

# Amazon Malaria Initiative/ Amazon Network for the Surveillance of Antimalarial Drug Resistance

Strategic Orientation Document on Supply Management  
and Quality Assurance for Drugs and Supplies Used  
in Malaria Diagnosis and Treatment



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# Amazon Malaria Initiative / Amazon Network for the Surveillance of Antimalarial Drug Resistance

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# 1

## Acronyms and abbreviations

**ACT:** Artemisinin Combination Therapy

**AMI:** Amazon Malaria Initiative

**CQ:** Chloroquine

**HSS/MT:** Essential Medicines and Technologies project

**L1:** Level 1

**L2:** Level 2

**L3:** Level 3

**LLIN:** Long-lasting insecticide-treated net

**MCM:** Medicine Quality Monitoring

**MSH:** Management Sciences for Health

**NMCP:** National Malaria Control Program

**OMCL:** Official Medicines Control Laboratory

**PAHO:** Pan American Health Organization

**PQ:** Primaquine

**PQM:** Promoting the Quality of Medicines program

**PRO:** Procurement and Supplies Management Area

**RAVREDA:** Amazon Network for the Surveillance of Antimalarial Drug Resistance

**RMP:** Regional Malaria Program

**SF:** Strategic Fund

**SPS:** Strengthening Pharmaceutical Systems program

**TLC:** Thin Layer Chromatography

**USAID:** U.S. Agency for International Development

**USP:** U.S. Pharmacopeial Convention



# 2

## Objective of the Strategic Guidelines

### 2.1 **General**

To provide elements that help ensure a continuous supply of quality-assured drugs and supplies for the diagnosis and treatment of malaria, with differentiated strategies for high- and low-incidence areas.

### 2.2 **Specific**

To describe tools for evaluating the availability of and access to quality-assured drugs and supplies.

To identify strategies with differentiated interventions for high- and low-incidence areas, within a quality assurance framework for the selection, procurement, distribution, and use components.





# 3

## Introduction

The Amazon Malaria Initiative (AMI), which is supported by the U.S. Agency for International Development (USAID), has provided technical assistance through several partners for malaria control in the countries that share the Amazon Basin, such as Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, and Suriname.

In recent years, all the Amazon Basin countries have experienced a dramatic decline in malaria incidence. The number of cases in the AMI participant countries dropped from 962,325 in 2000 to 668,687 in 2007, a 30% decline. Of the seven countries that are part of the initiative, only Colombia had an incidence in 2007 comparable to that at the beginning of the decade. The most significant reduction (greater than 90%) has been in Ecuador and Suriname. Malaria in Suriname is concentrated in a few areas where the population generally has limited access to health services.<sup>1</sup>

Several factors have combined to produce this favorable epidemiological situation. They include, among others, the adoption of artemisinin combination therapies (ACT) for the treatment of *Plasmodium falciparum*, the reduction of chloroquine (CQ) and primaquine (PQ) regimens for *Plasmodium vivax* from 14 days to 7 days in some countries, the introduction of long-lasting insecticide treated nets (LLIN), more efficient management of national programs, and actions that target populations at greater risk.

In 2008, the Strengthening Pharmaceutical Systems (SPS) program of Management Sciences for Health (MSH), one of the AMI partners, conducted a study on the implications of low incidence for drug supply management.<sup>2</sup>

1. Malaria in the Americas Forum 2009: "Counting Malaria Out" towards the 2010 Targets and the UN Millennium Development Goals. Available at: [http://new.paho.org/hq/index.php?option=com\\_content&task=view&id=1942&Itemid=1683&lang=en](http://new.paho.org/hq/index.php?option=com_content&task=view&id=1942&Itemid=1683&lang=en)
2. Sánchez López, A. and E. Barillas. 2009. Implications of the Low Prevalence of Malaria for Managing Medicine Supplies: Technical Report. Produced by the Strengthening Pharmaceutical Systems program at the request of the United States Agency for International Development as part of the Amazon Malaria Initiative. Arlington, VA: Management Sciences for Health. <http://www.usaidami.org/extras/Implications.pdf>

The study was based on a logical framework that outlines the potential implications of low incidence on drug supply management (Table 1).

Table 1: **Potential of reduced incidence of malaria to impact drug supply management**

Component of supply management	High incidence	Low incidence
Selection	<ul style="list-style-type: none"> <li>• Drugs in bulk</li> <li>• Long shelf life not a consideration</li> </ul>	<ul style="list-style-type: none"> <li>• Drugs in blister with long shelf life</li> </ul>
Planning for needs	<ul style="list-style-type: none"> <li>• According to expected morbidity</li> <li>• Working and buffer inventories available in all facilities and warehouses</li> <li>• Inventory of vital drugs (quinine in ampoule) maintained at all establishments</li> </ul>	<ul style="list-style-type: none"> <li>• Expected morbidity + emergency inventory for resurgence held in regional warehouses accordingly to vulnerability analysis</li> <li>• Inventory of vital drugs maintained at the regional warehouses or reference centers</li> </ul>
Procurement	<ul style="list-style-type: none"> <li>• National purchase from domestic or international suppliers</li> </ul>	<ul style="list-style-type: none"> <li>• Joint purchase of all drugs, or at least drugs for special cases</li> </ul>
Transport and storage	<ul style="list-style-type: none"> <li>• Independent (vertical) transportation and storage systems</li> </ul>	<ul style="list-style-type: none"> <li>• Integration of transportation programs and storage programs</li> </ul>
Inventory maintenance and management	<ul style="list-style-type: none"> <li>• Working and buffer inventories maintained at all levels of the supply chain according to morbidity</li> </ul>	<ul style="list-style-type: none"> <li>• Working and buffer inventories take account of vulnerability to resurgences</li> <li>• Probable increase in the percentage of expired products</li> </ul>
Use	<ul style="list-style-type: none"> <li>• Instructions given to patient by prescribing personnel, but drugs taken at home</li> </ul>	<ul style="list-style-type: none"> <li>• Treatment strictly supervised in every case</li> </ul>

The key findings of the field visit to four countries (Colombia, Ecuador, Peru, and Bolivia) from 15 February to 15 March 2009 were as follows:

1. There are no differentiated strategies for control of the disease in low versus high-incidence areas, nor, as a result, specific strategies for management of drug supply in the two scenarios.
2. All the countries studied had introduced ACT for the treatment of *P. falciparum*, which may account for the fact that there has been a proportionately greater reduction in *P. falciparum* cases than in *P. vivax* cases.
3. Along with the reduction in the number of malaria cases, there has been a reduction in severe malaria cases and other “special” cases such as malaria during pregnancy and resistance to first-line therapy. A related study conducted by MSH/SPS in 2008 found that Peru reported problems procuring quinine in ampoules due to distributors’ lack of interest in marketing these products in the low volumes that the country now requires.<sup>3</sup> A rapid evaluation done in 2009 revealed problems in first-line drug procurement for the same reasons.<sup>4</sup>

3. Briggs, J. and E. Barillas. 2009. Report of Study of Availability of Medicines to Treat “Special Cases” of malaria in South and Central America. Provided to the United States Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) program. Arlington, VA: Management Sciences for Health. <http://www.usaidami.org/extras/Informedeestudio.pdf>.

4. In none of the countries studied, even those with low incidence such as Ecuador, is the risk of outbreaks analyzed in order to estimate needs and plan for the distribution of drugs and supplies. As a consequence, policies are not in place to maintain buffer stocks in provinces that have significantly reduced the incidence of malaria for areas where transmission is not occurring, but a risk of outbreaks exists.
5. Only in Peru is the transportation and storage of drugs and supplies for malaria diagnosis and treatment integrated with the other public health supplies. In Bolivia, Ecuador, and Colombia the distribution chain is vertical. The National Malaria Control Programs (NMCPs) in these countries maintain their own warehouses, and have their own inventory systems and means of transportation. Given the reduction in incidence of malaria, these operations are relatively ineffective and excessively expensive.
6. At the time of the study, all countries conducted drug quality control in their central laboratories after procurement. They also evaluated quality at sentinel sites via basic<sup>5</sup> tests, although this practice was neither regular nor called for by the NMCPs. The standardized procedures that these countries use, with technical assistance from AMI, include a systematic approach to drug quality control throughout the supply chain. However, no country has addressed the question of procedures for quality control of drugs that will have a low turnover in areas with reduced incidence.
7. Treatment strictly supervised by health workers is recommended, and is operationally feasible to implement in low-incidence areas. The study found the practice being applied only in Peru. In Ecuador, it has not been considered, although incidence is low.

4. Barillas, E. 2009. *Análisis de la disponibilidad de medicamentos antimaláricos en los países que comparten la Cuenca de Amazonas*. Provided to the United States Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) program. Arlington, VA: Management Sciences for Health.
5. Thin layer chromatography for semi-quantitative measurement of the content of active ingredient.



# 4

## Strategies and Tools for Evaluating the Availability of and Access to Quality-Assured Drugs and Supplies

The specific tools used for the management of the drug supply in high and low-incidence malaria scenarios depends on the geographical distribution of the disease and the level of programmatic organization in place for implementing the various control interventions. As a part of the study mentioned previously, strategic and annual plans were analyzed, as well as the proposal presented to the Global Fund by the countries of the AMI initiative. However, none of the proposals explicitly included differentiated approaches to malaria control for high- and low-incidence areas.

An overall strategy for a national program would mean classifying the different areas of the country on the basis of the current incidence of the disease, parasite studies, and potential risk, so as to deploy the particular tools of each of the program's lines of work according to precise geographical criteria.

For the supply management and quality assurance component, the following strategies are proposed:

### 4.1 Periodic review of therapeutic regimens

Available Amazon Basin studies show *P. vivax* to be sensitive to CQ and PQ combinations. However, studies at the beginning of the decade found *P. falciparum* resistant to these same drugs. In the wake of this evidence, all the countries changed their therapeutic regimens to ACT. The most recent sensitivity studies still show *P. falciparum* being sensitive to ACT. Thus, changes in the treatment regimens currently in place are not expected in the short term.

Although all countries have shifted from their pre-ACT regimens, there is a multiplicity of combinations of different active ingredients and presentations. It became clear at the meeting in Cartagena, Colombia on 12–15 April, 2010 that the situation fails to take into account the availability of suppliers in the local market, the logistical capacity to manage a range of products in a large number of presentations, or the most recent recommendations of the World Health Organization (WHO).<sup>6</sup> The impact of these omissions has been aggravated by the reduction in the incidence of malaria in the region.

6. World Health Organization. 2010. *Guidelines for treatment of Malaria*. Geneva: World Health Organization, Global Malaria Program. Second Edition.

At the meeting, it was proposed to review the regimens in use, following the scheme shown in Table 2.

Table 2: **Proposal to standardize *P. falciparum* treatment regimen in the region**

Regimen	2010	Proposal *	Presentations of drugs **
Bolivia	AS+MQ (single-drug)	AS+MQ+PQ	Fixed dose or co-blister packs
Brazil	TMJ-LUM ACE-MQ	TMJ-LUM+PQ ACE MQ+PQ	Fixed dose for both combinations
Colombia	TMJ-LUM	TMJ-LUM+PQ	Fixed-dose combination
Ecuador	AS+SP (Co-blister)	TMJ-LUM+PQ	Fixed dose
Guyana	TMJ-LUM	TMJ-LUM+PQ	Fixed-dose combination
Peru (Coast/Amazon)	AS+SP AS+MQ (single-drug)	AS+MQ+PQ	Fixed dose or co-blisters
Suriname	ATM+LUM	ATM+LUM+PQ	Fixed-dose combination

\* The underlined therapeutic combination is among the suggested changes to current regimens.

\*\* The fixed-dose combinations do not include PQ.

TMJ: Artemether; ACE: Artesunate; LUM: Lumefantrine; MQ: Mefloquine; SP: Sulfadoxine-pyrimethamine

If the countries decide to change their regimens on the basis of this proposal in the medium term, they should realize that the decision to modify should be followed by the preparation of therapeutic guidelines, staff training, and a logistical organization that makes it possible to provide the entire system with adequate working and buffer inventories. In fact, some of the countries that attended the meeting in Cartagena, Colombia in 2010 have proposed to begin modifying their therapeutic regimens.

Under the proposed strategy, there would then have to be periodic reviews of therapeutic regimens using a methodology similar to that employed at the Cartagena workshop. The criteria for review would include, among other things:

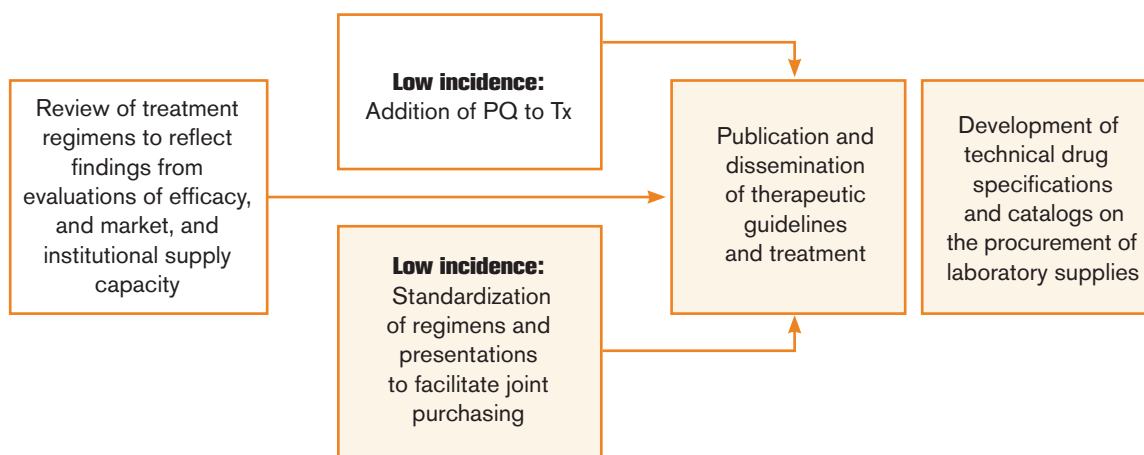
- The need for stable and easier to handle molecules and presentations, particularly for areas of low incidence where the turnover in inventory is low. Although blister presentations and long shelf life are always desirable, they are not critical for products that have high turnover. In a low-incidence scenario, however, inventories of low-turnover drugs must be maintained in health care facilities and warehouses. In these circumstances, depending on product expiration date, packaging and storage conditions and long shelf life may become more important.

- The availability of suppliers in the market, particularly suppliers of essential products that have low purchasing volumes, such as those required for severe cases.
- The possibility of standardizing regimens with that of other countries in the region to:
  - facilitate joint purchases that are coordinated regionally or through cooperation agencies, exchanges or donations
  - facilitate and supervise the treatment of patients living in border areas
  - implement resistance studies more easily and with better coordination
- The logistical capacity of local distribution systems to handle the number of presentations included in their regimens.

It is neither expected nor intended that all the countries should change their regimens frequently in light of these criteria. However, those that do make changes should take into account the fact that changing therapeutic regimens means:

- Including new drugs in national formularies and lists
- Preparing and disseminating standardized treatment guidelines
- Training staff in the use of the new formulations
- Organizing logistics for the supply of the new formulations, and withdrawing the obsolete formulations

Figure 1. **Strategic elements in drug selection**



Tx: Treatment

## 4.2 Planning for supply requirements in low-incidence areas

If the usual criteria for needs-based planning, such as historical consumption or expected morbidity, are followed, health care facilities in areas of low or no incidence may not receive any drugs. This may lead to hindering the treatment of patients, if and when they appear, as well as response to outbreaks and timely management of severe cases.

The recommended strategy consists of following the usual planning criteria for high-incidence areas. For low-incidence areas, planning should be based on the objective of ensuring that facilities have an inventory of drugs and supplies based on:

- the current situation and the epidemiological trends in the area
- the risk of outbreaks in light of ecological factors
- mechanisms that ensure the immediate provision of drugs and supplies in the event of need—for example, access to the closest regional drug warehouse

Facilities in very low-incidence areas that are highly populated and where access to regional warehouses is difficult should consider having a working inventory in every facility equivalent to 3–5 full treatments for each regular therapeutic category, and at least one treatment of severe cases. For areas of very low incidence with good access to departmental or regional warehouses, the strategic inventories at those warehouses can be maintained and moved to outlying locations as needed.

Maintaining an inventory of low-turnover drugs for diseases of epidemiological importance means a higher rate of loss due to expiration, even with strict and efficient management of the inventory. Thus, policies should be established to allow for the removal of expired drugs.

Changing suppliers, either because of changes in therapeutic regimens or as a result of changes in purchasing mechanisms, means a change in waiting periods, and consequently a revision of the annual planning of requirements. Reserve antimalarial stock requirements should be estimated in light of these aforementioned criteria, supply conditions, and the shelf life of the commonly used antimalarials. A buffer stock of 9–12 months may be sufficient in situations where delivery times are irregular. However, the size of the buffer stock must be established by each country based on its supply conditions and other available information. It should be distributed throughout the points of the supply chain. For example; 3 months of stock in health care facilities, 3 months in provincial warehouses, and 3 months at the central warehouse. Once a program's reserve stock levels and distribution have been established, the relevant criteria should be explicitly set forth in the program's operational procedures.



### 4.3 Development of strategic information systems for supply management

Supply management information systems that account for, at least, the consumption and supply at all the nodes of the delivery system (central warehouse, state provincial warehouses, and health care facilities) are complex, difficult to manage, and expensive to maintain. Information collected from MSH/SPS<sup>8</sup> showed that very few AMI member countries have information systems with these features.

In the absence of functioning supply information systems, whether comprehensive (covering all the drugs used by ministries of health) or those specific to the malaria program, MSH/SPS proposed the collection of data for a limited group of indicators that can foster strategic decision-making (Table 3). The source of information for these indicators in a country is its central warehouse, plus a sample of of the country's health care facilities that were supervised during the period studied, if the country has a supervision system.

Table 3. Proposed indicators of a strategic information system for supply management

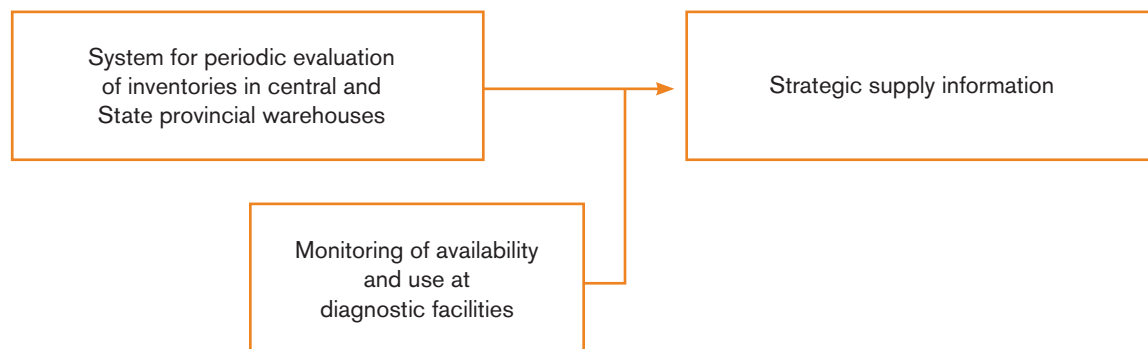
1	Percentage of antimalarial drugs available in the central warehouse at the end of the reporting period.
2	Stocks of antimalarial drugs in the central warehouse, expressed in months of supply given consumption levels.
3	Percentage of days during the period when there was a shortage of antimalarial drugs in the central warehouse.
4	Percentage of the drugs acquired during the period that were sent to quality control.
5	Percentage of the drugs analyzed that passed the quality test.
6	Monetary Value of the drugs that expired in the central warehouse during the period studied.
7	Percentage of Provincial states that withdrew the drug from the central warehouse on a timely basis.
8	Percentage of Provincial states warehouses where a shortage of CQ, PQ, or ACT in any of their presentations was reported during the period studied.
9	Value of the drugs that expired in the provincial warehouse in the last 6 months.
10	Percentage of health care facilities that were supervised during the period studied.
11	Percentage of health care facilities that at the time of the visit did not have all the supplies and laboratory equipment needed for diagnosis.
12	Percentage of health care facilities with a shortage of at least one of the first line drugs required for malaria treatment.
13	Percentage of health care facilities where the quantity of valid antimalarials at the time of the visit was not sufficient to meet demand until the next delivery.

8. Information included in: Barillas, E. et al., 2009. *Taller para el Mejoramiento del Sistema de Información de la Gestión del Medicamentos para la Malaria*. Lima, Peru, 21-23 April 2009.

The logic behind this proposal is that if all the drugs are available at the central warehouse plus at a representative sample of peripheral warehouses and supervised establishments at the time of the evaluation, and if the working inventory is sufficient to cover needs until the next delivery, then there are no major supply problems. An approach of this type does not obviate the need for a comprehensive system with online information on all storage and dispensing points, but it does ensure that there is a necessary minimum of information for making strategic decisions on supply management.<sup>9</sup>

“Vertical” information systems used by public health programs to monitor the supply of private-sector drugs tend to reflect fragmented supply systems. For the sake of operational efficiency, there is a tendency to integrate “vertical” systems in national supply management systems. The integration of information systems is even more significant when reduced incidence results in a lessened flow of information.<sup>10</sup>

Figure 2. **Strategic elements to improve information for supply management**



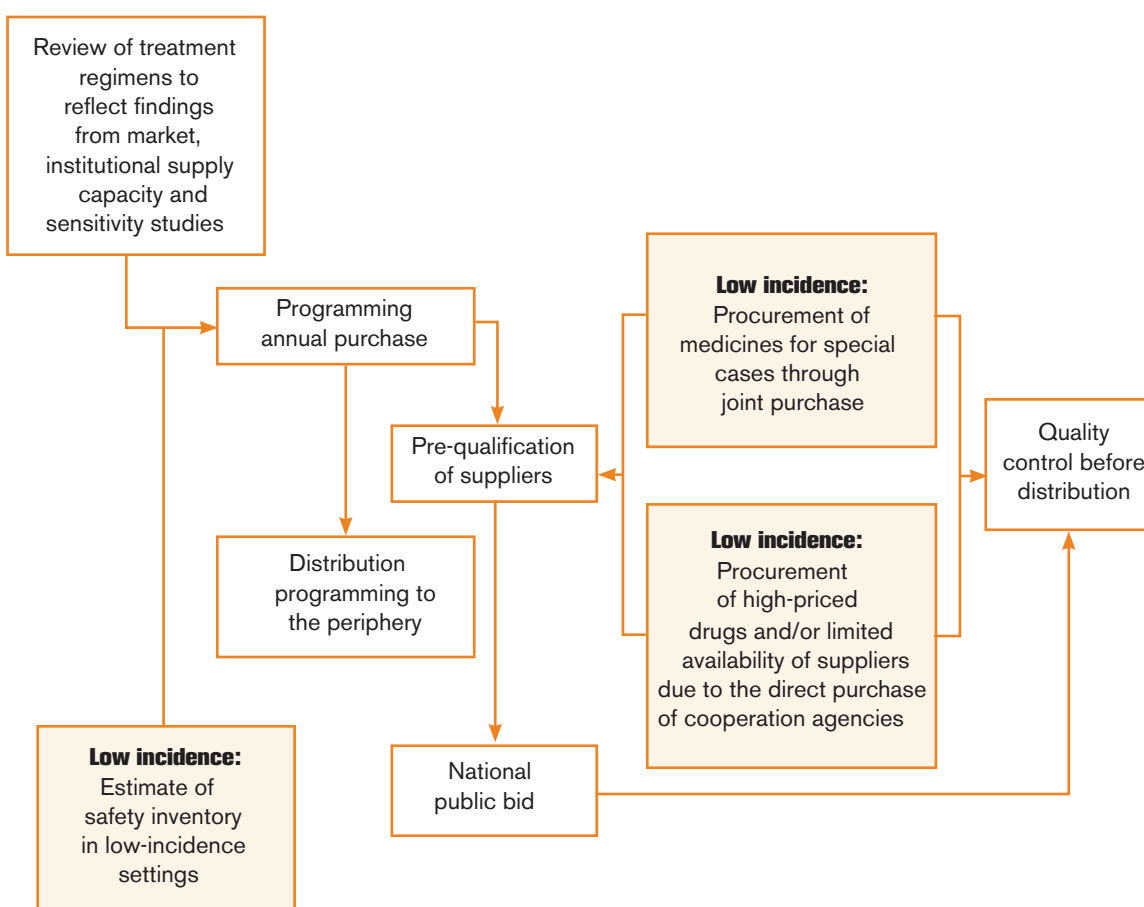
9. The collection of data for these indicators in four of the initiative's member countries and the dissemination of a technical report to decision-makers facilitated drug donations and promoted immediate purchasing in countries that faced potential shortages. (Barillas, E. 2009. *Análisis de la disponibilidad de medicamentos antimaláricos en los países que comparten la Cuenca de Amazonas.*)

10. MSH/SPS provides support to Ecuador and Bolivia for the integration of information systems.

## 4.4 Implementation of alternative mechanisms for drug procurement

In high-incidence situations there are commercial incentives for domestic or international suppliers to supply the public sector. When the number of cases diminishes, either the suppliers' financial interest wanes or the prices they quote rise significantly. This is the basic cause of drug shortages for the treatment of the few special cases that still occur in the region ("special" in terms of severity, malaria in pregnancy, or because of resistance to first-line therapies).<sup>11</sup> This problem has recently extended to first-line drug procurement in Peru, where several purchase lines remained blank in 2009 because there were not enough suppliers to declare bids legally valid.

Figure 3. **Strategic elements for programming and procurement of drugs**



11. Briggs, J. and E. Barillas. 2009. Report on Study of Availability of Medicines to Treat "Special Cases" of Malaria in South and Central America. Provided to the United States Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) program. Arlington, VA: Management Sciences for Health.

An alternative to solve this problem is direct purchasing through international cooperation agencies. The Strategic Fund of the Pan American Health Organization (SF/PAHO) provides this mechanism available to the region's countries. National purchasing and contracting legislation should permit the use of this mechanism and the arrangements that may be called for by the agreements that are signed—payment before receiving product, in particular. The SF/PAHO drug procurement procedures may be found in Annex 1, and the accompanying form is in Annex 2.

The review of treatment regimens used in the region and the possible standardization of some regimens at the regional level, opens up the possibility of organizing joint purchasing systems or conducting price negotiations with international suppliers. While an efficient joint procurement system is being organized, the drugs needed for the management of special cases may be obtained through donations. In other words, either through technical cooperation with agencies like SF/PAHO or by working directly with drug manufacturers. The quantities required in each country are so small that it is inefficient to put them through a process of national bidding, particularly if suppliers are not expected to be interested in supplying the local market.

#### **4.5 Integrating transportation, storage, and inventory management systems**

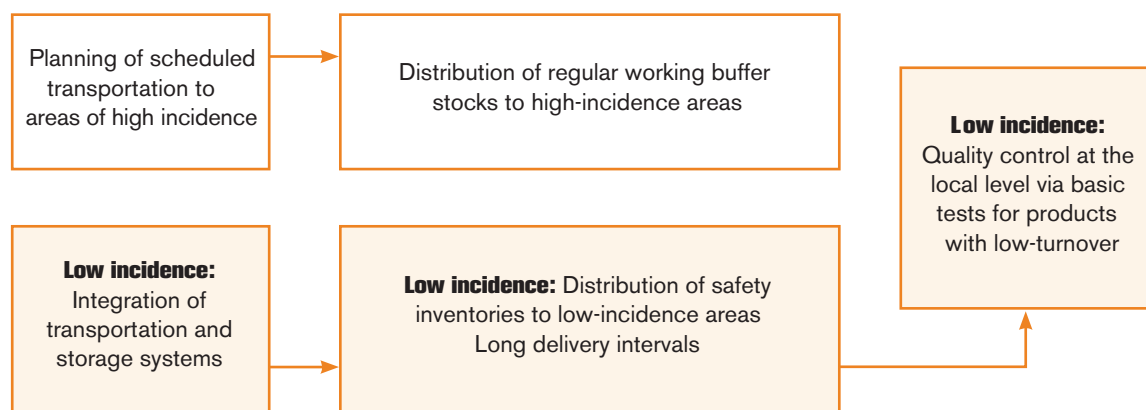
In high-incidence areas, independent vertical drug and inputs supply systems have been set up for NMCPs. Many central and State provincial warehouses in the region store products exclusively. Systems for inventory management, periodic needs, and transportation also tend to be independent of the systems governing other drugs and supplies used in public health facilities.

In low-incidence areas, vertical delivery systems are expensive and inefficient. To reduce operating costs and improve the overall efficiency of public sector logistics, it is necessary to integrate inventory storage, transportation, and management. In carrying out the integration, it should be borne in mind that some elements of the supply should continue to be handled as the responsibility of a specialized malaria control entity. This includes selection of drugs and inputs, planning for needs, and strategies for ensuring adherence to treatment.

Technical personnel from the malaria program should participate in establishing the criteria to be used in planning distribution to low-incidence areas. For example, in these areas it may be necessary to space deliveries because of low consumption, or to maintain strategic inventories in State provincial warehouses that can be moved to nearby facilities immediately.

In the process of integrating vertical delivery systems, it is important to make sure that the new procedures do not create breaks in the supply chain. One possibility is to make integration progressive, beginning at the central level and moving out from there, starting with virtual integration of inventories, information systems, and coordination of transportation to State provincial facilities, and moving if necessary to physical integration of inventories in single State provincial warehouses.

Figura 4. **Strategic elements for drug planning and procurement**



#### 4.6 Assurance and drug quality control

In order to ensure that products acquired are of good quality and do not deteriorate before being administered to the patient, drug quality control throughout the supply chain is essential, whatever the epidemiological situation. In most countries, the institution responsible for this will be the Official Medicines Control Laboratory (OMCL). It conducts validated or compendial tests to confirm that drugs meet the specifications established during the drug registration process. However, there are certain constraints involved in using compendial tests. The main issues are:

- lack of available services at the OMCL due to factors such as limited human or financial resources, geographical barriers to access, among others, and
- urgent need for results from quality control testing, so that the time for compendial tests is not available

Considering these constraints, the Promoting the Quality of Medicines (PQM) program implemented by the U.S. Pharmacopeial Convention (USP) has developed a three-level approach to quality control. The approach is based on three levels of analysis that use different quality control methodologies. The levels involve procedures of increasing complexity and are mutually complementary. Respectively, they involve:

- Level 1 (L1): visual and physical inspection
- Level 2 (L2): basic analytical tests
- Level 3 (L3): validated or compendial tests

The elements of these procedures, which are outlined in Table 4, are designed to address specific needs within the entire process involving the drugs. The approach can be used regardless of the prevalence of the disease.<sup>12</sup>

Table 4: **Features of the three levels of quality control** <sup>13,14</sup>

Level	Type of analysis	Type of test	Purpose	Personnel responsible for the analysis
1	Visual and physical inspection	<b>Visual:</b> <ul style="list-style-type: none"> <li>• Properties of the insert and packaging</li> </ul> <b>Physical:</b> <ul style="list-style-type: none"> <li>• Drug's appearance and physical condition</li> </ul>	<ul style="list-style-type: none"> <li>• To identify expired drugs and/or drugs accompanied by insufficient, mistaken, and/or fraudulent information; damaged packaging; and damage to or alterations in the state of the drugs.</li> </ul>	<ul style="list-style-type: none"> <li>• Personnel responsible for management at each stage of the supply chain, from procurement to use, and from the local level to the central level.</li> </ul>
2	Basic analytical test	<ul style="list-style-type: none"> <li>• Disintegration</li> <li>• Colorimetric reactions<sup>14</sup></li> <li>• Thin layer chromatography (TLC)</li> </ul>	<ul style="list-style-type: none"> <li>• To identify drugs that are deficient in any of four quality attributes: identity, content, purity, and (for solid presentations) disintegration.</li> </ul>	<ul style="list-style-type: none"> <li>• Personnel trained in basic tests</li> <li>• OMCL personnel</li> </ul>
3	Validated or compendial tests	<ul style="list-style-type: none"> <li>• As per specifications in the drug registry</li> </ul>	<ul style="list-style-type: none"> <li>• Evaluation of all critical quality attributes.</li> </ul>	<ul style="list-style-type: none"> <li>• OMCL personnel</li> </ul>

11. The article on this approach is in the process of internal revision, and the final version will be released in the course of 2011.

12. United States Pharmacopeia Convention Drug Quality and Information Program and collaborators. 2007. *Ensuring the Quality of Medicines in Resource-Limited Countries: An Operational Guide*. Rockville, MD: The United States Pharmacopeia Convention. Available at: [http://www.usp.org/pdf/ EN/dqi/ensuringQualityOperationalGuide.pdf](http://www.usp.org/pdf/EN/dqi/ensuringQualityOperationalGuide.pdf)

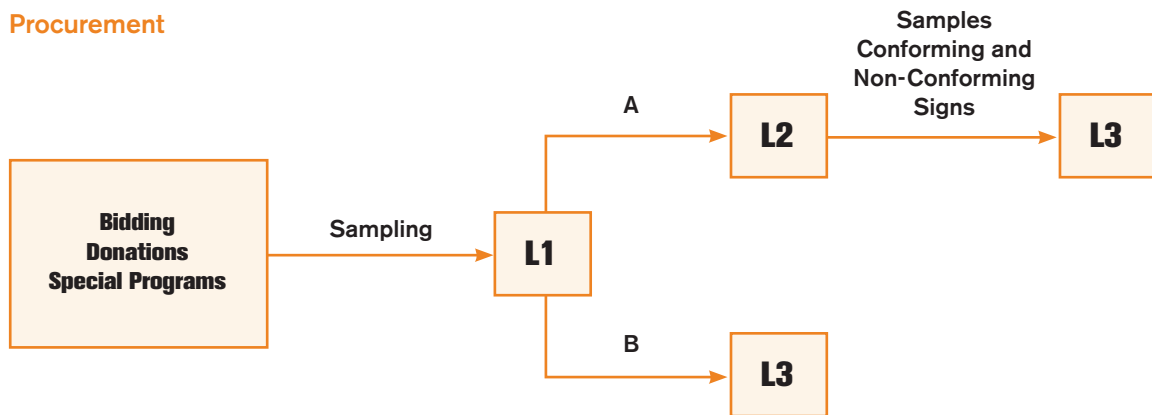
13. Whenever quality control processes are carried out, there should be visual and physical inspection (L1), whether or not second- and/or third-level tests are later performed.

14. Colorimetric methods are not recommended for drugs for which CCD methods exist. Colorimetric methods in the field can assess only one quality attribute (identity), whereas CCD provides information on three quality attributes (identity, content, and purity).

Figure 5 outlines the processes recommended for the implementation of the three-level approach at the various stages of the supply chain. Specific clarifications for these schemes and the use of the approach in situations of high and low incidence are detailed in the subsequent sections.

Figure 5: Implementation of the three-level approach in the supply chain

**Procurement**

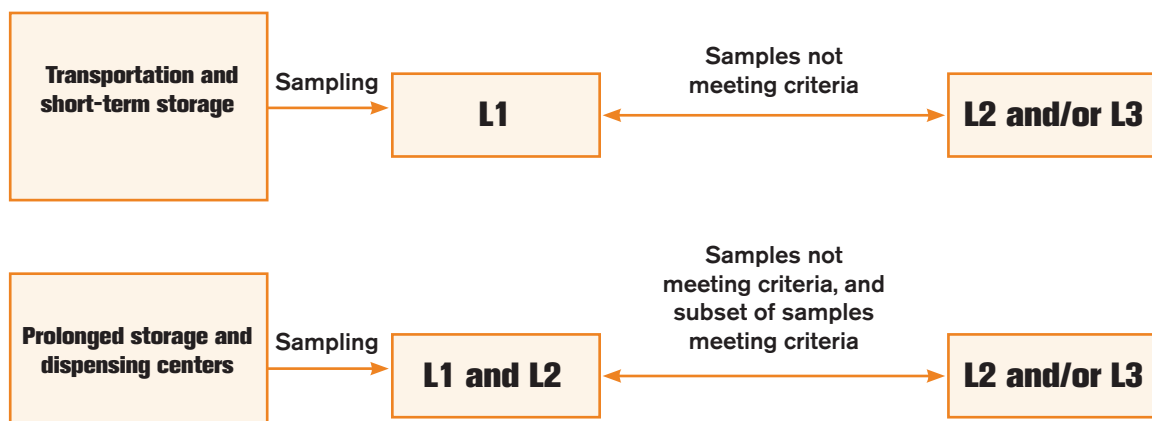


A -Drugs produced by reliable manufacturers with a previous history of good quality.

B -1: Lacking information on previous quality history

2: Drugs considered to represent a risk in light of the manufacturer's previous history or the product's attributes

**Distribution**



The dissemination of quality control results at the national and regional levels is important to give the public information on products of poor quality and to prevent their use.<sup>15</sup>

### *Procurement*

Regardless of the level of incidence, the quality of antimalarial drugs should always be evaluated after acquisition before they are distributed. It should also be taken into account that only L3 can ensure that a drug meets all the specifications set forth in the drug registry. As indicated in Figure 5, however, L2 will be used instead of L3 in some situations. The considerations involved are valid in both low and high-incidence areas. The decision on what level to use should be based on a risk analysis, taking into account the product's stability or other attributes, the previous history of the manufacturer, and storage conditions during shipment, among other things. For example:

- In the case of drugs for which there is already a previous history of good quality, and which are produced by reliable manufacturers, L2 can be used to confirm the quality of new lots. Included here are manufacturers prequalified by WHO and audited for the Good Manufacturing Practices publication of the U.S. Food and Drug Administration.
- In the case of drugs such as SP, where dissolution problems have frequently been documented, L3 should be used, since the basic L2 tests cannot detect that type of problem.
- In the case of drugs that are of high impact, either because the amount consumed is high or because they are used in managing severe cases, the advantage of using L3 at least in some lots should be considered, since it diminishes the risk of quality problems not detected by L2 testing.

Below are indications as to how the three-level approach can be used during procurement in specific scenarios that occur in high or low-incidence situations.

In areas with **high incidence**, L3 is advisable, but it can put a large burden on the LOCM if the volume of the drugs acquired is large. Thus, a combination of L2 and L3 is an alternative that can maximize the benefits of the process by applying quality control to a greater number of drugs or to more lots of a single drug. For products involving greater risk, for example, a limited number of batches can be subjected to L3 and the rest to L2. (See the combination of alternatives A and B in Figure 5.)

15. PQM has developed a database that, with prior consent of the countries, includes the results of quality control obtained in programs and/or initiatives with which PQM works. The information is freely available at: [http:// www.usp.org/worldwide/medQualityDatabase/](http://www.usp.org/worldwide/medQualityDatabase/)



In **low-incidence** areas, the volume purchased will be less, consisting of a single lot or a very small number of lots. Hence, if the product justifies it, L3 is recommended. However, in cases of low incidence it may be possible to make most of the purchases jointly as part of a group of several countries through the SF. Since quality assurance is used in selecting the manufacturers and in confirming quality before distribution, L2 may be used in these cases. (See alternative Figure 5.) In cases of outbreaks where donations are used, it is advisable to apply L3 unless the source is guaranteed, in which case quality can be confirmed through L2 testing.

### *Distribution*

The distribution chain should have a medicine quality monitoring (MQM) program with clear guidelines for sampling and analysis protocols. The protocols established should assign specific roles and responsibilities to all those involved in the process. PQM has created guidelines for the development of MQM protocols, which can be consulted and used by health authorities where relevant. The guidelines were created to assist in the planning and execution of drug sampling and analysis.

Given the impossibility of conducting MQM in all the health facilities in a country that is involved in storage and dispensing, the sampling protocols should take account of drug volume and the number of batches received, as well as risk factors for deterioration of drug quality. Such considerations will determine the frequency of MQM, the selection of sites, the types of drugs to be monitored, and/or the number of batches of each drug that should be sampled. During prolonged storage, for example, the frequency of sampling will depend on the storage conditions and/or the risk of deterioration in drug quality. In the absence of previous information, six months can be used as the sampling interval initially, and frequency can be adjusted based on the findings. Protocols that employ sampling with statistical data, as described at the end of this section, can also be useful.

In high-incidence areas or situations, when there is rapid turnover of inventory, with short periods of storage in central and/or regional warehouses and dispensing centers, the main recommendation is to evaluate the dispensing centers through L2 testing. In this case, the drugs with highest risk of deteriorating or those in areas with inadequate storage conditions must be prioritized (ex: high temperatures and/or humidity, direct exposure to sunlight, poor cooling, etc.).

In low-incidence areas, drugs will be stored for longer periods in central and/or State provincial warehouses or dispensing centers. Because of the slow turnover, all the sites should be subject to periodic L1 monitoring to ensure that expired drugs are not being held, and that those which should be disposed of and replaced under the guidelines established by the countries for this purpose are so dealt with. Furthermore, periodic L2 quality control tests should be implemented, with emphasis on those sites where the risk of deteriorating quality are greater due to prolonged storage under poor conditions. However, the limitations of L2 in terms of detecting certain quality attributes should

be borne in mind. When products with a high risk of deterioration in quality are stored for long periods, the desirability of L3 testing should be considered. It is important to reiterate that periodic analysis will help to establish the minimum frequency with which testing should be conducted.

In this context, it can be useful to conduct statistically representative samplings that take into account storage conditions as well as type of drug. If quality problems are found, it will then be possible to apply similar preventive and/or corrective measures to all relevant sites.

### *Adherence studies and impact assessment*

In high-incidence areas, patients tend to receive drugs at the health care facility, where the first administration is supervised, though treatment is continued and completed at home. Studies conducted by AMI show that adherence can be low, particularly in the case of prolonged therapeutic regimens such as those required for *P. vivax*. Initiatives for strict supervision of the entire treatment process in high-incidence areas have proven difficult to carry through, given the great deal of institutional, financial, and human resources required. In low-incidence areas, where eliminating the human reservoir is more important, strictly supervised treatment of the few cases diagnosed should be incorporated. In these areas, the practice is feasible with the regular institutional resources of a country's NMCP.

The countries that share the Amazon Basin have conducted multiple studies to evaluate adherence to different treatment regimens. The last round of studies, and a compilation of previous studies, were recently supported by MSH/SPS.<sup>16</sup>

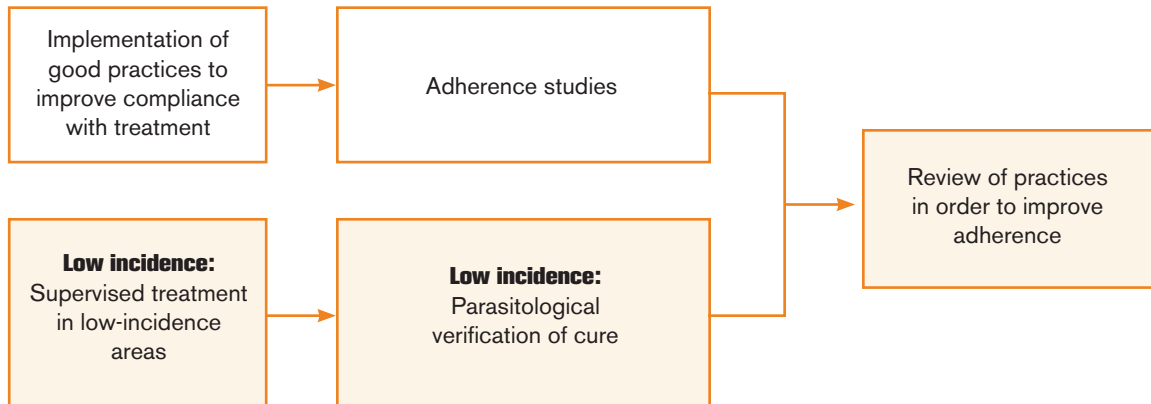
These studies pointed to difficulty in conducting field work, given the small number of cases. Since the studies conducted to date seem to agree on a group of central strategies to improve adherence (such as reducing treatment time with PQ for *P. vivax*, and giving patients graphic instructions, (see figure 6)), future studies should focus on:

- evaluating adherence to new therapeutic regimens; and
- evaluating practices that promote adherence, or that can potentially diminish it.

16. Strengthening Pharmaceutical Systems. 2009. Technical Report: *Analysis of Prescribing and Dispensing Practices and Adherence to Malaria Treatment in the Amazon Basin Countries*. Provided to the United States Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) program. Arlington, VA: Management Sciences for Health.

The implementation of multicenter studies would make the inclusion of a significant sample possible, even in low-incidence situations.

Figura 6. **Strategic elements for improving drug use**

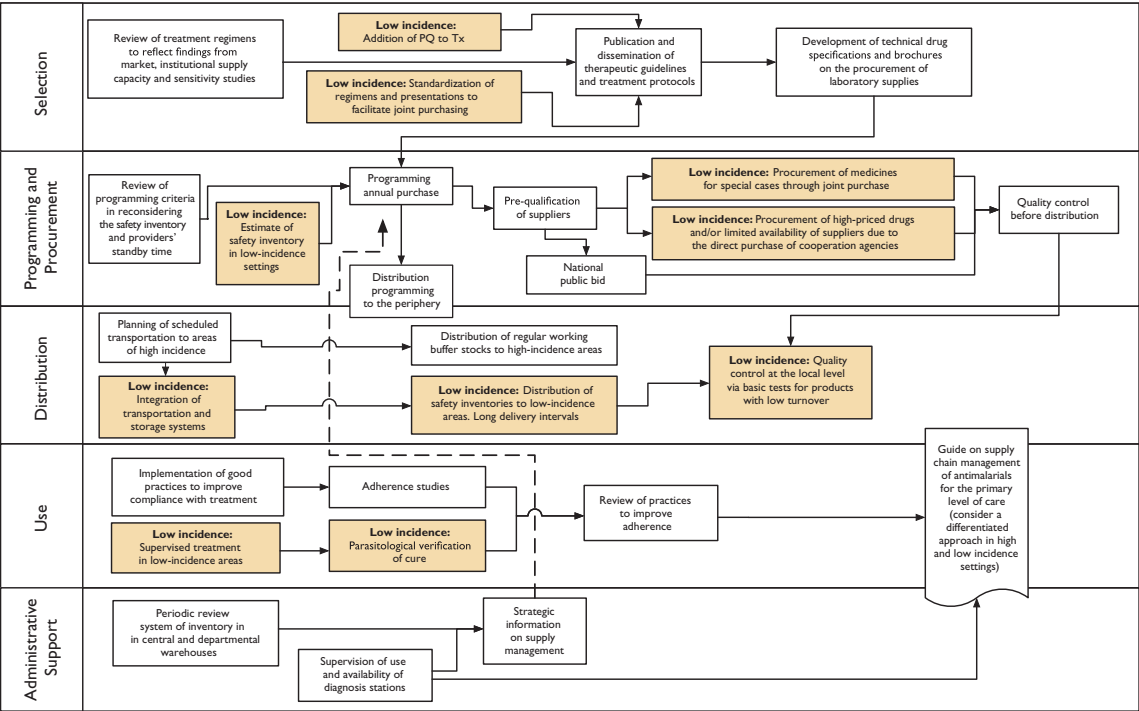


# 5

## Strategic Approach to Improve the Management of the Antimalarial Drug Supply in High and Low-Transmission Situations

The flowchart in Figure 7 shows the strategies that can be implemented by the region's countries to improve management of the supply of antimalarial drugs and of the inputs needed for diagnosis. The shaded parts of the figure show those strategies that should be given priority in low-incidence areas.

Figure 7. Strategic approach to improve the management of the antimalarial drug supply in high- and low-transmission situations





# 6

## Annexes

### Annex 1: **Proposal for the Consolidated Purchase of Antimalarial Drugs by the Countries of the Region of the Americas through the PAHO Strategic Fund and the Essential Medicines and Technologies Project (HSS/MT)**

#### *Background*

Access to antimalarial drugs in the region's countries is limited by factors such as insufficient availability in the national pharmaceutical markets (in particular because commercial incentives for domestic and international suppliers are lacking), regulatory constraints on international procurement in some countries, lack of distributors at the regional level, failure to list antimalarial drugs on the drug registry because their manufacturers are not represented in the countries and thus the availability of the drugs is limited, and problems within national drug supply management systems.

The above factors are more critical in the case of drugs needed to treat special cases such as severe malaria, malaria during pregnancy, and resistance to first-line drugs. In the latter case, smaller reserves are needed, and suppliers are even more limited.

These problems were examined in 2010 at the meeting for antimalarial drug selection and planning that was held as a part of AMI-RAVREDA. The Amazon Basin countries explained the causes of their drug shortages, including the problem of unmet calls for bids, and the problem of limited availability in national markets as a result of the small volumes of drugs needed, which makes these markets of little financial interest to suppliers. This situation occurs in other subregions as well, where some countries lack local manufacturers and have reported problems of counterfeiting and illegal marketing of drugs.

One solution to these problems is joint purchasing of antimalarial drugs by the region's countries through the SF. At the meeting, PAHO proposed that the countries submit their 2011 needs for antimalarial drugs, that the regional demand be consolidated, and that international competitive

bidding be held. The intention is also to work with prequalified manufacturing laboratories to plan production, to plan purchasing and delivery in advance, to shorten delivery times, and to substantially reduce the prices of the drugs.

HSS/MT, the Regional Malaria Program (RMP), and the Procurement and Supplies Management Area (PRO) at PAHO have coordinated to prepare an action plan for supporting the countries in this process (see Table 1 of this Annex).

Through the SF, PAHO held a first annual bidding for the joint purchase of antimalarial drugs for 2011. The bidding lasted from August to October of 2010, and followed this timetable:

1. In June, PAHO sent notices to its member countries' ministries of health or whatever other institutions were responsible for managing the supply of antimalarial drugs, inviting them to participate in the consolidated purchasing process. Each country sent PAHO a list of its antimalarial drug needs for the year.
2. The needs were presented in the format shown in Annex 2, specifying the drugs required and their pharmaceutical presentations. The countries were also requested to indicate the total number of units needed, with dosage quantities, as well as their technical, regulatory and administrative requirements. Finally, they indicated whether they needed partial or total deliveries.
3. The original request form had to be approved and signed by a representative of the ministry of health or other entity responsible for the supply of antimalarial drugs, and then sent to the PAHO/WHO Country Representative before 25 July 2010.
4. All the needs were consolidated in August 2010, and the bidding conditions were prepared according to the countries' needs.
5. Bidding took place in September and October 2010, and the results, including the suppliers and prices, were reported to the countries immediately, with a view to carrying out the purchase orders in January of this year.
6. The SF focal point at the PAHO/WHO Representative Office provided technical support for reviewing the bids and the countries' requirements, and answered questions that arose in the process. Once the information was reviewed, the PAHO/WHO representative e-mailed the request to Dr. James Fitzgerald ([fitzgeraldj@paho.org](mailto:fitzgeraldj@paho.org)) with a copy to Dr. Nora Girón ([gironn@hon.ops-oms.org](mailto:gironn@hon.ops-oms.org)).
7. Once the results of the bidding were in, the Procurement and Supply Management Area (PRO) sent each participating country a price estimate, the name of the supplier who had won the bid, and the delivery conditions. As soon as countries receive the price estimates, they should review them and indicate their approval if they have no objection. That information should be sent to PAHO, along with the voucher for the transfer of funds to the account established for this purpose.

8. On its web page, the SF will publish a general information bulletin with the results of the bidding, including the prices of the antimalarial drugs for 2011, in addition to sending the information to the countries through the country offices.

Table 1. **Action plan for the joint purchase of antimalarial drugs for 2011**

Activity	Timetable	Responsible
1. Invite countries in the region to present their antimalarial medicine needs and to participate in joint purchasing through the Strategic Fund	10 July 2010	<ul style="list-style-type: none"> <li>• HSS/MT, regional advisory entity for the SF, in coordination with RMP and PRO.</li> <li>• Representative offices: SF focal point and advisors, and people responsible for communicable diseases</li> </ul>
2. Review of the countries' needs on the basis of the parameters each has established for estimating its needs, defining its technical specifications, and establishing its quality requirements.	15 July 2010	<ul style="list-style-type: none"> <li>• Representative offices: SF focal point and advisors, and people responsible for communicable diseases (malaria) control.</li> </ul>
3. Shipment to PAHO of the antimalarials needed by the countries.	Deadline 25 July 2010	<ul style="list-style-type: none"> <li>• Ministries of health.</li> <li>• Institutions responsible for malaria control.</li> </ul>
4. Regional consolidation of the antimalarial drug requirements submitted by the countries.	7 August 2010	<ul style="list-style-type: none"> <li>• HSS/MT, regional advisor to the SF.</li> </ul>
5. Preparation of rules for the international competitive bidding.	Until 25 August 2010	<ul style="list-style-type: none"> <li>• PRO and HSS/MT.</li> </ul>
6. International competitive bidding.	September-October 2010	<ul style="list-style-type: none"> <li>• Drugs and technology area, HSS/MT.</li> <li>• PRO.</li> </ul>
7. Notification of the drugs and prices chosen.	November 2010	<ul style="list-style-type: none"> <li>• HSS/MT.</li> <li>• PRO.</li> </ul>
8. Price estimates sent to countries.	November 2010	<ul style="list-style-type: none"> <li>• PRO and HSS/MT.</li> </ul>
9. Purchase orders placed.	November 2010 or January 2011	<ul style="list-style-type: none"> <li>• Ministries of health.</li> <li>• Institutions responsible for malaria control.</li> </ul>



## Annex 2: Application Form for Requesting Antimalarial Medicines through the Strategic Fund 2011

Planned antimalarial drugs for acquisition through the Strategic Fund (SF) in 2011		
Country:		Programming year:
Date form filled out:		
Name and position of staff member responsible:		
E-mail:		Telephone:
Description of drug	Quantity needed for the year, in dosage units (tab, KAP, ampoule, vial, etc.)	Remarks
Chloroquine Phosphate, tab 250 mg (150 mg base)		
Primaquine phosphate, tab 5 mg		
Primaquine phosphate, tab 7.5 mg		
Primaquine phosphate, tab 15 mg		
Artesunate, tab 50 mg		
Artesunate, tab 100 mg		
Artesunate, iny., 60 mg vial		
Artesunate, tab 250 mg		
Artesunate+mefloquine 25+67.5 (base)		
Artesunate+mefloquine 50+135 (base)		
Artesunate+mefloquine 100+270 (base)		
Artesunate+mefloquine 100/220 (base)		
Amodiaquine 200mg+artesunate 50 mg		
Artemether 20 mg/lumefantrine 120 mg (tab 1X6)		
Artemether 20 mg/lumefantrine 120 mg (tab 2x6)		
Artemether 20 mg/lumefantrine 120 mg (tab 3x6)		
Artemether 20 mg/lumefantrine 120 mg (tab 4x6)		
Hydrochloride quinine Sol, iny., 300 mg/ml (2 ml amp)		
Sulphate quinine, tab 300 mg		
Mefloquine hydrochloride, tab 250 mg		
Sulfadoxine 500/pyrimethamine, tab 25 mg		
Amodiaquine, tab 153 mg (clorhidrato)		
Amodiaquine, tab 200 mg		
Artemether iny., 80 mg/ml (1 ml)		
Proguanil (hydrochloride), 100 mg		
Atovaquone + Proguanil 250+100 mg		
Atovaquone + Proguanil 62.5+25 mg		
Indicate the times required for delivery of the drug, and indicate the quarter		
Quarter in which the order would be placed	T1 _____ T2 _____ T3 _____ T4 _____	
Quarter in which delivery of product will be needed	T1 _____ T2 _____ T3 _____ T4 _____	
b. Attach the technical specifications for each drug, the regulatory conditions that the country requires for purchase, and the requirements for importation of these drugs. Indicate whether legislation includes any exception for public health reasons applying to importation of this product.		
c. Other observations to take into account in procurement.		

