FRAMEWORK FOR ARTEMISININ RESISTANCE PREVENTION, CONTAINMENT, AND ELIMINATION IN SOUTH AMERICA

Pan American Health Organization

World Health Organization
REGIONAL OFFICE FOR THE Americas

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Content

Abbreviations

ACD	active case detection
ACT	artemisinin-based combination therapy
FSAT	focused screening and treatment
GMS	Greater Mekong subregion (Cambodia, China, Lao Peoples Democratic Republic, Myanmar, Thailand, and Vietnam)
GPARC	Global Plan for Artemisinin Resistance Containment
GPIRM	Global Plan for Insecticide Resistance Management
G6PD	glucose-6-phosphate dehydrogenase
IRS	indoor residual spraying
LLIN	long-lasting insecticidal net
MDA	mass drug administration
MSAT	mass screening and treatment
NMCP	national malaria control program
PAHO	Pan American Health Organization
PCD	passive case detection
RAVREDA	Amazon Network for the Surveillance of Antimalarial Drug Resistance
RDT	rapid diagnostic testing
TES	therapeutic efficacy study
WHO	World Health Organization

Executive Summary

Artemisinin-based combination therapies (ACTs) are the recommended treatments for *Plasmodium falciparum* malaria in all malaria endemic areas of South America. Resistance of *P. falciparum* to the artemisinin drugs has already been detected in the Greater Mekong subregion of Southeast Asia and would represent a major setback to malaria control efforts if it were to develop in or spread to South America. Although artemisinin resistance has not been confirmed in the Americas, the interior of Guyana, Suriname, and French Guiana and bordering areas of Brazil and Venezuela (together known as the Guiana Shield) share many characteristics with the Greater Mekong subregion that increase the risk for selection of resistant parasites. These characteristics include higher levels of transmission of *P. falciparum* than in the rest of the Amazon Basin, highly mobile populations, ready availability and widespread use of a variety of antimalarial drugs of questionable quality, including artemisinin monotherapies, and lack of access to and use of formal malaria diagnostic and treatment facilities. Since the emergence of artemisinin-resistant *P. falciparum* in the Guiana Shield could seriously jeopardize malaria control efforts throughout South America, prevention of multidrug resistance including ACT resistance be seen as one of the highest malaria control priorities in the Region.

The present framework outlines a combination of activities intended to prevent the development of artemisinin resistance in South America, or to contain and eliminate resistance if it should be confirmed. It focuses on the Amazon Basin, which, excluding Haiti, accounts for 98% of all *P. falciparum* infections reported from the Americas. Within the Amazon Basin, particular emphasis is placed on the Guyana Shield, where the risk for selection of artemisinin-resistant strains is probably highest.

A longer-term objective of the framework is to eliminate *P. falciparum* malaria, as this will be the only sure way to avoid the selection of resistant parasites. The overarching goal of this framework is to protect ACTs – both the artemisinin component and partner drugs – as an effective treatment for *P. falciparum* malaria in the Americas. It is based on the Global Plan for Artemisinin Resistance Containment (GPARC) and lessons learned from ongoing artemisinin resistance containment projects in the Greater Mekong subregion. The framework recommends expanded coverage of malaria diagnostic and treatment services, intensified vector control to drive down transmission, strengthened malaria surveillance, and increased transborder collaboration, especially in terms of efforts to control the sale and use of artemisinin monotherapies. Since it is unlikely that national malaria control programs will be able to implement all the activities described in this framework simultaneously, a list of suggested priority activities has been included in the Annex.

Introduction

During the past 15 years, artemisinin-based combination therapies (ACTs) have become the first-line treatment for *Plasmodium falciparum* malaria in nearly all malaria endemic countries. Together with long-lasting insecticidal bed nets (LLINs), these drugs have played a major role in the dramatic progress since the year 2000 in reducing the global burden of malaria.

ACTs contain an artemisinin derivative combined with a partner drug. Five ACTs[1] are currently recommended by the World Health Organization (WHO). The role of the artemisinin compound is to reduce the parasite load rapidly during the first few days of treatment, while the partner drug is intended to eliminate any remaining parasites.

Artemisinin resistance was first reported from the Cambodia-Thailand border but has now been detected also in Lao PDR, Myanmar, and Viet Nam. Both the geographic spread of resistant strains and the spontaneous appearance of newly resistant strains have played a role in the geographic expansion of artemisinin resistance. Additionally, resistance to all the currently used partner drugs is suspected or has been confirmed in the Greater Mekong subregion (GMS). [2]

This emergence of multidrug resistance, including resistance to artemisinins, represents a major threat to malaria control efforts worldwide and has led to a call for malaria elimination in the GMS by 2030. The development of multidrug resistance in South America, including resistance to ACTs, would pose a serious threat to malaria control efforts throughout the Region.

Purpose of the Framework

The overarching goal of this framework is to protect ACTs – both the artemisinin component and partner drugs – as an effective treatment for *P. falciparum* malaria in the Americas. This framework is not intended to replace existing regional or country strategies for malaria control in South America. However, multidrug resistance is an issue of global concern that requires an aggressive and coordinated response at national and regional levels. Countries and implementing partners working in the Region, as well as stakeholders at the global level, are the primary target audiences.

In light of warning signals identified in the Guiana Shield,[3] the framework emphasizes activities needed in this geographic area, but not to the detriment of priority activities needed elsewhere and at the regional level. The transborder areas of the

[1] A sixth ACT, Pyramax® (a fixed dose combination of pyronaridine and artesunate), was given a positive scientific opinion under the terms of Article 58 of the European Medicines Agency (EMA) in February 2012 and is being considered for recommendation by WHO.

[2] Comprising Cambodia, China (Yunnan province), Lao People's Democratic Republic, Myanmar, Thailand, and Viet Nam.

[3] In this document, the term "Guiana Shield" refers collectively to the area comprising French Guiana, Guyana, Suriname, bordering areas of the states of Amapá, Pará, and Roraima in Brazil and the state of Bolivar in Venezuela.

Guiana Shield (Map 1) are among the most challenging settings for malaria control and elimination in the Americas because of their inaccessibility, highly mobile populations, lack of formal health facilities, and difficulties in maintaining well-trained malaria control staff.

Map 1. The Guianas and bordering areas of Brazil and Venezuela (Guiana Shield)

The plan does not include Central America or the Caribbean. Nearly all the Central American countries report fewer than 100 cases of *P. falciparum* annually. Chloroquine remains the first-line treatment for *P. falciparum* infections throughout Central America and the Caribbean. Artemisinin-based treatments are only used to treat cases of *P. falciparum* imported from areas with known chloroquine resistance.

The approach to resistance prevention described in the present framework is based on the guidance contained in the Global Plan for Artemisinin Resistance Containment (GPARC).[4] It draws heavily on the recommendations laid out in the 2013 WHO Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion,[5] as well as the lessons learned from ongoing containment and elimination projects in that subregion.

The framework has been discussed with countries and partners at two regional consultations. The first was held in November 2014 at Paramaribo, Suriname, and the final draft document was discussed at a March 2015 meeting in Rio de Janeiro, Brazil, attended by representatives of 19 of the 21 malaria-endemic countries in the Americas.

[4] WHO (2011). Global Plan for Artemisinin Resistance Containment (GPARC). Geneva: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/44482/1/9789241500838_eng.pdf?ua=1

[5] World Health Organization (2013). Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: Regional Framework for Action 2013-2015. Geneva: WHO. Available from: http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321_eng.pdf

Background

Drug Resistance in South America

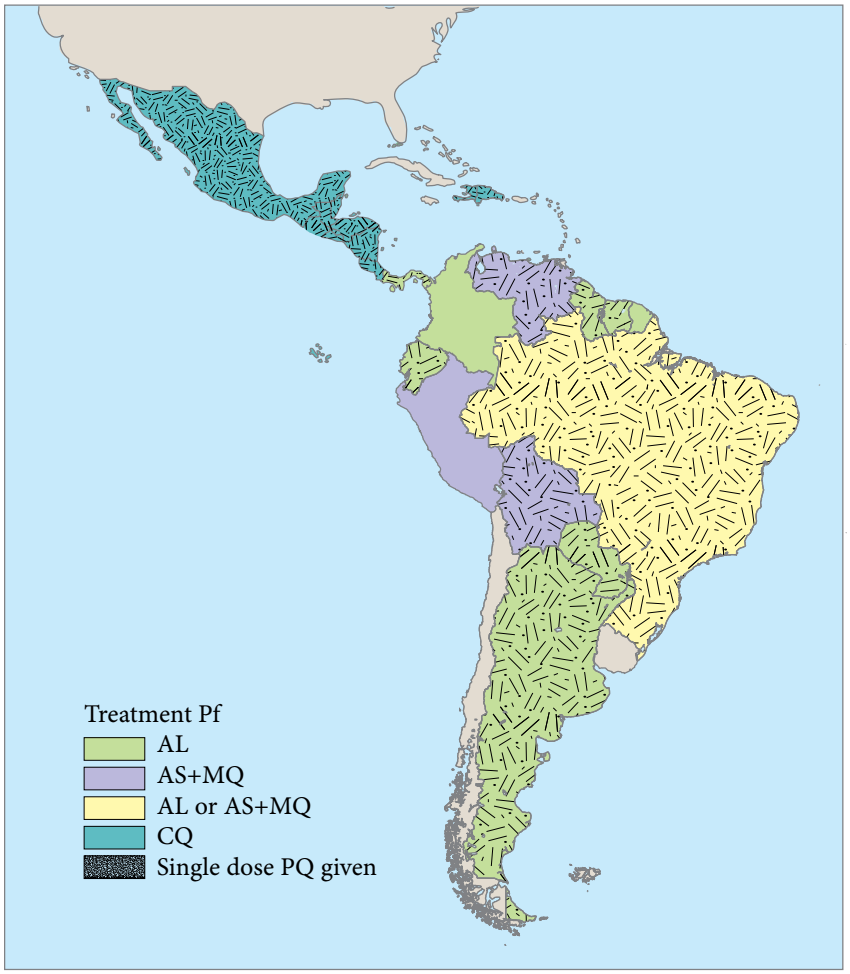
Antimalarial drug resistance is defined by WHO as "the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject."[6] For the artemisinins, WHO considers that a delay in parasite clearance, evidenced by an increased proportion of patients with parasitemia 72 hours after the start of treatment with an ACT, is an early warning sign of reduced *P. falciparum* sensitivity. However, infections are usually cured if treated with an ACT containing a partner drug that is still efficacious.

A molecular marker of artemisinin resistance was recently identified. Mutations in the Kelch 13 (K13) propeller domain were shown to be associated with delayed parasite clearance in vitro and in vivo. Analysis of this molecular marker showed that the C580Y mutation was the most prevalent form in parts of the Greater Mekong subregion, but many other mutations in and near the K13 propeller region were also found to be associated with artemisinin resistance.[7]

ACT has been widely adopted as the treatment for uncomplicated *P. falciparum* cases in South America following the identification of resistance to chloroquine and sulfadoxine-pyrimethamine. Chloroquine is still the first line treatment in Mexico and Central America, where this treatment remains efficacious (Map 2). Of the five approved ACT partner drugs, mefloquine and lumefantrine are currently used in South America. A third partner drug, piperaquine, could potentially be used in the future. High failure rates for ACTs with the two remaining approved partner drugs (sulfadoxine-pyrimethamine and amodiaquine) mean that they are unlikely to be of use as a first- or second-line treatment in the near future.

[6] WHO (1967). Chemotherapy of malaria: report of a WHO Scientific Group. Geneva: World Health Organization.

[7] WHO (2014). Status report on artemisinin resistance, September 2014. Available from: http://www.who.int/entity/malaria/publications/atoz/status_rep_artemisinin_resistance_sep2014.pdf



Map 2. *P. falciparum* treatment policy
Legend: AL: artemether-lumefantrine; AS+MQ: artesunate-mefloquine; CQ: chloroquine, PQ: primaquine.
Source: WHO Malaria Programme. World Malaria Report 2014. Geneva: World Health Organization.

In the Guiana Shield, malaria diagnosis and treatment is provided free of charge in the public sector. Artemisinin-based combination therapy plus a single dose of primaquine 0.25mg base/kg is the recommended treatment for confirmed *P. falciparum* infections in Guyana, Suriname, and Brazil; only in French Guiana is primaquine not part of the recommended therapy.

In 2011 and 2012, *P. falciparum* therapeutic efficacy studies (TESS) carried out in both Suriname and Guyana suggested that some strains of *P. falciparum* had delayed

parasite clearance, with an increased proportion of patients positive on day 3 following treatment with artemether-lumefantrine. On 21 February 2013, the Pan American Health Organization convened an informal meeting of malaria experts in Washington, D.C., to review the results of these studies. Because parasites were present on day 3 in confirmatory WHO standardized TESs, the meeting participants recommended studies of possible artemisinin resistance. In Suriname the confirmatory study assessed a 3-day course of artemisinin followed by mefloquine plus primaquine, while in Guyana the study used a 7-day course of artesunate followed by primaquine on day 8.

In October 2013, the Pan American Health Organization organized a meeting in Cayenne, French Guiana, to discuss the threat of artemisinin resistance in the Guiana Shield and consider approaches to dealing with this resistance if it should be confirmed. A follow-up meeting with malaria control program staff and stakeholders, held in Paramaribo, Suriname, in November 2014, reviewed updates on the two confirmatory resistance studies.

The artemisinin resistance studies in Suriname and Guyana were completed in 2014. They showed no evidence of delayed parasite clearance or increased treatment failures. Furthermore, no K13 mutations were found in any of the blood samples from subjects in either the Guyana or the Suriname studies or in 206 additional samples taken in French Guiana. These data contrast with the results of K13 sequencing done on samples from Guyana collected in 2010 found that 5.1% (5/98) of the samples had the artemisinin resistance associated with the K13 580Y mutation.

Malaria Epidemiology

Substantial progress has been made in reducing malaria over the past decade in South America. The area with the highest prevalence of malaria in the Americas is the Amazon Basin. This area, together with Haiti, accounts for the vast majority of all *P. falciparum* infections reported from the Region. Furthermore, many infections in the Amazon Basin probably go unreported because of lack of access to formal health services and high population mobility.

In 2013, the latest year for which complete surveillance data are available, Brazil reported 176,002 cases of malaria, far more than any other country in the Americas (Table 1). The majority of those cases came from the country's Amazon region and *P. falciparum* accounted for 17% of all infections. In addition, the number of malaria cases in Venezuela has been increasing over the past several years, and in 2013, 73,761 cases were reported, with 31% caused by *P. falciparum*. The areas with the highest levels of transmission were in the state of Bolivar bordering Guyana and Brazil.

Table 1. Cases of malaria and *P. falciparum* in South America, 2013		
Country	Total	P. *falciparum*
Bolivia	8,375	975
Brazil	176,002	29,717
Colombia	58,409	20,370
Costa Rica	5	1
Dominican Republic	579	576
Ecuador	378	161
El Salvador	7	-
French Guiana	875	538
Guatemala	6,163	101
Guyana	27,709	13,655
Haiti	20,957	20,957
Honduras	5,428	1,159
Mexico	499	4
Nicaragua	1,194	219
Panama	705	6
Paraguay	11	7
Peru	42,926	6,630
Suriname	843	420
Venezuela	73,761	22,777
Total 2013	424,826	118,273
Source: WHO Global Malaria Programme. World Malaria Report 2014, Geneva: World Health Organization.		

Guyana reported 27,709 malaria cases, 49% of them due to *P. falciparum*. Suriname reported only 843 cases, with 50% due to *P. falciparum*. In both countries, nearly all malaria cases come from the interior bordering Brazil. The coastal areas of both Guyana and Suriname have very few cases of malaria. French Guiana reported 875 cases, of which 61% were due to *P. falciparum*. The areas at highest risk are in the country's interior along the Oiapoque River, its eastern border with Brazil, and the Maroni River, its southwestern border with Suriname.

National malaria control programs in most of the countries in the Amazon Basin are generally characterized by strong leadership and management, clear malaria prevention and treatment policies that are in line with international guidelines, and well-trained, experienced, personnel. Over the past 10 to 12 years, malaria control efforts have been given technical support through a PAHO-led project, the Amazon Malaria Initiative. However, the NMCPs continue to face challenges in terms of limited staff and funding, difficulties accessing the isolated populations in the interior, and uncontrolled movement of workers across borders. Furthermore, increasing health system decentralization in many countries of the Americas has resulted in a loss of direct authority over and communication with malaria control workers at the peripheral level, who have been converted to multipurpose health staff.

Most of the people tested in the original 2011/2012 exercise carried out in Suriname and Guyana came from gold and/or diamond mining communities in the interior (Figure 1). These areas have several characteristics in common with the transborder areas of Southeast Asia, where resistance to both artemisinins and ACT partner drugs has already been confirmed, namely: a greater proportion of *P. falciparum* infections than in other areas of the Region; highly mobile populations with access to a broad range of antimalarial drugs of unknown quality, including multiple ACTs and artemisinin monotherapies; and a tendency to self-treat rather than seek care at formal health facilities.

The surge in the price of gold over the past decade has spurred an increase in mining activities throughout the Guiana Shield. Most mining operations in the Guyana and Suriname interior are small- to medium-scale enterprises ranging from individual miners up to 20 to 25 workers; only a few large mining companies are involved. Guyana has a national association of mine owners and Suriname has a similar organization for entrepreneurs working in the interior of the country. In both countries there are also many local community-based associations of miners.

In Suriname, about two-thirds of the estimated 12,000 to 15,000 gold miners in the Suriname interior are of Brazilian origin, while the remainder are mostly Surinamese Maroons of mixed African and indigenous descent. Nearly all are males between the ages of 18 and 45. The rest of the population in these mining areas is divided roughly equally between shop vendors, restaurant and hotel staff, and commercial sex workers.[8] Despite the large proportion of miners from Brazil, 95% of the reported malaria cases in Suriname are seen in Surinamese citizens or immigrants from French Guiana. This discrepancy suggests that many Brazilian miners with malaria never come to the attention of the NMCP because they seek treatment in the private sector, where substandard drugs, non-registered medicines, and artemisinin monotherapies are common.

In French Guiana, where it is more difficult to obtain mining licenses, it is estimated that about 10,000 miners work illegally, most of them from Brazil. Several larger mining companies also operate in the interior.

As for the situation in Guyana, information on the size and makeup of the population in the gold and diamond mining areas in the interior is more limited, but most of the miners are Guyanese citizens, with smaller numbers from Brazil. The Guyana Geology and Mines Commission reported that 17,000 people were employed in the mining sector in 2013 and estimated that the number rises to more than 20,000 when indirect employment is taken into account.

[8] Heemskerk M (2011). Small-scale gold mining in the transboundary areas of Brazil, Suriname, and French Guiana: social and environmental issues. New York: United Nations Development Programme.

Existing Strategic Guidance on Artemisinin Resistance Containment

The GPARC was launched in January 2011, based on extensive consultation with stakeholders and information in the Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010.[9] The overarching goal of the GPARC is to protect ACT as an effective treatment for *P. falciparum* malaria.

The main elements of the GPARC are summarized in the box below.

The GPARC "sets out a high-level plan of attack to protect ACTs as an effective treatment for *P. falciparum* malaria." The objectives of the GPARC are to:

- Define priorities for the containment and prevention of artemisinin resistance;
- Motivate action and describe responsibilities by constituency;
- Mobilize resources to fund the containment and prevention of artemisinin resistance;
- Increase collaboration and coordination for artemisinin resistance containment and prevention among relevant stakeholders; and
- Define governance mechanisms and indicators for continuous assessment of progress made in implementing the GPARC.

The GPARC has two goals:

- Prevent artemisinin resistance where it has not yet appeared; and
- Contain or eliminate artemisinin resistance where it already exists.

The plan makes five recommendations:

- Stop the spread of resistant parasites;
- Increase monitoring and surveillance to evaluate the threat of artemisinin resistance;
- Improve access to diagnostics and rational treatment with ACTs;
- Invest in artemisinin resistance-related research; and
- Motivate action and mobilize resources.

In higher-transmission areas, GPARC focuses on limiting the spread of resistance by lowering the burden of malaria through intensified malaria control, including increased access to diagnostic testing and appropriate treatment and scaling up the provision of health care services to migrant and mobile populations. In lower-transmission areas, activities seek to achieve an accelerated elimination of *P. falciparum* parasites.

The GPARC classifies geographic areas around known sites of artemisinin resistance into three tiers, based on the level and risk of resistance:

Tier I: Areas in which there is credible evidence of artemisinin resistance;

[9] WHO (2010). Global report on antimalarial efficacy and drug resistance: 2000–2010. Geneva: World Health Organization.

Tier II: Areas with significant inflows of people from Tier I areas, including areas immediately bordering Tier I; and

Tier III: Areas that are endemic for *P. falciparum* malaria but have no evidence of artemisinin resistance and have limited contact with Tier I areas.

In all three tiers, malaria control efforts should focus on:

- Parasitological diagnosis for all patients with suspected malaria;
- A full course of quality-assured ACTs plus primaquine for confirmed cases; and
- Vector control, as locally appropriate, to lower transmission rapidly and stop the spread of resistant parasites.

In Tier I areas (Figure 1), the GPARC recommends that malaria control programs mount an immediate multi-pronged response to contain or eliminate resistant parasites as quickly as possible. The aim should be rapid achievement of high-quality universal coverage with all three malaria control measures. In Tier II areas, the aim is to intensify malaria control measures to reduce transmission and limit the risk of emergence or the spread of resistant parasites by aggressively scaling up to universal coverage with high-quality interventions. Also, specific activities should be launched in Tier I and II areas to eliminate or contain resistant parasites. In Tier III areas, malaria control programs should focus on increasing coverage with parasitological diagnostic testing, quality-assured ACTs, and vector control, while improving the quality of implementation.

Recommendations of the global plan for Artemisinin resistance containment by TIER		
Tier III	**Tier II**	**Tier I**
Good control	Intensified and accelerated control	Intensified and accelerated control to universal coverage
More routine monitoring	Intensified monitoring, especially on border near foci	Intensified monitoring, especially around foci
Elimination of monotherapies and poor-quality drugs	Active elimination of monotherapies and poor-quality drugs	Aggressive elimination of monotherapies and poor-quality drugs
	Lower transmission; focus on mobile and migrant populations	Lower transmission; focus on mobile and migrant populations
		Consider ACD or MDA

Source: adapted from GPARC.

For purposes of artemisinin resistance containment and elimination efforts, GPARC considers that an increase in parasite clearance time is an early warning sign of artemisinin resistance that deserves a response similar to that for confirmed resistance.

Prevention of artemisinin resistance, or containment if it is identified, will depend on the continued efficacy of ACTs together with rigorous, high-quality implementation of malaria prevention and treatment interventions. A resistance prevention program should build on and be an integral part of ongoing efforts to control and eventually eliminate *P. falciparum* malaria from South America, which will be the only way to eliminate the threat of resistance. At the same time, resistance prevention activities

will contribute to the longer-term objective of driving down the burden of malaria at subnational, national, and regional levels.

Since multidrug resistance, including resistance to the ACTs, would represent a very serious threat to malaria control efforts in the Americas, this framework recommends that prevention efforts be initiated immediately, rather than waiting until resistance is detected in a TES or a clinical trial of artemisinin drug monotherapy. It is hoped that this proactive approach, with focus on the Guiana Shield, will reduce the risk of resistance developing in the Amazon Basin and the rest of South America.

Activities

A successful resistance prevention effort focused on the Guiana Shield will require NMCPs to achieve and sustain high-level coverage with key prevention, diagnostic, and treatment interventions for all populations living or working in these areas. The task will be particularly challenging because of the high population mobility and poor access to health services characteristic of these areas. Information from socio-behavioral studies of gold miners, loggers, and indigenous and other groups living and working in the Guiana Shield should be used to guide the selection and prioritization of activities to prevent and treat malaria. Since behaviors and preferences may vary from one subgroup of the population to another, NMCPs will need to tailor their approaches to the local residents. It should be kept in mind that malaria transmission is not uniform throughout the Guiana Shield; NMCPs will need to be flexible and take the local epidemiology of disease into account in planning their activities.

Implementation Activities in the Guiana Shield

1. Improved case detection and treatment of malaria

High-quality parasitologic diagnosis of all cases of suspected malaria and prompt treatment with a quality-assured ACT will be critical to preventing the development of artemisinin resistance. Including primaquine for its gametocytocidal effect will limit the transmission of parasites, including resistant parasites. Currently, all reported cases of malaria in the Americas are based on parasitologic diagnosis, either by microscopy or rapid diagnostic testing (RDT). In the interior of the Guiana Shield, most diagnoses are made at local health posts or in larger towns, where patients may travel for treatment. Thus, most reported infections are captured by the passive case detection system, although it can be assumed that there are many more cases of malaria infection than ever come to the attention of the NMCPs.

National malaria treatment policies in the countries of the Guiana Shield consist of a schizonticide (chloroquine for *P. vivax* and an ACT for *P. falciparum*) plus primaquine. The use of fixed-dose combinations of the ACTs ensures increased patient compliance compared with the administration of an artemisinin and a separate partner drug. Changes in national treatment policies should only be made when more than 10% of subjects enrolled in a well-performed TES show therapeutic failure, as currently recommended by WHO. A significantly declining trend in treatment efficacy over time, even if failure rates have not yet fallen to the ≥ 10% cutoff, should alert programs to undertake more frequent monitoring and to prepare for a potential policy change.[10] Primaquine has been used for many years in the Americas for the radical treatment of *P. vivax* and as a single-dose gametocytocide for *P. falciparum* infections without previous

[10] WHO (2015). Guidelines for the treatment of malaria. 3rd ed. Geneva: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf

testing for glucose-6-phosphate dehydrogenase (G6PD) deficiency. In low-transmission areas and areas with artemisinin resistance, WHO recently recommended the inclusion of single low-dose primaquine (0.25 mg/kg bodyweight) with ACT for patients with *P. falciparum* malaria to reduce transmission. For this dosing, G6PD testing is not required.[11] French Guiana remains the only area within the Guiana shield where official treatment policies for *P. falciparum* infections do not include a single dose of primaquine as a gametocytocide. Efforts should be made to update those policies and bring them in line with WHO recommendations as soon as possible.

Although all reported cases of malaria in the Americas are based on parasitologic diagnoses, in the transborder areas of the Guiana Shield a large but still unknown proportion of patients with suspected malaria treat themselves with medicines purchased in the private sector. A variety of antimalarial drugs, including many ACTs and artemisinin monotherapies, are available from private pharmacies, shops, and itinerant drug sellers throughout the mining areas.[12] A recent socio-behavioral study in Suriname found that the most common reason for not seeking diagnostic testing and treatment from formal health facilities is distance from or difficulty in traveling to a health post.[13] As a first step toward improving malaria case detection and treatment, NMCPs should increase the number and geographic distribution of adequately supplied and supervised passive case detection (PCD) posts throughout the mining areas so that accessibility is no longer a barrier to parasitologic diagnosis, treatment, and reporting. Ministries of Health and NMCPs will also need to make sure that no barriers exist to the use of RDT by non-laboratory personnel. Suriname has already taken steps in this direction by establishing malaria service delivery posts in mining communities. Local residents, usually with no previous health service experience, are trained to perform RDT, take blood smears (for examination later by a trained microscopist) and administer ACTs with the first dose under direct observation. These malaria service deliverers work out of their homes and are paid about US$ 100 per month. Currently, about 25 malaria service deliverers are in operation, two-thirds of whom are women. They are supervised and resupplied with materials, usually on a quarterly basis.

In addition to increasing the number and accessibility of "official" PCD posts, NMCPs should consider other ways to improve coverage with high-quality diagnostic and treatment services for those patients who might first seek treatment in the private sector. Since the best approach may vary by country, depending on the local epidemiology of malaria, and/or on the basis of local behavior patterns and preferences, NMCPs may need to test several different approaches before deciding on the best one(s) for their particular setting.

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[11] Ibid.

[12] Pribluda VS et al. (2012). Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005-2010 period. Malaria J 11: 202.

[13] Heemskerk M (2013). Study on knowledge, attitudes and practices of malaria and malaria treatment in the small scale gold mining sector in Suriname (PowerPoint presentation).

- One option would to be set up PCD posts in each medium-sized or larger mining or logging site and train a person at that site as a volunteer malaria worker (ideally the owner or a field supervisor). If these volunteers are provided with free RDT and antimalarial drugs, they would be able to carry out diagnostic testing on anyone with suspected malaria from that site and the surrounding area and then administer artemether-lumefantrine plus primaquine in the event of a confirmed diagnosis of *P. falciparum*. The volunteers could also be trained to record and report patient information on a simple surveillance form. While miners might not like to have their fingers pricked, free treatment with an ACT at or close to their place of work should be an attractive incentive. For a mine or logging company owner, it would be hoped that the reduction in time lost from work by their employees would make up for any inconvenience in supporting a PCD post at their site.
- Another option would be to provide private sector drug sellers, both formal and informal, with free RDT, ACT, and primaquine in return for having them perform RDT on clients with suspected malaria, treat those with a positive result with quality-assured antimalarials provided by the NMCP, and report the case to higher levels of the health system. The drug sellers should also agree to stop selling other antimalarial drugs (especially other ACTs, artemisinin monotherapies, and injectable artemisinins for uncomplicated malaria). They would receive training and by the Ministry of Health or NMCP, and facilities that met with all the requirements would be certified as official malaria diagnosis and treatment posts. The private drug sellers would benefit by being able to sell drugs provided free of charge by the NMCP at essentially the same prices they would charge for these drugs if they had to buy them at wholesale prices, although regular supervision would be needed to ensure that they did not overcharge and/or provide treatment without first confirming the infection. This approach of working collaboratively with private drug sellers is probably more likely to be successful in reducing the use of poor quality or unapproved antimalarial drugs than threatening drug sellers with legal action and/or trying to control and monitor the medicines they dispense, given the inaccessible settings of many mining areas.

As a general policy, providing ACTs directly to local residents for self-administration whenever they believe they have malaria is not recommended in settings such as the transborder areas of the Guiana Shield, where elimination is the longer-term goal and where case reporting will be critical to monitoring progress.

National malaria control programs will have to decide which approach or combination of approaches works best in their country, but regardless of the method chosen, it is clear that the number of PCD posts in the mining areas of the transborder regions of the Guiana Shield will need to be increased considerably. Increasing the number of posts will require more supervisors to train, oversee, and resupply the PCD workers. National malaria control programs will also need to continue reinforcing country capacity in malaria microscopy with regular supervision in order to reduce misdiagnoses to a minimum.

Since it is likely that many residents in mining and logging communities do not complete their courses of antimalarial medication, treatment at health facilities and PCD posts could be strengthened by instituting directly observed therapy for confirmed cases of malaria, particularly all *P. falciparum* infections, together with follow-up to document treatment outcome. Although directly observed therapy will be difficult to implement properly, it should become more feasible with an increase in the number of PCD posts at mining sites, considering the small number of *P. falciparum* infections that occur. Based on their local situations, NMCPs may want to consider whether it is worth the additional effort that will be required to ensure a high-quality program.

National malaria control programs in the Americas have a long history of the use of active case detection (ACD) in malaria control efforts. Currently, ACD is only being used in the interior of Suriname and Guyana, and then primarily when an increase in malaria cases above a certain threshold is observed. The decision on when and where to use ACD will depend on local conditions and the status of malaria control efforts. It may be most appropriate in mining and logging communities with persistent transmission where PCD is not performing as well as expected, in situations of weak acceptance and compliance with malaria control measures, or in the investigation of foci of continuing transmission as part of a malaria elimination effort.

The role of mass drug administration (MDA), which is defined as the administration of a complete antimalarial treatment to all members of a community or larger area without prior diagnostic testing, is unclear in situations where the objective is to prevent or contain artemisinin resistance. Ongoing pilot studies of MDA in the Greater Mekong subregion may provide a better understanding of its role in malaria control and elimination programs. However, given the tradition of well-functioning PCD networks in the Americas, the strong culture of parasitologic diagnosis before treatment, and difficulties implementing MDA in areas with unorganized and sometimes illegal workers spread over large areas, MDA should probably be held in reserve at the present time.

Delivering high-quality malaria diagnostic and treatment services to residents of the transborder areas of the Guiana Shield will be a major challenge. Given that the populations are highly mobile, any effort to deal with malaria in these areas must have a regional, multicountry focus. In addition, Ministries of Health and NMCPs should understand that salary incentives will probably be required in order to ensure that field staff are prepared to work long-term in the interior, where living conditions are so difficult.

2. Ensuring an uninterrupted supply of essential commodities

High-quality diagnosis and treatment of malaria are dependent on a strong supply chain management system. Stock-outs not only interfere with prompt and accurate diagnosis and the treatment of individual patients but can also result in a loss of credibility in the services provided through the public health sector. A patient who has been unable to obtain treatment at a formal health facility is less likely to return the next time he or she is ill and may revert to the private sector, where substandard medicines and artemisinin-based monotherapies are much more prevalent.

In the Region, considerable effort has been invested over the past six to eight years in improving supply chain management systems for malaria commodities in the countries of the Amazon Basin through the PAHO-led Amazon Malaria Initiative, which has worked to strengthen malaria control programs in the Region. With declining levels of malaria transmission in most countries in South America over the past decade, training and technical support has focused on such issues as:

- How to estimate supply needs in settings where malaria transmission is variable or very low;
- How to record and report available supplies;
- How and when to request additional supplies, allowing for delivery time;
- What emergency measures need to be taken if a stock-out occurs;
- How large a buffer stock to keep on hand at different levels of the health system; and
- When and how to deal with excess supplies.

Currently, stock-outs of commodities for the diagnosis and treatment of malaria are not a major problem in most areas where public health services are available. Building on that base, Ministries of Health and NMCPs need to continue to address weaknesses in the supply management system, focusing particularly on ensuring reliable delivery of diagnostic, treatment, and prevention commodities to the most peripheral levels of the health system.

In the transborder areas of the Guiana Shield, the type of antimalarial drugs found in the private sector varies from site to site. Many medicines are brought in from urban areas and are subsequently used or resold in the interior. Periodic monitoring of the quality of antimalarial drugs circulating in the private sector should continue to be a high priority for NMCPs. In the case of RDT, the best way to ensure high diagnostic performance will be to use tests that have been evaluated by the WHO-FIND-CDC Product Testing Programme for malaria RDT and that meet the WHO-recommended criteria for RDT procurement.[14]

3. Scaled up and sustained coverage with vector control measures

In the transborder area of the Guiana Shield, high coverage with vector control interventions offers the best approach for reducing malaria transmission and ultimately preventing the selection of artemisinin-resistant parasites. With support from the Global Fund for AIDS, Tuberculosis and Malaria, long-lasting insecticidal bed nets (LLINs) have already been distributed in the interiors of Suriname, Guyana, and Brazil, but further information about mosquito net ownership, usage, and impact on malaria morbidity in these areas is urgently needed in order to make the most cost-effective use of LLINs in these areas. The effectiveness of insecticide-treated bed nets may be limited in low-transmission areas or in places where mosquito biting occurs mainly in the early evenings when most residents are still outdoors. Furthermore, many workers sleep in hammocks, and hammock nets, rather than traditional bed nets, may be more appropriate.

[14] WHO (2015). Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs). Geneva: WHO; September 2014 (rev. March 2015). Available from: http://www.who.int/malaria/publications/atoz/rdt_selection_criteria/en/index.html

Since housing is often makeshift and many miners and loggers sleep in open structures covered by a roof but without walls, indoor residual spraying (IRS) is likely to be much less effective than LLINs. In the coastal areas of both countries, where malaria transmission is low, no malaria control rationale exists for either net distribution or IRS, although LLINs may play a role in reducing the transmission of endemic lymphatic filariasis.

Achieving and sustaining high LLIN coverage in highly mobile populations, such as those of the interiors of the countries that make up the Guiana Shield, presents special challenges, since residents may not stay in one place long enough to benefit from net distribution programs or health education messages related to the nets, and they may see little value to preventive health measures when treatment is so readily available. To ensure that cost is not a barrier to net ownership, NMCPs should provide all nets free of charge. Since pyrethroids are currently the only insecticides available for the treatment of mosquito nets and other netting material, routine surveillance for insecticide resistance will need to be carried out in areas where nets are distributed, together with entomologic surveillance to monitor possible changes in vector behavior.

Acceptance and compliance with malaria prevention and control measures, such as vector control and diagnostic testing and treatment, can be a major problem in highly mobile populations. Communication approaches for gold miners, loggers, and indigenous groups need to be culturally appropriate, easy to understand, and actionable.

Open-pit gold and diamond mining can be quite destructive to the environment, leaving large excavations that may collect water and become important mosquito breeding sites. In such settings, man-made malaria can be an issue, although little is known about this problem in the interior of the Guiana Shield, where *Anopheles darlingi* is the principal vector. For this reason, studies of man-made malaria should be a priority on the operational research agenda for these countries. Evidence showing that abandoned open-pit mines are important Anopheles breeding sites may cause NMCPs to consider source reduction or larval source management measures.[15]

4. Monitoring and supervising staff performance

Regular supervision of health workers is fundamental to ensuring that activities are implemented as planned and that high standards of performance are maintained. Supervision can also play an important role in continuing staff education. National malaria control programs should have clear guidance for staff supervision, including:

- Plans for training staff in supportive supervision;
- Schedules and plans for the supervisory visits;
- How, when, and what to report to more senior staff on the results of the supervisory visits;
- How, when, and what to provide as feedback to the staff and facilities supervised; and
- Who has responsibility for follow-up action to resolve any problems that have been identified.

[15] WHO (2013). Larval source management: a supplementary measure for malaria control; an operational manual. Geneva: World Health Organization.

This guidance should include plans for regular supervision of malaria diagnostic testing and treatment at health facilities and by PCD volunteers at the community level, as well as recommendations for monitoring diagnosis and treatment in the private sector. Plans should also be made for the supervision of LLIN distribution, indoor residual spraying, and any other vector control operations. The use of a printed checklist for supervisory visits will help ensure that all aspects of the work are reviewed, while also serving as a permanent record for more senior staff.

Regular supervision of control activities will be required to ensure the success of efforts to prevent artemisinin resistance and, ultimately, to eliminate *P. falciparum* malaria. Supervisors should live close to where they work. Ministries of Health, NMCPs, and funding partners should understand that salary incentives and transportation to facilitate movement around the mining and indigenous communities will be needed for malaria staff who live and work long-term in these areas.

5. *Engaging other sectors in prevention and elimination efforts*

Most patients with confirmed malaria reported from Suriname and Guyana and French Guiana come from gold mining regions in the interior of these countries, where the population is highly mobile. Such workers are more likely to seek care from unregulated private vendors, increasing their risk of exposure to inappropriate therapy, including artemisinin monotherapy and substandard or counterfeit drugs.

Both Suriname and Guyana have national associations of mine owners, and smaller, community-based associations of miners. National malaria control programs should engage with officials of these associations and their members to gain insight into mining operations, the labor relationship between miners and their employers, and factors that might influence their attitudes and behavior with regard to the prevention and treatment of malaria. Since the success of efforts to prevent artemisinin resistance in the Guiana Shield will depend to a great extent on securing the understanding and cooperation of miners and mine owners, this outreach should be given high priority in NMCP strategies and plans.

6. *Improved collection and use of surveillance data to target and assess operations*

A strong surveillance system with rapid reporting and analysis of data, followed by use of that data to inform malaria control measures, will be critical to any effort to prevent the development of resistance and ultimately eliminate *P. falciparum* malaria.[16] Such systems require considerable investment, both financial and human. It should be kept in mind that when disease surveillance is strengthened and expanded, the number of reported cases is likely to increase, creating the false impression of a resurgence.

[16] WHO (2012). Disease surveillance for malaria elimination: an operational manual. Geneva: World Health Organization.

Most malaria-endemic countries in the Americas have well-performing passive malaria surveillance systems with treatment and case-reporting at health facilities and by volunteer malaria workers at the village level. These volunteers are supervised and provided with diagnostic supplies and antimalarial drugs by NMCP field workers. Although data on malaria cases reported through this surveillance system are based on parasitologic diagnoses with microscopy, or more recently with RDT, delays in reporting are relatively commonplace. In the transborder areas of the Guiana Shield, it is likely that many residents with suspected malaria obtain treatment from shops, pharmacies, or informal drug sellers without ever undergoing diagnostic testing, but the magnitude of this problem is unknown.

To prevent the development of resistance and ultimately achieve *P. falciparum* elimination, efforts must be made to improve the detection of patients with malaria in the Guiana Shield. The primary focus should be on expanding the number and distribution of PCD posts to capture a greater proportion of suspected malaria cases, although NMCPs may decide to complement PCD with ACD. At the same time, NMCPs will need to strengthen the timeliness of case reporting and the use of this information to guide malaria control activities. If NMCPs decide to expand their PCD networks by setting up malaria diagnostic and treatment posts in mining and logging camps or with private drug sellers, considerable effort will need to be invested in ensuring high-quality record keeping at these sites. Basic patient information (age, sex, place of residence, result of test, and treatment administered) should be recorded in the same manner as at traditional PCD posts. The NMCP field staff responsible for supervision of these posts and the restocking of materials should follow standard procedures in evaluating the quality of diagnosis, record keeping, and treatment by PCD workers.

Ideally, epidemiologic data should be disaggregated to the lowest possible level to allow a rapid response tailored to local conditions. To achieve this result, the data need to be collated in a simple tabular or graphic format and local staff must be trained in interpretation and use of the data. As malaria cases decline and malaria programs approach elimination, the programs will need to begin epidemiologic investigation of all cases in line with WHO guidance.[17] As much as possible, NMCPs engaged in resistance prevention efforts should make use of standard WHO-recommended malaria prevention and treatment indicators. The WHO Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion[18] includes a list of suggested indicators for use at the regional level that can be adapted by NMCPs in the countries of the Amazon Basin to monitor regional and national progress, which include the following:

[17] Ibid.

[18] WHO (2013). Emergency Response to Artemisinin Resistance in the Greater Mekong Subregion: Regional Framework for Action 2013-2015. Geneva: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/79940/1/9789241505321_eng.pdf

1. Proportion of patients with suspected malaria tested with microscopy or RDT;
2. *P. falciparum* and *P. vivax* infections confirmed by microscopy or RDT;
3. Proportion of confirmed outpatient *P. falciparum* cases that received appropriate antimalarial treatment according to national policy;
4. Proportion of health facilities without stock-outs of first-line antimalarial drugs and diagnostics in the previous three months;
5. Number of counterfeit or substandard antimalarial drugs in private pharmacies and shops;
6. Number of planned studies of insecticide resistance completed;
7. Percentage of the population at risk potentially covered by bed nets distributed;
8. Proportion of NMCP staff members who received relevant training and/or participated in monitoring and evaluation activities related to malaria during the year;
9. Proportion of monthly reports received on time from health facilities and volunteer workers;
10. Number of planned WHO standardized drug efficacy studies completed;
11. Status of national efforts to ban artesunate monotherapy;
12. Number of people reached with special interventions targeting mobile and migrant populations;
13. Interruption of *P. falciparum* malaria by administrative units; and
14. Funding (domestic and external) for artemisinin resistance prevention and *P. falciparum* elimination.

A critical factor in the success of PCD networks is the availability of well-trained personnel to oversee the network and keep the surveillance posts stocked with diagnostic testing supplies and antimalarial drugs. Investment in data collection without sufficient personnel to analyze and use the data, however, is unlikely to yield the needed results. Obtaining funding for the increased number of staff that a well-functioning surveillance system requires should be a high priority for the NMCP.

Priorities for Implementation

The transborder areas of the Guiana Shield are likely to be among the most difficult settings for malaria control and elimination in the Americas. National malaria control programs need to continue driving down the malaria burden there. This effort will also help prepare the way for the longer-term goal of malaria elimination.

Since it will not be possible for Ministries of Health and NMCPs to simultaneously implement all the activities described in this plan, and since existing levels of funding will probably not be sufficient to support full implementation of activities throughout the transborder areas, some prioritization will be required:

- Each country will need to develop a detailed plan of action and accompanying budget for resistance prevention and ultimate *P. falciparum* elimination to guide their work, gain political commitment and support, and seek additional funding from prospective donors;
- Although questions remain about how best to implement different approaches to malaria prevention, treatment, and surveillance in mining and indigenous communities, NMCPs should prioritize efforts to improve the detection and treatment of malaria cases and scale up coverage of insecticide-treated nets, as these interventions will have the greatest impact on the malaria burden. The improvement of case detection and treatment will, in turn, make it possible to strengthen the malaria surveillance system, which will become increasingly important as malaria transmission declines; and
- While this scale-up is under way, NMCPs will also need to engage indigenous groups, miners, loggers, and enterprise owners in collecting information on the behavior of patients when seeking treatment for malaria and the factors that influence their acceptance of and compliance with malaria prevention and treatment measures.

NMCPs may need to pilot these scaled-up interventions in indigenous and mining communities while assessing their effectiveness and impact, and then, as funding allows, expand to remaining areas.

Progress in improving case detection and treatment and scaling up coverage with insecticide-treated bed nets will depend on having well-functioning supply chain management systems in place, coupled with regular monitoring and supportive supervision of malaria workers in the field. Efforts to strengthen these processes should proceed in parallel with the expansion of prevention and treatment activities, but they are likely to take longer to show progress.

Two regional activities should also be prioritized:

- Ministries of Health and national drug regulatory authorities should work together to develop an enforceable regional agreement on banning the marketing and sale of oral artemisinin monotherapies; and
- Representatives of NMCPs working in the Guiana Shield, including field staff in the transborder areas, should meet on a regular basis (perhaps as frequently as quarterly) to exchange information on progress and problems with malaria control/elimination efforts, as well as to ensure standardization and complementarity of approaches.

Supportive Activities

1. Strengthened program coordination and management

A successful program of resistance prevention and *P. falciparum* elimination will require strong management and effective coordination of multiple activities and partners by Ministries of Health and NMCPs. The NMCP should be the lead agency in this effort and establish coordination bodies on resistance prevention and malaria elimination that meet regularly to review current surveillance and operations data, identify problems, and define corrective actions. These coordination bodies should engage with relevant departments within the Ministry of Health and other ministries, as appropriate, as well as with implementing partners, civil society, and the private sector. A government official of appropriate seniority should chair the meetings.

NMCPs that are leading efforts to eliminate malaria will also need clear chains of command with well-trained workers who are dedicated full time to malaria activities. Elimination will not be possible if workers can be shifted away from their malaria control duties to other activities. This point needs to be understood by authorities within the Ministry of Health centrally as well as by provincial- and district-level staff, since in many countries all workers at the more peripheral levels of the health system are supervised by and report to local health authorities.

Separate streams of funding for resistance prevention and *P. falciparum* elimination can pose a challenge to integration of these efforts into ongoing malaria control activities. Resistance prevention activities should not be seen as being independent of control activities; rather, they should to be designed and implemented with a view to intensifying and accelerating local, national, and regional efforts to control and eliminate malaria.

Cross-border coordination will be key to preventing resistance and eliminating *P. falciparum* malaria in the Guiana Shield. Representatives of NMCPs in these countries should begin to meet on a regular basis (perhaps as frequently as quarterly) to exchange information on progress and problems with malaria control operations, as well as to ensure standardization and complementarity of approaches. Coordination should also be encouraged at higher levels in the Ministries of Health to remove any potential barriers to diagnosis and treatment services for non-citizens who cross borders seeking medical attention. Malaria program staff working in the interior should be included in these meetings, as they will be the ones charged with implementing any new recommendations or activities.

The Pan American Health Organization can help by facilitating cross-border meetings and intercountry coordination. French Guiana is an overseas department of France and as such presents some unique challenges. For example, it is required to follow European regulations on the provision of treatment, which means, that non-medical staff are not allowed to test for malaria or provide treatment.

2. *Priority operations research and testing of new tools for prevention and elimination as they become available*

NMCPs should prioritize operational research on factors that influence the behavior of miners, loggers, and indigenous groups as it relates to seeking malaria treatment and complying with malaria prevention and treatment measures, since progress in preventing the development of resistance and eliminating *P. falciparum* malaria will require a better understanding of these behaviors. Involving local residents in the design of malaria control measures will help to ensure the success of these efforts. As the NMCPs proceed with implementing improved case detection, treatment, surveillance, and vector control measures in transborder areas, they should also work with research partners to refine and evaluate the feasibility, effectiveness, and cost of these approaches, keeping in mind that it will be easier to influence behavior change if the number of messages to be communicated can be limited to just two or three.

Numerous research projects are already under way in the Amazon Basin, including studies on improving parasitologic diagnosis, entomology, and vector control, with funding from national governments, research organizations, private foundations, and other donors. In April 2013, PAHO called together researchers and public health workers in the Region to develop recommendations on priority research topics for the Americas. A list of the topics that were identified in the area of resistance prevention and/or malaria elimination is given in the Annex. Through WHO, NMCPs in the countries of the Amazon Basin should be kept apprised of research planned or already under way in the Greater Mekong subregion that might be relevant to prevention efforts in the Guiana Shield, such as studies to evaluate the feasibility and effectiveness of MDA in reducing the prevalence of *P. falciparum* and resistant parasites.

3. *Monitoring of antimalarial therapeutic efficacy*

PAHO organized the Amazon Network for Surveillance of Antimalarial Drug Resistance (RAVREDA) in 2001 to promote and support routine monitoring of the therapeutic efficacy of antimalarial drugs. This network played a critical role in providing the evidence that has led national malaria treatment policies to shift from chloroquine and sulfadoxine-pyrimethamine to ACTs throughout the Amazon Region.

Conducting therapeutic efficacy studies (TESs) to evaluate first-line and alternative antimalarial drugs has become increasingly challenging in the Americas because of the declining prevalence of *P. falciparum* infections. It could take 12 months or longer to enroll a sufficient number of patients for a trial. Until about 2008, most countries in the Amazon Basin had been carrying out TESs every two to three years as recommended by WHO, but in the past five years the frequency of testing has fallen off and concerns have been raised about quality control in the tests that were performed. While these problems might not be so critical if all the strains are sensitive to the drugs being tested, they assume much greater importance when resistance is suspected.

Given the threat of resistance, countries will need to continue to conduct high-quality TESs to inform national treatment policy and identify foci of possible resistance. Studies of ACTs or clinical trials of artesunate monotherapy should be a particularly high priority in the transborder areas of the Guiana Shield. Since it may not be possible

to conduct TESS every two to three years in all the countries because of the decline in *P. falciparum* prevalence, NMCPs should consider multicenter studies. All studies should adhere closely to the most recent WHO protocol,[19] with a strong emphasis on data quality. In addition, studies must include an analysis of day 3 positivity rates, treatment failures up to 42 days (depending on the partner drug's half life), and testing for the prevalence of K13 mutations and other relevant molecular markers in day 0 blood samples.

Although population-level screening for artemisinin resistance may ultimately be possible by testing for mutations in the K13 propeller domain of the *P. falciparum* genome, TESS will remain the method of choice for decisions related to national malaria treatment policies. Those policies should be changed if well-conducted TESS show more than 10% treatment failure. A significantly declining trend in treatment efficacy over time, even if failure rates have not yet fallen to the ≥ 10% cutoff, should alert programs to undertake more frequent monitoring and to prepare for a potential policy change. New first-line drugs should be selected on the basis of a minimum average cure rate of 95%.

4. Strengthening pharmaceutical regulation of antimalarial drugs

Since migrant workers in the gold- and diamond-mining areas of the Guianas, Brazil, and Venezuela are usually paid by the day, rapid relief of symptoms and return to work is their primary concern when they become ill. This situation fosters a culture of treatment-seeking behavior in which self-diagnosis and rapid treatment with the most readily available antimalarial drugs, usually purchased from private pharmacies, shops, or itinerant drug sellers, takes precedence over diagnostic testing, concerns about drug quality, or adherence to a full course of therapy. The cost of medicines is not a major concern for most gold miners and local pharmacies, and shops cater to this demand by stocking a wide range of antimalarial drugs of variable quality, including many ACTs and artemisinin monotherapies.[20]

Ministries of Health in the Guiana Shield need to take prompt action to halt the availability and use of oral artemisinin monotherapies and non-regulated ACTs in the private sector and reinforce correct treatment protocols in public health facilities. National regulatory authorities are responsible for regulating the importation of both pharmaceutical raw materials and finished products and they play a critical role in limiting the availability and sale of poor-quality, substandard, and counterfeit products within and across borders. Regulatory control to limit the distribution of such products will also depend on effective implementation in collaboration with law enforcement, customs, and other agencies. Successful examples of such programs in the Greater Mekong subregion may be adapted to countries in the Americas.

Over the past six to eight years, most of the countries in the Amazon Basin have carried out quality testing of antimalarial drugs from the public and private sectors as

[19] WHO (2009). Methods for surveillance of antimalarial drug efficacy. Geneva: World Health Organization. Available from: http://apps.who.int/iris/bitstream/10665/44048/1/9789241597531_eng.pdf

[20] Evans L. et al. (2013). Quality of antimalarials collected in the private and informal sectors in Guyana and Suriname. Malaria J 11:203-210.

part of the PAHO-led Amazon Malaria Initiative Project. However, these monitoring activities have not been performed consistently and no recent data are available from several of the countries. Efforts need to be directed toward strengthening national regulatory authorities and laboratories engaged in testing the quality of medicines. As NMCPs in the Guiana Shield scale up their resistance prevention efforts, routine monitoring of antimalarial drug quality should be reinstated and continue, with special focus on the formal and informal private sector, where substandard drugs are much more common than in public sector facilities.

5. *Advocacy and communication to build political support and secure funding for prevention and elimination activities*

Given the potentially severe consequences of multidrug resistance for malaria control efforts in South America, including resistance to ACTs, a much higher level of political awareness and support is needed at the regional level and in affected countries. Advocacy, based on a well-designed communication plan, should be used to keep antimalarial drug resistance high on both the domestic and regional political agendas. Working with relevant partners, PAHO should regularly brief regional and national political leaders and government officials on progress in malaria control and elimination, with emphasis on the rationale, importance, and urgency of resistance prevention and its role in the push toward malaria elimination.

Guiana Shield countries will need significantly increased funding if they are to implement the activities recommended in this plan. In each country, the national malaria control program should prepare plans and budgets for intensified and expanded prevention, treatment, and surveillance based on a thorough assessment of needs.

In exploring opportunities for mobilizing additional external financing, PAHO should work with Ministries of Health and NMCPs on the preparation of proposals to potential donors. Efforts should also be made to ensure that adequate domestic resources are allocated to the NMCPs and malaria control activities. Implementing these activities may require Ministry of Health authorization to offer salary incentives to NMCP workers living and working in the mining areas. At the same time, mine owners must be encouraged to recognize the advantages of investing in the health of their workers.

Prevention of Artemisinin Resistance in Other Areas of South America

Although the primary focus of this framework document is the Guiana Shield, Ministries of Health and NMCPs responsible for neighboring areas and countries will need to increase their vigilance for signs of reduced *P. falciparum* sensitivity to ACTs and ensure that measures are in place to help prevent the emergence of artemisinin resistance.

Measures aimed at preventing the emergence of resistance largely mirror those of malaria control, and most countries are already carrying out many of the critical activities necessary to protect their first-line ACTs. All reported malaria diagnoses in

public health facilities and by volunteer malaria workers are based on parasitologic testing. All treatment of *P. falciparum* infections in both public health facilities and village-level malaria workers is with quality-assured ACTs, which in some countries include primaquine for its transmission-blocking effect. Information on confirmed cases is routinely reported up through well-functioning surveillance systems. Most countries have systems for monitoring the quality of their antimalarial drugs, and malaria control interventions are being scaled up. Although the quality of interventions is generally high, it does vary from country to country, and most NMCPs could benefit from efforts aimed at improving their performance. In particular, NMCPs in countries outside the Guiana Shield should focus their efforts on:

- Improving coverage with vector control measures to help drive down transmission and limit the potential impact of resistance if it were to emerge;
- Intensifying surveillance and ensuring rapid, complete treatment of all confirmed malaria cases, especially among mobile and migrant populations along border areas and near foci of transmission;
- Reducing the use of oral artemisinin monotherapies and substandard and counterfeit antimalarial drugs from the private sector through education and enforcement; and
- Sustaining regular, high-quality monitoring of drug efficacy to track the potential extension of artemisinin resistance and ensure that recommended first-line treatments remain effective.

Resistance Prevention and Malaria Elimination

Most of the approaches and tools that are used in resistance prevention activities are applicable to and complement malaria elimination efforts. In addition, efforts to prevent artemisinin resistance will directly contribute to the goal of elimination by increasing public and political awareness and commitment, promoting better collaboration between programs and sectors, and enhancing surveillance and cross-border coordination.

Artemisinin-based combination therapy (ACT) is the first-line treatment for *P. falciparum* malaria throughout South America. Elimination of this parasite will depend on the continued efficacy of existing ACTs or the development of new, non-artemisinin-based combination therapies. Regional resistance prevention should be the current priority of NMCPs in South America. *P. falciparum* elimination will be very challenging and remains a longer-term goal.

Both resistance prevention and malaria elimination require the rigorous, high-quality implementation of interventions. Although the countries of the Guiana Shield have not yet declared malaria elimination as a national goal, the incidence and prevalence of malaria, particularly *P. falciparum* malaria, have fallen dramatically in this subregion over the past decade. As NMCPs continue to drive transmission down, they should assign higher priority to the elimination of *P. falciparum* than to the elimination of *P. vivax*.

Quality-assured RDT and microscopy are the primary diagnostic tools for the confirmation and management of cases of suspected clinical malaria in all epidemiological situations, including areas of low transmission, because of their good performance in detecting clinical malaria, their widespread availability, and their relatively low cost.

Submicroscopic *P. falciparum* and *P. vivax* infections are common in both low- and high-transmission settings. Several nucleic acid amplification (NAA) techniques are available, which are more sensitive in detecting malaria than RDT and microscopy. Generally, the use of highly sensitive diagnostic tools should be considered only in low-transmission settings where malaria diagnostic testing and treatment are already widespread and parasite prevalence rates are low (e.g. < 10%). The use of NAA-based methods should not divert resources from malaria prevention and control or from the strengthening of health care services and surveillance systems. In malaria programs, these methods should be considered for epidemiological research and surveys to map submicroscopic infections in low-transmission areas. They might also be used for identifying foci for special interventions in elimination settings. [21]

[21] WHO (2014). Policy brief on malaria diagnostics in low-transmission settings. Available from: http://www.who.int/entity/malaria/publications/atoz/malaria-diagnosis-low-transmission-settings-sep2014.pdf

Annex

Research Priorities for Artemisinin Resistance Prevention in South America (Washington, D.C., April 2013)

- Socio-behavioral characteristics of miners, private drug sellers, indigenous groups, and other residents of transborder areas of the Guianas and Brazil, with focus on:
  - Treatment-seeking behavior of malaria patients;
  - Factors that are barriers to or influence the acceptance of diagnostic testing, antimalarial drugs, and insecticide-treated nets; and
  - Factors involved in labor relations between miners and mine owners, especially those that could influence access to and acceptance of malaria prevention and treatment activities.

  (Cost-effective prevention and elimination efforts will require better understanding of the attitudes and behavior of miners, mine owners, drug sellers, indigenous groups, and other residents of mining communities with respect to malaria prevention and treatment. Studies should focus on collecting information that is actionable.)

  Evaluation of different approaches to malaria case detection and reporting in mobile and transient populations and indigenous communities.

- Refinement of the use of ACD in malaria elimination settings, including focused screening and treatment (FSAT) and mass screening and treatment (MSAT).
- (FSAT involves paid malaria workers taking blood samples from selected high-risk residents or population groups for rapid diagnostic testing or microscopy and then providing full malaria treatment for those with confirmed infections. In the case of MSAT, paid malaria workers perform RDT or take blood smears from all members of a community or larger area and then treat those who are positive.).
- Development of improved, reliable diagnostic tools for low-density parasitemia.
- (Many carriers of malaria are asymptomatic, even in areas of low endemicity. Deployable diagnostic tools for detecting low-density parasitemia will be essential for successful elimination efforts.).
- Use of MDA for the elimination of malaria parasites.
- (Research is needed on the potential coverage, operational issues, effectiveness, and safety of MDA as a means of curing infections and blocking transmission.)
- Use of the newly identified K13 molecular marker for artemisinin resistance to map resistance in the Guiana Shield and guide treatment policies.
- The role of indoor residual spraying (IRS) in preventing the development of artemisinin resistance.

- (Insecticide-treated bed nets are already fairly widely used in the Amazon region, but the use of IRS in these settings needs to be more clearly defined.).
- Evaluation of the acceptance and effectiveness of different personal protection methods, including repellents and impregnated cloth, among miners and other residents of communities in the transborder areas of the Guiana Shield.
- Assessment of the role of abandoned open-pit mines as Anopheles breeding sites in the interior of the Guiana Shield.
- Assessment of different procedures for triggering a response to increases or changes in transmission, such as foci of reintroduced malaria or malaria outbreaks in mobile populations, which may necessitate the deployment of additional resources to an area.

Pan American Health Organization

World Health Organization

EGIONAL OFFICE FOR THE Americas

525 Twenty-third Street, NW
Washington, DC 20037, EUA
Tel: +1 (202) 974 –3000
www.paho.org

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