procedures- Records of internal quality control- Records of the EPE- Records of indirect control- Audit and supervision reports- Corrective measures | <ul style="list-style-type: none">• Post-analytical phase<ul style="list-style-type: none">- Validation of results- Registry- Issuance- Notification- Delivery terms |
| <ul style="list-style-type: none">• Physical infrastructure<ul style="list-style-type: none">- Sampling room- Technical space- Administrative space- Storage space | <ul style="list-style-type: none">• Complementary examinations<ul style="list-style-type: none">- Rationale- Modalities of shipment outside the country |
| <ul style="list-style-type: none">• Staffing<ul style="list-style-type: none">- Post profile- Competency requirements- Training program- Continuing education- Satisfaction/motivation | <ul style="list-style-type: none">• Records<ul style="list-style-type: none">- Confidentiality- Access |
| <ul style="list-style-type: none">• Materials and equipment<ul style="list-style-type: none">- Inventory- Management of procurement- Manuals on utilization- Input management and maintenance | <ul style="list-style-type: none">• Biosafety<ul style="list-style-type: none">- Standards- Environmental protection- Waste disposal |
| <ul style="list-style-type: none">• Pre-analytical phase<ul style="list-style-type: none">- Registry of patients- Sampling- Identification- Transport- Registry- Maintenance | <ul style="list-style-type: none">• Maintenance<ul style="list-style-type: none">- Programming of prevention- Instrument calibration- Corrective measures |

Annex 2: List for the Qualification of the EPE

| Slide | Reference | | | | Laboratory Evaluated | | | | | | |
|----------------------------|-----------|---------|---------------------|--------------------|----------------------|-----------------------|---------|--------------------|---------------------|--------------------|--------------------|
| | Result | Species | Stage | | Result | | Species | | Stage | | |
| | | | <i>Trophozoites</i> | <i>Gametocytes</i> | <i>Ideal count</i> | <i>Count obtained</i> | | <i>Ideal count</i> | <i>Trophozoites</i> | <i>Gametocytes</i> | <i>Ideal count</i> |
| | | | | | | | | | Yes | Yes | |
| | | Pf | | | | | Pf | | Yes | No | |
| | | Pf | | | | | Pv | | No | No | |
| | | | | | | | | | Yes | No | |
| | | Pv | | | | | | | | | |
| | | Pf+Pv | | | | | Pf | | | | |
| | | Pf+Pv | | | | | Pv | | | | |
| | | Pf+Pv | | | | | Pv+Pf | | | | |
| | | Pf+Pv | | | | | Pf+Pm | | | | |
| | | Pv | | | | | Pf+Pv | | Yes | No | |
| | | Pm | | | | | Pf | | No | Yes | |
| Count | | | | | | | | | | | |
| Final qualification | | | | | | | | | | | |

* = Identification and nonidentification of *P. falciparum*.
 Evaluation of the capacity to diagnose the stage is performed only for mono-infections.

Annex 3: List of Participants

- Keith Carter, Regional Malaria Advisor, PAHO Headquarters, Washington, DC
- Mario Valcárcel, Communicable Diseases Advisor, PAHO-Venezuela
- Roberto Montoya, Coordinator, RAVREDA/AMI Project, PAHO-Brazil
- Jean Marc Gabastou, PAHO Headquarters, Washington, DC
- Leopoldo Villegas, Tumeremo, Venezuela
- Magda Rodríguez de Gaviria, Malariología, Venezuela
- Mehudy Medina E., Malariología, Venezuela
- Magda Magris C., Caicet, Venezuela
- Sonia Gutiérrez González, National Institute of Health, Peru
- Geane Maria de Oliveira, CGLAB, Brazil
- Truus Derks, Suriname
- César Díaz, National Malaria Program, Ecuador