

 **EMERGENCY
RESPONSE TO
ARTEMISININ
RESISTANCE**
IN THE GREATER
MEKONG SUBREGION

REGIONAL FRAMEWORK FOR ACTION
2013-2015



World Health
Organization



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Abbreviations

ACD	active case detection
ACT	artemisinin-based combination therapy
APLMA	Asia-Pacific Leaders Malaria Alliance
ASEAN	Association of Southeast Asian Nations
ERAR	emergency response to artemisinin resistance
FSAT	focused screening and treatment
GMS	Greater Mekong subregion (Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam)
GPARC	Global plan for artemisinin resistance containment
GPIRM	Global plan for insecticide resistance management in malaria vectors
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 programme
PTE	presumptive therapy for elimination
RDT	rapid diagnostic test
TEG	technical expert group
TES	therapeutic efficacy studies
WHO	World Health Organization

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1. Background

Expanding access to artemisinin-based combination therapies (ACTs) in malaria-endemic countries has been integral to the remarkable recent success in reducing the global malaria burden. No alternative antimalarial medicine is currently available offering the same level of efficacy and tolerability as ACTs. The emergence of artemisinin resistance in the Greater Mekong subregion¹ (GMS) is therefore a matter of great concern. Resistance to other antimalarial medicine was also detected first in GMS, eventually appearing elsewhere. In Africa there is evidence that the spread of resistance coincided with increases in child mortality and morbidity.²

This framework focuses on artemisinin resistance. All ACTs contain an artemisinin derivate combined with a partner drug. There are currently five³ ACTs recommended by WHO. The role of the artemisinin compound is to reduce the main parasite load rapidly during the first days of treatment; the role of the partner drug is to eliminate any remaining parasites. A high proportion of patients infected with artemisinin-resistant strains of *Plasmodium falciparum*, are still parasitaemic 72 h after the beginning of treatment; however, patients are currently still cured if they are treated with an ACT containing a partner drug that is still effective in the geographical area. If resistance to artemisinins exists, it is more likely that resistance to the partner drugs will also develop, and vice versa. Consequently, resistance to ACT partner drugs is also an important concern, and must be monitored carefully.

P. falciparum resistance to artemisinins has been detected in four countries in the GMS: Cambodia, Myanmar, Thailand and Viet Nam (Figure 1). Containment activities were started in 2008 on the Cambodia–Thailand border and are now being conducted in all four countries (Box 1).

In late 2011, a group of international development partners, in collaboration with WHO, initiated a *Joint assessment* of the response to artemisinin resistance in the GMS. Between November 2011 and February 2012, a team reviewed documents and visited Cambodia, China, Myanmar and Viet Nam, including areas affected by artemisinin-resistant malaria. Information for Thailand and the Lao People's Democratic Republic was collected from documents and interviews⁴.

The conclusion was that “.... a good, if delayed, start has been made to addressing artemisinin resistance in the GMS. In some areas the impact has already been impressive. In general, the approach outlined in the *Global plan for artemisinin resistance containment* (GPARC)⁵ and several associated national level strategies and plans was found to be appropriate.... However, overall the assessment is sobering. It is impossible to avoid the conclusion that not enough is yet being done, with enough intensity, coverage and quality, to respond to a problem that could not only slow future progress but also undo the gains already made in malaria control worldwide.” The report calls for “a very large increase in attention to this issue”.

¹ Comprising Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.

² Trape JF (2001). The public health impact of chloroquine resistance in Africa. *American Journal of Tropical Medicine and Hygiene*, 64:12–17.

³ A sixth ACT, Pyramax® (fixed-dose combination of pyronaridine and artesunate), was given a positive scientific opinion by the European Medicines Agency (EMA) under Article 58 in February 2012 and is being considered for recommendation by WHO.

⁴ The findings are summarized in the *Joint assessment report of the response to artemisinin resistance in the Greater Mekong subregion*. The assessment was sponsored by Australian Agency for International Development and Bill and Melinda Gates Foundation and conducted in partnership with the United Kingdom Department for International Development, the United States Agency for International Development and WHO (<http://malaria2012conference.com/cms/wp-content/uploads/2012/10/Joint-Assessment-of-the-Response-to-Artemisinin-Resistance.pdf>).

⁵ WHO (2011). *Global plan for artemisinin resistance containment*. Geneva, World Health Organization.

The *Joint assessment* recommended increased action in ten areas. This framework is in follow-up to the recommendations of the *Joint assessment*. It also takes into account the report of the first meeting of the technical expert group (TEG) on drug resistance and containment (June 2012).

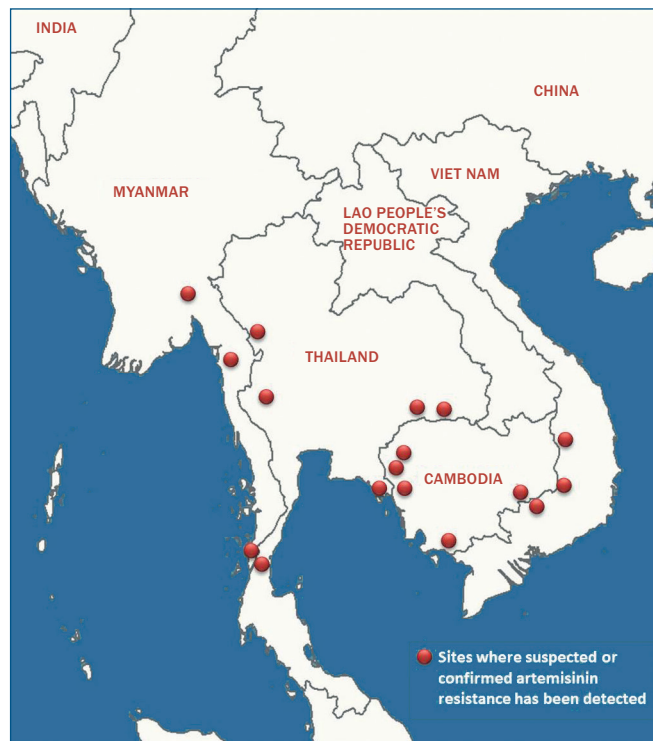


Figure 1. Sites where suspected or confirmed artemisinin resistance has been detected as of 2012

Box 1. Note on use of the term 'artemisinin resistance containment'

The aim of the first response to artemisinin resistance along the Cambodia–Thailand border was to contain the problem to that geographical area. Evidence of resistance has now been detected at several other sites, indicating that the initial hopes of containment in one area was not fulfilled, either because of spread of resistance or its spontaneous emergence elsewhere. Nevertheless, the strategies that are applied to eliminate resistant parasites in any areas where resistance is detected can reasonably be considered as efforts to 'contain' the problem. These efforts are not addressing only artemisinin resistance but also at resistance to ACT partner drugs. However, the GPARC and plans in four countries describe activities designated as artemisinin resistance containment; this term has been retained for this plan. In higher transmission areas, containment efforts focus on limiting the risk of spread by lowering the malaria burden through intensified malaria control, by increasing access to diagnostic testing and appropriate treatment, and by scaling-up provision of health care services to migrant and mobile populations. Containment programmes in lower-transmission areas seek to achieve an accelerated elimination of *P. falciparum* parasites.

2. Purpose of the framework

This framework highlights key action areas in which progress is urgently needed in the coming years if we are to contain resistance and move towards elimination of malaria in GMS. It recalls the overarching containment goal of protecting ACTs as an effective treatment for *P. falciparum* malaria. The framework seeks to do this by rallying stakeholders to urgently scale-up and increase the effectiveness of interventions to address artemisinin resistance.

This framework is not intended to replicate or replace existing global, regional or country strategies for the containment of artemisinin resistance, nor those for malaria control and elimination. Nor is this framework intended as a detailed workplan. Instead it aims to draw attention to the quality of implementation of strategies on the basis of lessons learnt from the current containment projects and the conclusions of the *Joint assessment*.

The framework focuses on the GMS but recognizes that artemisinin resistance is an issue of global concern which requires concerted and coordinated effort at global, regional and national levels. Countries and implementing partners working in the region, as well as stakeholders at the global level are the primary target audience for the framework.

For the purposes of this framework, geographical ‘priority areas’ are defined as the areas designated as tiers I and II (see Box 2), consistent with the terminology used in the GPARC. In general, the framework avoids reference to specific geographical or administrative areas in countries, referring instead to ‘containment tiers’. The exact geographical extent of artemisinin resistance may change, while the basic principles of containment will remain valid for newly affected areas. While field activities in tier III areas are not emphasized, strengthening good malaria control in tier III areas is crucial in the national and regional efforts to eliminate malaria and contain resistance.

The framework will first briefly outline the already existing guidance for artemisinin resistance containment, then describe the areas where action is urgently needed to further progress in the efforts to contain resistance.

Box 2. Classification of geographical areas into tiers of artemisinin resistance

Tier I: Areas where there is credible evidence of artemisinin resistance.

Tier II: Areas with significant inflows of people from tier I areas, including those immediately bordering tier I.

Tier III: Areas with no evidence of artemisinin resistance and limited contact with tier I areas.

The working definition of artemisinin resistance is:

- an increase in parasite clearance time as evidenced by $\geq 10\%$ of cases with parasites detectable on day 3 after treatment with an ACT (suspected resistance); or
- treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for 7 days, or the presence of parasites at day 3 and recrudescence within 28 or 42 days (confirmed resistance).



3. Existing strategic guidance for artemisinin resistance containment

3.1 GLOBAL PLAN FOR ARTEMISININ RESISTANCE CONTAINMENT: THE STRATEGIC FRAMEWORK

The GPARC launched in January 2011, was based on information in the *Global report on antimalarial drug efficacy and drug resistance: 2000-2010*⁶. The objectives of GPARC are summarized in Box 3.

Box 3. Main elements of the *Global plan for artemisinin resistance containment*

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:

- contain or eliminate artemisinin resistance where it already exists;
- prevent artemisinin resistance where it has not yet appeared.

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;
- motivate action and mobilize resources.

In tier I areas, the aim is to mount an immediate, multifaceted response to contain or eliminate resistant parasites as quickly as possible. In tier II areas, the aim is to intensify malaria control in order to reduce transmission and to limit the risk of emergence or spread of resistant parasites. In tier III areas, prevention and preparedness should focus on increasing coverage with parasitological diagnostic testing, quality-assured ACTs and vector control (Figure 2). In all tiers, high-quality malaria control should comprise:

- parasitological diagnosis for all patients with suspected malaria;
- a full course of quality-assured ACTs for confirmed cases (plus primaquine, in compliance with current WHO treatment guidelines); and
- vector control, as locally appropriate, to lower transmission rapidly and stop the spread of resistant parasites.

⁶ WHO (2010). *Global report on antimalarial efficacy and drug resistance: 2000–2010*. Geneva, World Health Organization.

In tier I areas, it is important to move to universal high-quality coverage with these elements as quickly as possible. Tier II areas should intensify malaria control activities that include these elements and also move aggressively to achieve universal coverage with high-quality interventions. In tier III areas, while the risk of resistance is lower, every effort should be made to expand coverage with these basic malaria control practices progressively and to improve their quality. In tiers I and II areas, additional specific activities should be launched to contain or eliminate resistant parasites.

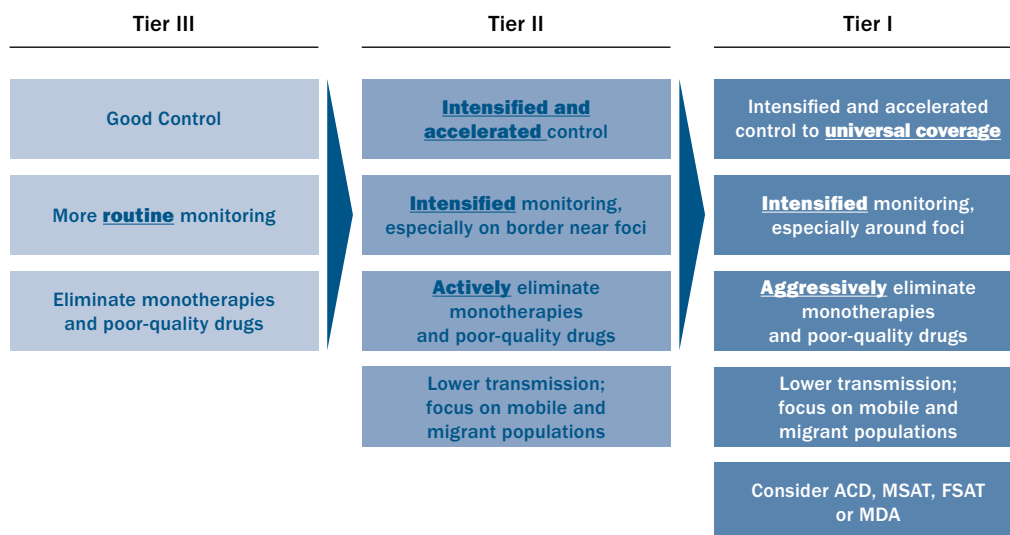


Figure 2. Recommendations of the *Global plan for artemisinin resistance containment* by tier

3.2 COUNTRY-SPECIFIC ARTEMISININ RESISTANCE CONTAINMENT

Special efforts specifically designed for artemisinin resistance containment have been initiated in the four countries in which suspected or confirmed resistance has been identified: Cambodia, Myanmar, Thailand and Viet Nam. The objectives of the plans and strategies for containment in countries overlap and include:

- rapid detection of symptomatic malaria cases in target areas, ensuring effective treatment and gametocyte clearance;
- detection of asymptomatic cases through active case detection (ACD), focused screening and treatment (FSAT), mass screening and treatment (MSAT) and limited mass drug administration (MDA);
- decreasing drug pressure for selection of artemisinin resistant malaria parasites by promoting parasitological diagnosis before treatment of uncomplicated malaria and stopping use of oral artemisinin-based monotherapies;
- preventing transmission of resistant parasites by mosquito control and personal protection;
- improving access to services for mobile and migrant populations by approaches such as:
 - > training volunteers in diagnostic testing and treatment;
 - > providing free screening and treatment points in locations that are easily accessible for these populations; and
 - > engaging the private sector in offering high-quality diagnostic testing and treatment;

- promoting containment or elimination of resistant parasites by behaviour change communication, community mobilization and advocacy;
- undertaking basic and operational research to ensure evidence-based strategies; and
- providing effective management and coordination for rapid high-quality implementation.

Maps showing the areas designated as tiers I, II and III for the countries with suspected or confirmed artemisinin resistance will be made available on GMP's web site. These tiers can be expected to evolve as information on artemisinin resistance changes.

3.3 ARTEMISININ RESISTANCE CONTAINMENT IN THE CONTEXT OF MALARIA ELIMINATION STRATEGIES

The containment of artemisinin resistance must build on and be an integral part of ongoing efforts to control and eventually eliminate malaria. The ultimate aim of the focused, rigorous effort to contain artemisinin resistance is to eliminate resistant malaria parasites. The activities therefore contribute to the longer-term efforts to eliminate malaria at subnational, national and regional levels.

Cambodia, China, Thailand and Viet Nam have declared malaria elimination as a national goal. Cambodia⁷ has set a target of national elimination of malaria by 2025, while China⁸ aims to eliminate malaria nationwide by 2020. Viet Nam⁹ has set specific subnational targets, the Lao People's Democratic Republic¹⁰ plans to eliminate malaria in selected provinces and Thailand¹¹ has a long-term plan to eliminate malaria at the district level. In general, the intention is to eliminate malaria deaths and *P. falciparum* malaria first, with elimination of malaria due to other *Plasmodium* species, notably *P. vivax*, as a longer-term goal.

Elimination of *P. falciparum* malaria depends on the continued efficacy of ACTs. An aggressive response to artemisinin resistance will contribute to malaria elimination, and elimination activities contribute to the containment of artemisinin resistance. Containment and elimination require rigorous, high-quality implementation of interventions of proven efficacy. New, promising interventions that have not yet been fully tested in the field can be prioritized as long as they are evaluated simultaneously.

The regional response to artemisinin resistance is urgent, while regional malaria elimination is a longer-term endeavour. The containment of artemisinin resistance will directly and strongly contribute to that endeavour by increasing awareness and political commitment, resulting in more funding from domestic and external sources, scaling-up of high-quality prevention and control activities that cover even difficult-to-reach populations, better collaboration between programmes and among sectors, better surveillance and tools and well-coordinated cross-border activities for health and development more broadly. The approaches that are refined in current containment activities can then be used in elimination.

⁷ Cambodian Ministry of Health. *National strategic plan for elimination of malaria in the Kingdom of Cambodia 2011–2025*.

⁸ Chinese Ministry of Health. *Action plan of China malaria elimination (2010–2020)*.

⁹ Viet Nam Ministry of Health. *National strategy for malaria control and elimination for the period of 2012–2015*.

¹⁰ Lao People's Democratic Republic Ministry of Health. *National strategy for malaria control and pre-elimination 2011–2015*.

¹¹ Thailand Ministry of Health. *National strategic plan for malaria control and elimination in Thailand 2011–2016*.



4. Priority Actions

The *Joint assessment* highlighted factors that hinder or delay progress in containment. The actions that are urgently required are shown in Figure 3 and described in the following pages.

FULL COVERAGE WITH HIGH-QUALITY INTERVENTIONS IN PRIORITY AREAS	TIGHTER COORDINATION AND MANAGEMENT OF FIELD OPERATIONS
ACTION 1 INCREASE QUALITY OF AND COVERAGE WITH KEY INTERVENTIONS IN THE PRIVATE AND PUBLIC SECTOR	ACTION 4 STRENGTHEN COORDINATION OF FIELD ACTIVITIES
ACTION 2 ENGAGE HEALTH AND NON-HEALTH SECTORS TO REACH HIGH-RISK POPULATIONS	ACTION 5 MONITOR STAFF PERFORMANCE AND INCREASE SUPPORTIVE SUPERVISION
ACTION 3 IMPLEMENT MEASURES TO ENSURE CONTINUOUS AND UNINTERRUPTED SUPPLY OF ESSENTIAL COMMODITIES	ACTION 6 PROMOTE THE INTEGRATION OF RESISTANCE CONTAINMENT, IN MALARIA ELIMINATION AND CONTROL EFFORTS WHILE MAINTAINING A FOCUS ON RESISTANCE
BETTER INFORMATION FOR ARTEMISININ RESISTANCE CONTAINMENT	REGIONAL OVERSIGHT AND SUPPORT
ACTION 7 IMPROVE COLLECTION AND USE OF DATA TO TARGET OPERATIONS	ACTION 11 ENHANCE ACCOUNTABILITY AND EXCHANGE OF INFORMATION
ACTION 8 FAST-TRACK PRIORITY RESEARCH AND REFINE TOOLS FOR CONTAINMENT AND ELIMINATION	ACTION 12 BUILD POLITICAL SUPPORT AT ALL LEVELS
ACTION 9 INCREASE MONITORING OF ANTIMALARIAL THERAPEUTIC EFFICACY AND STRENGTHEN THE THERAPEUTIC EFFICACY NETWORKS WORLDWIDE	ACTION 13 FACILITATE PROGRESS AND REGIONAL COOPERATION ON PHARMACEUTICAL REGULATION, PRODUCTION, EXPORT AND MARKETING
ACTION 10 INCREASE MONITORING OF INSECTICIDE RESISTANCE	ACTION 14 CREATE A REGIONAL COMMUNITY OF PRACTICE ON APPROACHES TO HIGH-RISK AND HARD-TO-REACH POPULATIONS
	ACTION 15 SUPPORT CROSS-BORDER COORDINATION

Figure 3. Four areas in which action is urgently needed

FULL COVERAGE WITH HIGH-QUALITY INTERVENTIONS IN PRIORITY AREAS

A priority for all levels of management is to ensure steady progress to and maintenance of, universal coverage with key prevention, diagnostic and treatment interventions for all populations living or working in containment tiers I and II areas. Impressive achievements have been made in some areas and steady progress in others; however, the overall level of coverage and the continuity and quality of operations are not yet adequate. Migrants, mobile populations and other population groups that have poor access to health services are a particular challenge.

ACTION 1

INCREASE QUALITY OF AND COVERAGE WITH KEY INTERVENTIONS IN THE PRIVATE AND PUBLIC SECTOR

The key interventions are:

- parasitological diagnosis of all cases with suspected malaria, including those treated in the private sector;
- a full course of treatment for all patients with *P. falciparum* malaria with an appropriate quality-assured ACT and primaquine (in line with WHO recommendations);
- use of long-lasting insecticidal nets (LLINs) or hammock nets;
- personal protection measures for those not adequately protected by nets;
- indoor residual spraying (IRS) (as appropriate).

The national treatment policy should be changed if therapeutic efficacy studies (TES) show more than 10% treatment failures. New antimalarial medicines should be selected on the basis of a minimum average cure rate of 95%.

A clear policy must be in place in all countries on the use of primaquine in the treatment of *P. falciparum* malaria to block transmission of parasites. At its meeting in September 2012, the WHO malaria policy advisory committee recommended an update in the policy on use of primaquine as a gametocytocide to treat *P. falciparum* malaria in areas threatened by artemisinin resistance and elimination areas (Box 4).

Box 4. Updated WHO policy recommendation on use of a single dose primaquine as a gametocytocide in the treatment of *P. falciparum* malaria (October 2012)

A review of the safety and effectiveness of primaquine as a gametocytocide of *P. falciparum*, indicated that a single dose of 0.25mg base/kg body weight is effective in blocking transmission and is unlikely to cause serious toxicity in subjects with any glucose-6-phosphate dehydrogenase deficiency (G6PD) variant. On this basis, the malaria policy advisory committee recommends the following:

- A single dose of 0.25 mg base/kg body weight primaquine should be given to all patients (except for pregnant women and infants <1 year of age) with parasitologically confirmed *P. falciparum* malaria on the first day of treatment, in addition to an ACT, in:
 - > areas threatened by artemisinin resistance where single-dose primaquine as a gametocytocide for *P. falciparum* malaria is not being implemented; and
 - > elimination areas that have not yet adopted primaquine as a gametocytocide for *P. falciparum* malaria.
- In countries already using a 0.75 mg base/kg body weight single dose of primaquine in the treatment of *P. falciparum*, WHO recommends to continue with the current policy until more information on the efficacy of the lower dose is available.

In tier III areas, the coverage and quality of malaria control must also be improved. This will reduce the potential impact and spread of artemisinin resistance if it were to emerge or be introduced in tier III.

Countries must have clear strategies with regard to the private sector. In some countries, the private sector is no longer allowed to treat patients with malaria, while in others, it plays a central role in providing access to malaria services. It is essential to work with the private sector to improve the quality of the services delivered and therefore the overall coverage of all populations with diagnostic and treatment services. The activities include ensuring that all treatment given is in line with national treatment guidelines and working quickly towards provision of a parasitological diagnosis for all suspected cases of malaria in both the formal and the informal sectors. Work is also needed to withdraw oral artemisinin-based monotherapy from the private sector and to stop the use of injectable artemisinins for uncomplicated malaria. If the private sector is not engaged, many countries will not achieve universal coverage, especially of marginalized populations.

Coverage with vector control interventions such as LLINs has, in some areas, been extensive, but maintaining a high level is difficult, requiring close monitoring and immediate action when a decline in coverage is projected.

Populations living in remote areas represent a challenge. Limited access to the health system and other barriers, such as language, must be overcome to allow full coverage. Pockets of underserved populations should be detected in routine or special surveys.

ACTION 2

ENGAGE HEALTH AND NON-HEALTH SECTORS TO REACH HIGH-RISK POPULATIONS

Both health and non-health sectors must be engaged to proactively apply and evaluate established and innovative approaches to malaria prevention and treatment for populations at high risk for contracting or spreading drug-resistant malaria. Population groups may be at high risk due to their occupation, working for instance in mining in forested areas; others are at risk due to their mobility. People moving into new areas are more likely to seek care from unregulated, private vendors often increasing their risk of exposure to substandard drugs or oral artemisinin-based monotherapy.

Mobile and migrant populations are a diverse group. They include individuals and groups who are temporarily moving either within or outside their home country, often for temporary or seasonal work; internally displaced persons moving to find new areas due to political conflict or for other reasons; and national security forces, which are often clustered near borders. The population groups most at risk in a given country or region should be clearly defined.

A number of different approaches are being used successfully to improve access to malaria prevention and treatment for these populations. Interventions include: transit route interventions, such as offering screening and treatment at bus stations; work-site interventions, including training malaria migrant volunteers and working with labour organizers; training community or village volunteers for diagnostic testing, treatment, referral and surveillance; engagement of private sector providers by training, supervision, and supply of quality assured commodities; and working with labour organizations, employers and others to provide services to those not reached through any of the methods mentioned above. Other relevant sectors, such as labour and immigration authorities, extractive industries, and construction companies, must be engaged. Interventions for improving access for high-risk populations should be

integrated into national strategies, plans and proposals for containment, control and elimination. These interventions, especially when newly deployed in a given area, need to be evaluated regularly and adjusted as required. Those that are successful should be rapidly expanded.

Special communications approaches for high-risk populations are needed that ensure messages are culturally appropriate, easy to understand, and actionable. Care should be taken that such approaches do not lead to stigmatization of certain groups.

ACTION 3

IMPLEMENT MEASURES TO ENSURE CONTINUOUS AND UNINTERRUPTED SUPPLY OF ESSENTIAL COMMODITIES

An uninterrupted supply of essential commodities for testing and treating malaria saves lives and is essential to contain artemisinin resistance. Stock-outs result in a loss of credibility in the public health sector. A patient who has the experience of being unable to get treatment at a formal health facility is less likely to return, and may revert to substandard medicines or artemisinin-based monotherapies purchased through informal drug vendors. Stock-outs can thus hinder progress towards artemisinin resistance containment and elimination.

Unfortunately, stock-outs of medicines, including antimalarials, are still common in many countries worldwide, including those in the GMS. Stock-outs can be caused by lack of funding, delayed procurement at central level or problems in distribution. Stock-outs in the field are often caused by lack of clear guidance or problems of planning, management and reporting. Besides stock-outs, poor management and planning can also cause excess stock, expired supplies and waste of resources^{12,13}.

Detailed, high-quality data can be used to make good estimations of future supply needs. However, estimations will never be perfect. Changes in previous patterns will inevitably be seen in some areas due to, for instance, variations in rainfall or population movements, leading to an increase in malaria cases or demand for services. The supply system must be able to rapidly respond to such fluctuations. Potential solutions vary between countries. In some countries, creating a system where weekly supply levels are given via SMS or the Internet may be a part of the solution. Other countries may, in the short term, have to rely on paper-based solutions. Nevertheless, all countries should have clearly defined standard operating procedures for managing supplies and, ideally, a designated person responsible for all malaria commodities.

Standard operating procedures for supply management must as a minimum define:

- how to estimate supply needs;
- how to correctly transport and store supplies;
- how to record and report available supplies;
- how and when to request additional supplies allowing for delivery time;
- what emergency measures to take if a stock-out occurs;
- how large a buffer stock to keep at different levels of the health system;
- when and how to report excess supplies;
- the role of supervision; and
- who is responsible for each function in the management of supplies.

¹² WHO (2010). *Good procurement practices for artemisinin-based antimalarial medicine*. Geneva, World Health Organization.

¹³ WHO (2011). *Good practices for selecting and procuring rapid diagnostic tests for malaria*. Geneva, World Health Organization.

Repeated or prolonged stock-outs represent a management failure and the reasons must be investigated and rectified.

TIGHTER COORDINATION AND MANAGEMENT OF FIELD OPERATIONS

Artemisinin resistance containment will not be achieved by ‘business as usual’. The demand for good management and strong coordination increases with the requisite rise in ambitions in terms of coverage, surveillance, reporting and burden reduction combined with an augmentation in funding and number of partners.

ACTION 4 STRENGTHEN COORDINATION OF FIELD ACTIVITIES

Containment entails additional activities as well as increasing the intensity of already ongoing activities. This, in addition to the potential increase in the number of partners, means that there is a need to strengthen the coordination of field activities. This is done partly through the establishment of a coordination body for artemisinin resistance containment in each affected country. Furthermore, it must be ensured that staff roles with respect to artemisinin resistance containment at all levels of the health system are clearly defined, and, where needed, focal points for activities are designated.

Countries affected by artemisinin resistance require a coordination body for artemisinin resistance containment that meets regularly, reviews current surveillance and operations data, identifies problems and defines corrective action that need to be systematically followed-up. This coordination body should engage not only the relevant departments within the ministry of health, but should also engage other ministries as appropriate, as well as implementing partners, civil society and the private sector. A government official of appropriate seniority should chair the meetings, with support from WHO as needed.

Coordination and the implementation of activities can be furthered with appropriate designation of national and subnational focal points for containment. For the artemisinin resistance containment to be effective there needs to be a strong ‘chain of command’ ensuring that the national policy is implemented and the implementation verified.

ACTION 5 MONITOR STAFF PERFORMANCE AND INCREASE SUPPORTIVE SUPERVISION

Supportive supervision is fundamental to ensuring that activities are implemented as planned and at the necessary level of quality. Supervision can, moreover, play an important role in the continuing education of staff at all levels. Consequently, supervision, audit and feedback are key interventions advocated for by WHO to promote more rational use of medicines in primary care¹⁴. Nevertheless, systematic supervision carried out by staff trained specifically in their supportive roles is often neglected. Unfortunately, this has also been found to be the case in ongoing containment activities. Consequently, there is a need to strengthen the role of monitoring and supervision. This includes formulation of clear strategies detailing:

¹⁴ WHO (2012). *The pursuit of responsible use of medicines: sharing and learning from country experiences*. Geneva, World Health Organization.

- plans for training of staff in a supervisory role;
- schedules and plans for the supervisory visits;
- how, when and what to report to the higher levels on the results of the supervision visit;
- how, when and what to provide as feedback to the staff and facilities supervised;
- who is responsible for following-up action to resolve identified problems.

A strategy should include plans for general supervision of malaria testing and treatment at health facilities and by volunteers at community level as well as guidance for strengthening supervision in private sector. This strategy should engage the variety of implementing partners supporting the national malaria control programme (NMCP) in their efforts. Furthermore, plans should be laid out for supervision of, for instance, malaria microscopy, distribution of LLINs and IRS. Country-level containment strategies should include plans for supervision; adequate budgets should be allocated for supervisory activities.

Field activities will go according to plan only if health workers and officials at all levels know what is expected of them. Their roles must be defined, and supported by concise, easy-to-follow standard operating procedures. Where additional work is required beyond normal job descriptions, or where salaries and motivation are very low, the use of performance incentives should be considered.

ACTION 6 **PROMOTE THE INTEGRATION OF RESISTANCE CONTAINMENT, IN MALARIA** **ELIMINATION AND CONTROL EFFORTS WHILE MAINTAINING A FOCUS ON RESISTANCE**

Different sources of funding for containment, control and elimination can pose a challenge to the overall integration of the efforts to contain resistance into ongoing activities to control and eliminate malaria. Containment activities cannot be seen as activities done parallel to control and elimination activities but should to be designed and implemented with a view to intensify and accelerate subnational, national and regional efforts to control and eliminate malaria. Similarly, elimination and control plans should be designed so requisite focus is given to areas with resistance. National coordination mechanisms must monitor activities and national strategies and plans must support the alignment of field activities to ensure achievement of agreed upon targets and solve identified bottlenecks.

BETTER INFORMATION FOR ARTEMISININ RESISTANCE CONTAINMENT

High-quality, timely information from programme implementation, on epidemiology and on areas of confirmed or suspected resistance are needed to direct activities. While progress has been made in all these areas, immediate action is needed both on the collection and improved use of data.

ACTION 7 **IMPROVE COLLECTION AND USE OF DATA TO TARGET OPERATIONS**

A system effectively reporting programme implementation data (what happens, where and when) and an effective malaria surveillance system provide programmes with essential information^{15,16}. This information is needed to direct resources to the populations most in need

¹⁵ WHO (2012). *Disease surveillance for malaria elimination: an operational manual*. Geneva, World Health Organization.

¹⁶ WHO (2012). *Disease surveillance for malaria control: an operational manual*. Geneva, World Health Organization.

and respond to unusual trends, such as a significant increase in cases or the absence of a decrease in the number of cases despite widespread implementation of interventions. As a result, progress can be accelerated and wastage of resources avoided.

The development of effective surveillance systems requires significant investments, both financial and human. A critical factor in the functioning and sustainability of such systems is the availability of well-trained personnel. Investment in data collection systems without a corresponding investment in human resources to analyse the data and use the information generated is unlikely to yield the needed results. Ultimately, data should be used to influence decisions, and it is the quality of the decisions as well as the quality of the data that in the end will help achieve containment of resistance and elimination.

While the features of the surveillance system are different from country to country, efforts have been made to strengthen the timeliness and detail of the data in areas with ongoing artemisinin resistance activities. However, more action is also needed in terms of the use of these data to guide operations. Data need to be analysed regularly at the lowest level possible to allow for the maximum tailoring of local responses. For this to happen, data needs to be available when needed and in a practical format (such as graphs and easily interpreted tables), and staff at all levels of the health systems needs to be regularly trained in use of data to, on a weekly or monthly basis, answer and act on questions such as:

- Are there unusual changes in the number of cases?
- Do some areas have a divergent pattern of disease requiring a special intervention, such as a continuing high level of malaria transmission in areas in which there is a high coverage with vector control intervention and good access to high-quality diagnosis and treatment?
- Are targets being met both in terms of testing and reporting and the proportion of confirmed *P. falciparum* cases treated in accordance with national treatment policy?
- Which areas, facilities or volunteers are testing and reporting adequately and which are experiencing problems?

Such data collection and analysis efforts are being embedded in containment activities throughout the GMS, including activities beyond the formal government health sector. More work is needed to routinely obtain information from the non-health sector on current or foreseen population movement or initiation of new development projects such as road construction or new mining activities. The short-term solution is to provide additional guidance to countries and stakeholders on malaria services for populations working in development projects. In the longer term, regulation or legislation should be facilitated to include a health component as mandatory in all development projects.

In many low endemic areas, efforts are needed or already underway to reorient the surveillance system towards elimination. This includes ensuring that all cases receive a parasitological diagnosis, immediate and complete reporting, and full investigation of all cases and foci. Whenever possible, this should, in areas of suspected or confirmed resistance, be supplemented by treating all *P. falciparum* cases using directly observed treatment and followed up to ensure and document treatment outcome.

The surveillance system should be complemented by periodic prevalence surveys with sufficiently sensitive methods, surveys collecting information on key issues such treatment-seeking behaviour and LLIN use as well as surveys targeting high-risk groups using for instance, ‘respondent-driven sampling’.

ACTION 8

FAST-TRACK PRIORITY RESEARCH AND REFINE TOOLS FOR CONTAINMENT AND ELIMINATION

Progress in some critical research areas would help to further advance progress in the efforts to contain resistance and eliminate malaria (Annex 1). Information on progress on these research topics must be publicly available and reported to stakeholders. One topic of high priority research is MDA or ‘presumptive therapy for elimination’ (PTE)¹⁷, a term that can be applied to describe the hybrid MDA in an elimination context. MDA has been discussed as a tool for containment. Since an expert meeting in 2011¹⁸, WHO has called for large scale pilot studies to evaluate the feasibility and effectiveness of MDA both in reducing the overall burden of *P. falciparum* and in the proportion of parasites resistant to artemisinins.

A number of operational research projects are ongoing in the region, including studies on entomology, and vector control. It is important to ensure that information gained is shared across the region. WHO and partners will convene informal meetings between researchers and NMCP managers to stimulate collaborative research efforts across the region and thereby maximize the use of resources and skills.

In addition to research, the tools and method used as part of the containment, control and elimination efforts should continually be refined.

ACTION 9

INCREASE MONITORING OF ANTIMALARIAL THERAPEUTIC EFFICACY AND STRENGTHEN THE THERAPEUTIC EFFICACY NETWORKS WORLDWIDE

Therapeutic efficacy studies (TES) evaluating the efficacy of first-line and alternative antimalarial drugs are critical for informing national treatment policy, identifying new foci of artemisinin resistance, and updating maps of the extent of artemisinin resistance. This information underpins the planning and direction of all work on containment. Routine TES should be performed in compliance with the most recent WHO protocol¹⁹, with a strong emphasis on data quality. TES should include both the analysis of day 3 positivity rate and treatment failures after 28 or 42 days. Information from other sources, such as research initiatives, can be used to supplement available information from the TES.

The drug efficacy networks organized and supported by WHO are listed in Annex 2. Strong subregional monitoring networks are needed to support TES producing high-quality data. Networks provide important benefits, including encouragement and incentives for countries to conduct regular monitoring, identification of regional trends, coordination of a regional response when required and sharing data. The meetings in the networks develop plans for TES in the coming years based on estimated needs. The networks must continue to function according to agreed standards under WHO coordination (or be revitalized where they are not fully active). As a priority adequate resources must be allocated to the Mekong TES network, the networks in adjacent subregions and to WHO mechanisms to oversee the networks.

¹⁷ Baird JK (2012). Primaquine toxicity forestalls effective therapeutic management of the endemic malaras. *International Journal of Parasitology*, 42:1049–1054.

¹⁸ WHO (2011). *Consideration of mass drug administration for the containment of artemisinin-resistant malaria in the Greater Mekong subregion: report of a consensus meeting*. Geneva, World Health Organization.

¹⁹ WHO (2009). *Methods for surveillance of antimalarial drug efficacy*. Geneva, World Health Organization.

Networks in Africa and the Americas must also be active to detect, as rapidly as possible, any occurrence of artemisinin resistance on those continents.

The existing foci of resistance have first been identified by TES conducted by NMCPs or national research institutes supporting NMCPs. Once suspected resistance has been identified, confirmatory studies must be performed as well as additional research conducted by national or international researchers using the best available tools such as in vitro studies and molecular markers.

Once molecular marker(s) for artemisinin resistance are identified and confirmed, it may be possible to institute population level screening for artemisinin resistance, and then select sites for TES based on identification of potential hotspots.

ACTION 10

INCREASE MONITORING OF INSECTICIDE RESISTANCE

The focus of this framework is antimalarial drug resistance. Nevertheless, the growing problem of insecticide resistance cannot be ignored, as use of insecticides plays a key role in decreasing malaria transmission and therefore containing drug resistance and contributing to malaria elimination. Achieving universal coverage with appropriate vector control tools is a fundamentally important activity in tier I and tier II areas. Therefore, failure to address the issue of insecticide resistance could undermine regional efforts to contain and eliminate artemisinin resistant parasites.

Insecticides are mostly used in form of LLINs and, to a lesser extent, IRS. The effectiveness of these interventions depends on the effectiveness of the insecticides used. Pyrethroids are currently the only insecticides available for treatment of mosquito nets and other materials.

In 2012, the *Global plan for insecticide resistance management in malaria vectors* (GPIRM)²⁰ was launched. The GPIRM calls for the development of national monitoring plans that include collection of data regarding vector distribution, vector attributes that are relevant for transmission and control (biting and resting preferences), and susceptibility (and thus resistance) to currently used insecticides. Country capacity and expertise needs to be built for designing monitoring plans and collecting and interpreting entomological data.

A bi-regional (regional offices for South-East Asia and the Western Pacific) workshop was held in March 2012²¹ on insecticide resistance and malaria vector mapping. Varying degrees of resistance have been detected in primary or secondary vectors in the GMS countries. The workshop recommended revitalizing, continuing and extending the annual monitoring of insecticide resistance, updating available information on vector distribution, strengthening the national capacity as well as strengthening collaboration among NMCPs, research institutes and other partners. The regional Asia-Pacific Insecticide Resistance Monitoring Network should be used for information exchange, coordination and capacity-building.

²⁰ WHO (2012). *Global plan for insecticide resistance management in malaria vectors*. Geneva, World Health Organization.

²¹ WHO Regional Office for the Western Pacific (2012). *Bi-regional meeting to monitor insecticide resistance and mapping of malaria vectors in the Greater Mekong subregion*. Manila, World Health Organization (draft meeting report).

REGIONAL OVERSIGHT AND SUPPORT

Across affected countries and in the region as a whole, the level of political awareness, engagement and support, and the coordination and oversight of different partners working on artemisinin resistance, is not at a level compatible with an issue of high global public health importance requiring urgent action. The challenges today are of a different magnitude than those of the first containment effort in 2008, but overall regional coordination has not kept up with the move from one cross-border project between two countries to the present situation of responses in four countries. Most of the activities are funded nationally, and inter-country cooperation and collaboration are urgently needed.

WHO, as a convening authority on health in the United Nations system, has a key role in supporting affected countries to ensure the success of artemisinin resistance containment. To do this effectively, WHO is establishing a new regional hub in Phnom Penh, Cambodia. WHO will continue to provide technical support to countries based on a constantly updated assessment of available information from research, surveillance and field operations, in close collaboration with a wide variety of implementing partners. The assessment of information will be done in conjunction with the TEG on drug resistance and containment, which reports to the WHO Malaria policy advisory committee. In addition, WHO will lead multi-country monitoring of progress, identify gaps and provide or organize support when needed. This is an essential role considering the importance of artemisinin resistance for worldwide malaria control. WHO action cannot, however, be effective without the political commitment and concerted action of its Member States, both in the GMS and beyond.

ACTION 11

ENHANCE ACCOUNTABILITY AND EXCHANGE OF INFORMATION

Clear, timely reporting on implementation of activities, coverage with interventions and their public health impact, facilitates oversight and accountability. A WHO regional 'hub' will provide support to strengthen national monitoring and evaluation systems, to generate high-quality national data and to improve exchanges of information across borders. The regional hub will establish a database on resistance, epidemiology, entomology, policies and programme implementation for containment, control and elimination, allowing access of countries and partners to the data.

A monitoring 'score-card' will promote the use of a standardized set of indicators (Annex 3). The score-card will not replace the use of a national set of indicators, nor will it provide detailed data at subnational levels. The role of the score-card is to enhance accountability among affected countries and highlight key issues in the drive towards containment and elimination. The score-card indicators will be made available and updated regularly online and reported to key stakeholders annually.

ACTION 12

BUILD POLITICAL SUPPORT AT ALL LEVELS

A higher level of political awareness and support are needed at regional level and in the affected countries. Antimalarial drug resistance must be kept on both the domestic and international political agenda. With support of partners, antimalarial drug resistance has received increased political attention; the establishment of the Asia-Pacific Leaders Malaria Alliance (APLMA)²²,

²² For details, see Malaria2012conference.com, which includes the *Consensus on malaria control and elimination in the Asia-Pacific*.

an important outcome of the meeting Malaria 2012, Saving Lives in the Asia-Pacific, held in Sydney, Australia, in late 2012, will keep the issue high on the agenda.

Working with relevant partners, WHO will regularly brief regional, national and subnational political leaders and government officials on malaria control, malaria elimination (where appropriate) and artemisinin resistance containment emphasizing the rationale, importance and urgency of artemisinin resistance containment and the role of containment in the push towards elimination.

Statements such as the *Declaration of the 7th East Asia Summit on Regional Responses to Malaria Control and Addressing Resistance to Antimalarial Medicines*²³ are important tools. The statement reaffirm the political commitment to increase efforts in eliminating malaria in the region and support implementation of the GPARC and its related operational plans, noting that the plan calls for sustained national monitoring of the efficacy of antimalarial medicines. Continued efforts will be made to engage the relevant parts of different regional political bodies such as APLMA, Association of Southeast Asian Nations (ASEAN), Asia-Pacific Economic Cooperation and South Asian Association for Regional Cooperation and to take advantage of regional meetings (such as the East Asia Summit) to promote the importance of artemisinin resistance containment as a public health, health security, and regional development issue.

ACTION 13

FACILITATE PROGRESS AND REGIONAL COOPERATION ON PHARMACEUTICAL REGULATION, PRODUCTION, EXPORT AND MARKETING

Major issues related to the manufacture and sale of antimalarial drugs cannot be addressed without a concerted regional effort involving the pharmaceutical sector. This work is to be set in the context of a growing regional interest in ensuring access to high-quality medicines and rational use of medicines, including antimicrobials. Ensuring the continued effectiveness of antimicrobials and their rational use is critical to curbing the emergence of multi-drug resistant organisms, including *Plasmodium* parasites.

This effort includes working with countries to strengthen regulatory authorities and practices and to monitor antimalarial drug quality. It also includes working with pharmaceutical companies to raise production standards and quality control and overcome bottlenecks to pre-qualification of antimalarial drugs. This would allow more regional producers of ACT to supply the international market globally and provide an incentive to stop marketing and sale of oral artemisinin-based monotherapy. The pharmaceutical sector of the Asia-Pacific region also represents a potentially powerful force to contribute to development of new antimalarial drugs and diagnostics as well as other health products.

Most ministries of health have taken action to stop the use of oral artemisinin-based monotherapies in the public sector and to discourage their use more broadly. National regulatory authorities have the responsibility to regulate the local production, marketing authorization, importation and exportation of both pharmaceutical raw materials and finished products. Therefore, they play a critical role in halting the production of oral artemisinin-based monotherapy and limiting the sale of poor-quality, substandard and counterfeit products within nations and across borders. Regulatory enforcement to limit the distribution of the latter will

²³ ASEAN (2012). *Declaration of the 7th East Asia Summit on Regional Responses to Malaria Control and Addressing Resistance to Antimalarial Medicines*. Phnom Penh, Association of Southeast Asian Nations.

also depend on effective enforcement in collaboration with national, regional level with law enforcement agencies, customs and others. There are now successful examples of such enforcement programmes in the GMS that can be adapted to other country contexts. An enforceable regional agreement banning the marketing and sale of oral artemisinin-based monotherapy could be one aim and will also require regional level regulatory collaboration through existing mechanism pharmaceutical harmonization within ASEAN and new initiatives.

A number of stakeholders need to be involved in developing a plan of action in order to better understand the issues from different perspectives. These stakeholders include representatives of ministries of health (and other relevant ministries), national drug regulatory authorities, independent experts familiar with the pharmaceutical sector, representatives of the pharmaceutical industry and relevant regional bodies such as the ASEAN working group on pharmaceutical products and APLMA's taskforce on access to high-quality medicines and other technologies for malaria in the Asia-Pacific region.

ACTION 14

CREATE A REGIONAL COMMUNITY OF PRACTICE ON APPROACHES TO HIGH-RISK AND HARD-TO-REACH POPULATIONS

The importance of interventions for high-risk populations is recognized in Action 2. Their importance must be recognized not only in each affected country but also at regional level. Migration, especially for work, is increasing in the GMS. Many of the companies that attract migrants work across borders and undertake large projects, such as construction of a large deep-sea port in a part of Myanmar classified as tier I and construction of a highway crossing areas with artemisinin resistance. It is a regional responsibility to ensure that, with rapid regional development, the many migrants have access to health services, including for malaria. There is growing experience from pilot studies in various countries in reaching migrant and other mobile populations effectively. This experience must be shared among countries, thus creating a 'community of practice' involving people in different disciplines throughout the GMS, who can share information on successful approaches and solve mutual challenges. Any large-scale project in a malaria-endemic area in the GMS should be accompanied by a plan to ensure that migrant workers have the necessary personal protection against malaria and access to information, diagnostic testing and treatment.

ACTION 15

SUPPORT CROSS-BORDER COORDINATION

In the GMS, artemisinin resistance has been detected mainly close to international borders. Therefore, current containment projects are focused on both sides of such border areas. Strong coordination is needed, both between central authorities and locally. Meetings have been held and are planned, mainly for central level staff in ministries of health, to promote exchanges of information and discussion of policy. More cross-border meetings are needed at subnational level to prepare plans covering neighbouring provinces or districts. These should facilitate regular exchanges of information, coordinated vector control and interventions to improve access to prevention, diagnostic testing and treatment for cross-border migrants. These activities are relevant to areas with artemisinin containment activities and areas in which elimination is envisaged. All these strategies are more likely to succeed if they are supported by activities in neighbouring provinces.

5. Implementation of activities under the framework

Progress in the fight to protect ACTs as an effective treatment for *P. falciparum* malaria depends on action at subnational, national, regional and global levels. The activities required at each level are described in Annex 4. A wide range of stakeholders should be engaged to address the cross-cutting issue of resistance. On the basis of the actions described above, WHO will work with countries to update their national strategic plans.

5.1 MANAGEMENT OF THE FRAMEWORK

In response to the call for better field operations and better coordination of containment activities in the countries with suspected or confirmed artemisinin resistance, WHO has launched an initiative to coordinate and support the emergency response to artemisinin resistance (ERAR) in the GMS. As part of this initiative, WHO is establishing a regional hub in Phnom Penh, Cambodia, which will work with partners to help coordinate and guide implementation of the actions listed in this emergency response. WHO will also provide technical support from its headquarters and the regional offices for South-East Asia and the Western Pacific. Additional staff will be located in country offices in the region to provide region-wide support in certain technical areas. Some of the activities planned within this initiative are listed in Box 5.

Box 5. Activities planned as part of WHO coordination of the regional response to artemisinin resistance

- Establish a regional hub in Phnom Penh, Cambodia.
- Organize an annual stakeholder forum involving ministries of health, WHO, other international organizations, nongovernmental organizations, development partners and researchers.
- Release annual regional reports and newsletters.
- Launch a regional web site with information on activities and meetings.
- Create a regional database on resistance, epidemiology, entomology, policies and programme implementation.
- Promote data quality and comparability and the use of data for programme planning.
- Provide additional technical support especially in the areas of pharmaceuticals, and access for migrant and mobile populations.
- Organize and support subregional networks for monitoring therapeutic efficacy.

The regional hub and related WHO activities are overseen by a technical and management committee consisting of representatives of WHO headquarters, the regional offices for the Western Pacific and for South-East Asia and WHO country offices in GMS countries. The chairperson of this body is the Director of the WHO Global Malaria Programme at headquarters.

5.2 MONITORING AND EVALUATION

Periodic assessments are incorporated in ongoing containment projects supplementing the overall malaria programme reviews.

National monitoring and evaluation plans have been developed, and data are being collected on a number of indicators for malaria control and elimination as well as containment activities. However, the data collected have not been used systematically at a regional level to track progress, facilitate a rapid response to emerging problems and bottlenecks, nor to allow for the sharing and discussions of lessons learnt.

To rectify this deficit, a score-card has been prepared, listing indicators for following regional and national progress. Monitoring will, as much as possible, employ indicators already widely used. The purpose of the metric is neither to capture all elements of malaria control for all countries nor to replace the specific monitoring in place for each programme or project. The indicators are meant to focus on tiers I and II but also track overall national information on progress (Annex 3). In addition, a regional database in the regional hub will be developed to give an overview of available information for activities, policies, funding and data on drug efficacy.

From the regional hub and in with collaboration partners, increased support will be given to promote quality of data as well as the comparability of data reported from, for instance, surveys. As highlighted in action point 7, the quality of the action taken based on the data is as important as the data itself. Therefore, support will also be given to trainings, materials and use of technology to improve staff ability to use the data for planning and directing activities.

5.3 FUNDING

Funding for containment can be seen as an investment to protect the gains made in malaria control in the past decade as well as an investment towards subnational, national and regional elimination in the GMS. Since publication of the GPARC, tiers I and II have extended to include areas along the Myanmar–Thailand border and the Cambodia–Viet Nam border. Consequently, the funding required for interventions in these tier areas has increased. In the GPARC, it was estimated that the annual cost of containment operations in tier I areas is US\$ 10–20 per person at risk.

The regional hub in Phnom Penh, Cambodia, will coordinate fund-raising by preparing plans based on analyses of needs and will support fund-raising for regional and country activities. To explore options for raising additional, sustained financing, WHO will work with partners in forums including the APLMA's taskforce on regional financing for malaria and other communicable disease threats. To meet the threat of artemisinin resistance, both international and domestic funding must be increased. Many economies in the region are growing rapidly, and WHO and partners must ensure that adequate resources are allocated even in countries where malaria appears to be a disease of the past or to exist only in remote areas. Industries, especially those operating in border regions, must be encouraged to recognize the advantages of investing in the health of their labourers.

Annex 1:

Priorities for research and refinement of tools

HIGH-PRIORITY RESEARCH:

- MDA for elimination of artemisinin-resistant parasites
 - > Research is needed on the potential coverage, operational issues, effectiveness and safety of MDA and PTE²⁴, using treatment to cure patients and treatment to block transmission.
- personal protection for special population groups
 - > Various personal protection measures, including repellents and impregnated cloth, are being tested. The research should be extended and evaluated and the results used to guide activities.
- use of gametocytocidal drugs
 - > Primaquine could significantly reduce malaria transmission and could have a major role in containment and elimination. In October 2012, WHO released a policy recommendation for use of a single dose of primaquine as a gametocytocide for the treatment of *P. falciparum* malaria²⁵. A WHO evidence review group on primaquine that met in August 2012 identified research gaps. Those of highest priority are to establish²⁶:
 - > dose–response relations for transmission-blocking activity in different locations;
 - > the severity of acute haemolytic anaemia in people with different variants of G6PD deficiency;
 - > the efficacy and safety in pregnant women, infants, HIV-infected patients and people with different variants of enzymes known to be involved in drug metabolism (e.g. cytochrome P450); and
 - > factors such as formulation, supply, policy and sociological aspects that influence use of primaquine, including coverage.
- reliable diagnostic tools for low-density parasitaemia
 - > Many asymptomatic carriers have been found even in areas of low endemicity in the GMS. Deployable diagnostic tools for detecting low-density parasitaemia are essential for moving towards elimination.
- molecular marker for artemisinin resistance
 - > Research is being conducted globally to identify a molecular marker for artemisinin resistance. Once this is identified, field methods will be required for using the marker to map resistance and guide implementation.

²⁴ For discussions on research gaps in MDA, see WHO (2011). *Consideration of mass drug administration for the containment of artemisinin resistant malaria in the Greater Mekong subregion*. Geneva, World Health Organization.

²⁵ WHO (2012). *Updated WHO policy recommendation (October 2012). Single dose primaquine as a gametocytocide in Plasmodium falciparum malaria*. Geneva, World Health Organization.

²⁶ The full list is given in the meeting report WHO (2012). *WHO Evidence review group: The safety and effectiveness of single dose primaquine as a P. falciparum gametocytocide*. Geneva, World Health Organization.

- multiple first line therapies
 - > Modelling of multiple first line therapies is ongoing. Field testing is needed if modelling indicates that use of multiple first line therapies could help prevent spread of resistance.

Besides the research areas mentioned above, research is ongoing globally in the search for new drugs and modelling the socio-economic impact of artemisinin resistance.

REFINING TOOLS:

A number of tools and methods should be refined and their use more clearly defined:

- ACD, FSAT and MSAT
 - > ACD is being used in remote areas and among special population groups. Its optimal use in different settings should be refined.
 - > FSAT and MSAT may play significant roles in elimination and containment operations, which are likely to increase as diagnostic methods for detecting low parasitaemia improve.
- reporting methods
 - > Reporting of e.g. number of cases, supply levels and stock-outs is an integral part of containment activities. The reporting methods must be improved regularly to ensure fast, appropriate action.
- trigger response plans
 - > Countries should have clearly defined standard operation procedures for triggering a response, such as foci of reintroduced malaria, malaria outbreaks among migrants, or an influx of migrants, which necessitate the deployment of additional resources or staff to an area.
- established vector control methods
 - > IRS, LLINs and insecticide-treated nets are already widely used in the region. The extent to which IRS should be used instead of or with other vector control methods should, however, be more clearly defined.

Annex 2:

Subregional networks to support national monitoring of antimalarial drug efficacy

The subregional networks aims at strengthening the country-members' capacity to monitor antimalarial drug as a basis for the formulation and implementation of evidence-based malaria treatment policies.

ACTIVE NETWORKS:

- Amazon Network for the Surveillance of Antimalarial Drug Resistance (RAVREDA): Brazil, Colombia, Ecuador, Guyana, Plurinational State of Bolivia, Peru, Suriname, the Bolivarian Republic of Venezuela.
- Horn of Africa Network for Monitoring Antimalarial Treatment (HANMAT): Djibouti, Eritrea, Ethiopia, Saudi Arabia, Somalia, Sudan, Yemen.
- Mekong Malaria Antimalarial Drug Resistance Network: Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand, Viet Nam.
- Pakistan-Iran-Afghanistan Malaria Network (PIAMNET): Afghanistan, Islamic Republic of Iran, Pakistan.

NETWORKS THAT WERE INITIATED OR REVITALIZED AFTER THE LAUNCH OF GPARC IN JANUARY 2011:

- BBINS Malaria Drug resistance Network: Bangladesh, Bhutan, India, Nepal, Sri Lanka.
- Pacific Malaria Drug Resistance Monitoring Network: Indonesia, Timor-Leste, Malaysia, Papua New Guinea, the Philippines, Solomon Islands, Vanuatu.

NETWORKS NOT PRESENTLY ACTIVE:

- East African Network for the Monitoring of Antimalarial Treatment (EANMAT): Burundi, Kenya, Rwanda, Uganda, the United Republic of Tanzania (mainland and Zanzibar).
- Réseau d'Afrique de l'Ouest pour le Traitement Antipaludique I (RAOTAP I): Cape Verde, Gambia, Guinea, Guinea-Bissau, Mauritania, Senegal.
- Réseau d'Afrique de l'Ouest pour le Traitement Antipaludique II (RAOTAP II): Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, Niger, Nigeria, Sierra Leone, Togo.
- Réseau d'Afrique Centrale pour Traitement Antipaludique (RACTAP): Angola, Cameroon, the Central African Republic, Chad, Congo, Democratic Republic of the Congo, Equatorial Guinea, Gabon.

Annex 3:

Indicators for score-card

INDICATORS		BREAKDOWN BY	DEFINITION
1	Funding (domestic and external) available for malaria control, elimination and containment activities	Country	Funding for malaria control, elimination and containment disaggregated in domestic and external funding (in US\$)
2	Artesunate monotherapy ban status	Country	
3	Numbers of drug efficacy studies completed	Country	According to target agreed to by the country
4	Number of studies of insecticide efficacy completed according to WHO protocol	Country	According to target agreed to by the country
5	Completeness of reporting	Country, tier	Number of monthly reports received from health facilities and volunteers in relation to the number expected
6	Percentage of suspected malaria cases that have had a diagnostic test	Country, tier, (and sector where available)	Number of suspected malaria cases attending health facilities who were tested with microscopy or rapid diagnostic test (RDT)
7	Percentage of the population at risk potentially covered by nets distributed	Country, tier	Number of LLINs distributed in last three years x 1.8/population at risk
8	Percentage of health facilities without stock-outs of first-line antimalarial treatment and diagnostics	Country, tier	Should be standardized
9	Proportion of confirmed outpatient <i>P. falciparum</i> malaria cases that received appropriate antimalarial treatment according to national policy	Country, tier	Included as appropriate treatment in countries that recommend primaquine for <i>P. falciparum</i>
10	Number of people reached with special interventions targeting mobile and migrant populations	Country, tier and intervention	The interventions will differ by countries but will include migrant volunteers, worksite and screening points
11	Availability of counterfeit or substandard antimalarial drugs as reported in surveys	Country	
12	Confirmed malaria cases (by species)	Country, tier	The number of people with suspected malaria confirmed by either microscopy or RDT
13	Malaria deaths due to malaria	Country, tier	The number of inpatient death with a diagnosis (by RDT or microscopy) of malaria
14	Interruption of <i>P. falciparum</i> malaria in administrative units	Country, tier	Number of administrative units in which local <i>P. falciparum</i> malaria transmission was interrupted in comparison with the number in 2011

Annex 4:

Activities required at subnational, national and supranational level

FULL COVERAGE WITH HIGH-QUALITY INTERVENTIONS IN PRIORITY AREAS

ACTION 1: INCREASE QUALITY OF AND COVERAGE WITH KEY INTERVENTIONS IN THE PRIVATE AND PUBLIC SECTOR

<p>Subnational</p> <p>According to national plans and strategies, including:</p> <ul style="list-style-type: none"> • Train volunteers, health staff and private providers. • Provide diagnostic testing and treatment. • Conduct behavior change communication on prevention, seeking diagnostic testing and treatment when ill, completing prescribed treatments, and avoiding the use of substandard medicines and monotherapies. • Vector control: distribute LLINs, IRS, and other personal protection. 	<p>National</p> <ul style="list-style-type: none"> • Prepare and update containment or prevention plans consistent with the recommendations of the GPARC and the ERAR. • Update treatment policies to include use of primaquine as a gametocytocidal agent. • Prepare and update strategies that include the private sector to promote parasitological diagnosis of all suspected cases. • Prepare or adapt training materials and guidelines. • Mobilize resources. • Organize and implement activities according to national plans and strategies. 	<p>Supranational</p> <ul style="list-style-type: none"> • Facilitate translation of policies and recommendations into implementable strategies and proposals including strategies on the use of primaquine in <i>P. falciparum</i> treatment, promotion of parasitological diagnosis and strategies for the private sector. • Provide technical support in the implementation of strategies and proposals. • Support needs analysis and resource mobilization. • Support to development of training materials.
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ACTION 2: ENGAGE HEALTH AND NON-HEALTH SECTORS TO REACH HIGH-RISK POPULATIONS

<p>Subnational</p> <p>According to national plans and strategies, including:</p> <ul style="list-style-type: none"> • Communicate regularly with local employers of workers at high risk for malaria (e.g. plantations, construction) to ensure access to appropriate prevention, diagnostic testing and treatment of malaria. • Manage initiatives to target high-risk populations that includes use of volunteers and behaviour change communication. 	<p>National</p> <ul style="list-style-type: none"> • Prepare and update national strategies to reach all populations with essential malaria prevention, diagnostic testing and treatment services, including the community, workplaces and the private sector. • Incorporate approaches to high-risk populations in general proposals and strategies. • Engage with all relevant sectors and with government agencies and ministries such as agriculture, construction, mining, justice, commerce, defence, education, tourism and immigration. 	<p>Supranational</p> <ul style="list-style-type: none"> • Provide technical support for setting national policies and implementing strategies to ensure access of high-risk populations to high-quality prevention, diagnostic testing and treatment for malaria.
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ACTION 3: IMPLEMENT MEASURES TO ENSURE CONTINUOUS AND UNINTERRUPTED SUPPLY OF ESSENTIAL COMMODITIES

<p>Subnational</p> <p>According to national plans and strategies, including:</p> <ul style="list-style-type: none"> • Monitor and report stock levels. • Make projections of needs, and request and redistribute supplies. • Train health staff in reporting commodity levels. • Monitor and evaluate stock-outs of essential commodities, and take immediate corrective action. 	<p>National</p> <ul style="list-style-type: none"> • Prepare or update standard operating procedures for managing supplies. • Clearly designate the personnel responsible for managing commodities. • Prepare training materials, and train staff in commodity management. • Update systems for reporting supplies to make best use of locally appropriate technology. • Monitor stock levels. • Procure supplies. 	<p>Supranational</p> <ul style="list-style-type: none"> • Support optimization of procurement procedures, including regional monitoring of stock levels in all countries and projections of needs. • Support emergency procurement. • Conduct regional training, and support preparation of training materials. • Support the design, testing and adaptation of new supply monitoring systems, including support in the use of modern technology.
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TIGHTER COORDINATION AND MANAGEMENT OF FIELD OPERATIONS

ACTION 4: STRENGTHEN COORDINATION OF FIELD ACTIVITIES

Subnational	National	Supranational
<p>According to national plans and strategies, including:</p> <ul style="list-style-type: none">• Hold regular meetings of all implementing partners, including in the private sector and the community.• Establish clearly designated focal points for activities, where necessary.	<ul style="list-style-type: none">• Meet regularly in an established group responsible for coordinating the national response to artemisinin resistance.• Draft and circulate minutes from all national coordination meetings; ensure that actions are clear and are followed-up at subsequent meetings.• Clearly define roles at all levels.• Clearly define the mechanism for information-sharing among all stakeholders.• Maintain a clear line of command.	<ul style="list-style-type: none">• Train national and subnational personnel in the overall management and coordination of activities.• Support information-sharing among all stakeholders.• Provide technical support for urgent resolution of any bottlenecks identified at subnational and national meetings.

ACTION 5: MONITOR STAFF PERFORMANCE AND INCREASE SUPPORTIVE SUPERVISION

Subnational	National	Supranational
<p>According to national plans and strategies, including:</p> <ul style="list-style-type: none">• Conduct training in supervision.• Draw up schedules of and plans for supervisory visits.• Ensure that staff receive feedback after supervisory visits.• Establish a system to ensure follow-up on any problems identified.	<ul style="list-style-type: none">• Ensure an allocated budget for supervision.• Prepare and update a strategy for supervising staff.• Prepare plans for training staff in supervision.• Define how, when and what to report of the results of a supervisory visit.• Define how, when and what to provide as feedback to the staff and facilities supervised.• Consider incentives for staff to perform better.	<ul style="list-style-type: none">• Train national and subnational personnel in supervision of staff and activities.• Provide technical support and prepare training materials for supervision and feedback.

ACTION 6: PROMOTE THE INTEGRATION OF RESISTANCE CONTAINMENT, IN MALARIA ELIMINATION AND CONTROL EFFORTS WHILE MAINTAINING A FOCUS ON RESISTANCE

Subnational	National	Supranational
<ul style="list-style-type: none">• Ensure that activities contribute to strengthening local health system to promote sustainability.	<ul style="list-style-type: none">• Ensure that plans for containing artemisinin resistance are prepared in the context of national malaria control and elimination.• Ensure that all proposals and projects for containing artemisinin resistance build on existing activities, and avoid duplication.• Harmonize monitoring and evaluation plans.	<ul style="list-style-type: none">• Provide technical support and guidance for harmonizing activities.• Promote integration of containment into region-wide malaria control and elimination.

BETTER INFORMATION FOR ARTEMISININ RESISTANCE CONTAINMENT

ACTION 7: IMPROVE COLLECTION AND USE OF DATA TO TARGET OPERATIONS

<p>Subnational</p> <p>According to national plans and strategies, including:</p> <ul style="list-style-type: none"> • Train staff in collecting, analysing and using data. • Procure and distribute reporting materials. • Establish systems to follow up actions identified from data analysis. 	<p>National</p> <ul style="list-style-type: none"> • Prepare training materials, and train staff in reporting, collecting and using data on programme implementation and surveillance. • Prepare and distribute reporting materials. • Collect and use data on programme implementation to manage operations. • Regularly use detailed results of surveillance to identify problems and to target operations. • Move progressively to use of data on each malaria case, especially in tier I and II areas. • Update reporting systems to make best use of locally appropriate technology. • Conduct surveys as needed to complement routine data. 	<p>Supranational</p> <ul style="list-style-type: none"> • Prepare training materials, and train staff in collecting and using data on programme implementation and surveillance. • Promote use of standard, defined indicators. • Support optimized use of modern technology to improve surveillance and response. • Provide technical support for surveys and standardization of survey protocols among countries.
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ACTION 8: FAST-TRACK PRIORITY RESEARCH AND REFINE TOOLS FOR CONTAINMENT AND ELIMINATION

<p>Subnational</p>	<p>National</p> <ul style="list-style-type: none"> • Draft protocols, adapt generic protocols, and review protocols of research institutions as required. • Conduct research. • Convene meetings of researchers with the national malaria control programme to set priorities for operational research. • Use research findings to adapt national policies or implementation guidance, to refine national strategies for containing artemisinin resistance and to prepare funding proposals. 	<p>Supranational</p> <ul style="list-style-type: none"> • Promote and facilitate research on identified priorities. • Support collaborative research in order to maximize use of resources, skills and samples. • Identify mechanism to coordinate research and share data. • Provide technical support for drafting protocols. • Promote standardization of protocols for operational research throughout the region. • Promote use of research findings to adapt national policies or implementation guidance, as appropriate, to prepare or refine national strategies for containing artemisinin resistance and to prepare funding proposals. • Regularly share information on progress in priority research with all stakeholders. • Support resource mobilization or advocacy for research priorities, as appropriate.
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ACTION 9: INCREASE MONITORING OF ANTIMALARIAL THERAPEUTIC EFFICACY AND STRENGTHEN THE THERAPEUTIC EFFICACY NETWORKS WORLDWIDE

Subnational	National <ul style="list-style-type: none"> • Routinely conduct studies of therapeutic efficacy according to the latest WHO protocol. • Adapt national malaria treatment policy on the basis of the results of routine TES. • Share the results of studies promptly to ensure rapid response to new information. • Conduct confirmatory studies in areas where resistance is suspected. • Conduct additional research to complement TES. 	Supranational <ul style="list-style-type: none"> • Organize meetings of subregional networks to monitor therapeutic efficacy and plan future studies. • Support confirmatory studies in areas where resistance is suspected. • Support additional research to complement TES. • Regularly update maps of tiers on the basis of the latest research. • Regularly share information on the evolution of artemisinin resistance.
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ACTION 10: INCREASE MONITORING OF INSECTICIDE RESISTANCE

Subnational	National <ul style="list-style-type: none"> • Prepare or update national plans for managing insecticide resistance in line with the GPIRM. • Monitor insecticide resistance annually, and use the results to adjust national and subnational vector control plans, as appropriate. • Obtain updated information on the distribution of malaria vectors, and use in programme management. • Ensure adequate human capacity at all levels for management of a high-quality vector control programme. 	Supranational <ul style="list-style-type: none"> • Support preparation or updating of national plans for managing insecticide resistance in line with the GPIRM. • Provide technical support in the review of protocols. • Support strengthening of country capacity for collecting and interpreting data. • Promote collaboration among NMCPs, research institutes and other partners.
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REGIONAL OVERSIGHT AND SUPPORT

ACTION 11: ENHANCE ACCOUNTABILITY AND EXCHANGE OF INFORMATION

Subnational <ul style="list-style-type: none"> • Share information on progress and challenges with subnational stakeholders and national authorities. • Gather and share data with affected communities. • Report data as requested by national authorities. 	National <ul style="list-style-type: none"> • Report data annually for the regional 'score-card'. • Share information on progress and challenges with stakeholders. 	Supranational <ul style="list-style-type: none"> • Collect information for the score-card, and publish it. • Set up and update a regional database on resistance, epidemiology, policies and programme implementation for containment, control and elimination. • Promote information exchange between countries, including convening cross-border meetings. • Prepare an annual progress report on containment of artemisinin resistance. • Brief stakeholders regularly on the situation and progress with regard to artemisinin resistance containment through newsletters and other materials.
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ACTION 12: BUILD POLITICAL SUPPORT AT ALL LEVELS

Subnational	National	Supranational
<ul style="list-style-type: none"> Brief selected subnational political leaders, government officials and other stakeholders about malaria control and elimination and artemisinin resistance. 	<ul style="list-style-type: none"> Brief selected national and subnational political leaders, government officials and other stakeholders about malaria control and elimination and artemisinin resistance. 	<ul style="list-style-type: none"> Engage regional political bodies in maintaining resistance to antimalarial drugs high on the political agenda as an issue of public health, health security and regional development. Brief political leaders, government officials and other stakeholders about malaria control and elimination and artemisinin resistance. Prepare advocacy materials, and support the preparation of national advocacy materials.

ACTION 13: FACILITATE PROGRESS AND REGIONAL COOPERATION ON PHARMACEUTICAL REGULATION, PRODUCTION, EXPORT AND MARKETING

Subnational	National	Supranational
<ul style="list-style-type: none"> Monitor the quality of antimalarial drugs and the availability of substandard and fake medicines and oral artemisinin-based monotherapy in the public and private sectors, in line with national guidance. 	<ul style="list-style-type: none"> Continue action to prevent importation, distribution and use of oral artemisinin-based monotherapy according to best regional practice. Strengthen the capacity of the national drug regulatory authority to set and enforce policies to combat substandard, spurious, falsified, falsely labelled and counterfeit medicines and oral artemisinin-based monotherapy. Enhance subnational capacity to regularly monitor the quality of antimalarial drugs. 	<ul style="list-style-type: none"> Prepare a plan of action to ensure that all antimalarial products that are manufactured or traded in the GMS are of high quality. Provide technical support to strengthen regulatory authorities and practices. Improve the exchange of best practices. Provide technical support for monitoring antimalarial drug quality. Provide technical support to regional pharmaceutical companies to raise production standards, improve quality control and overcome bottlenecks to pre-qualification of antimalarial drugs. Work towards an enforceable regional agreement on banning the registration, marketing, sale and export of oral artemisinin-based monotherapy. Work with relevant regional bodies on pharmaceutical regulation, production, export and marketing.

ACTION 14: CREATE A REGIONAL COMMUNITY OF PRACTICE ON HOW TO IMPROVE ACCESS FOR HIGH-RISK AND HARD-TO-REACH POPULATIONS

Subnational	National	Supranational
		<ul style="list-style-type: none"> • Support annual reviews of approaches to malaria prevention and treatment for high-risk and hard-to-reach populations with all relevant partners. • Conduct regional situation analyses to identify high-risk and hard-to-reach populations, involving both epidemiologists and social scientists. • Proactively test innovative approaches to malaria prevention and treatment for high-risk and hard-to-reach populations, and share results with national authorities and implementing partners. • Engage with regional and global stakeholders in various sectors to identify and promote innovative practices to increase access to the preventive, diagnostic and treatment services that are essential to contain artemisinin resistance.

ACTION 15: SUPPORT CROSS-BORDER COORDINATION

Subnational	National	Supranational
<ul style="list-style-type: none"> • Share and promote exchanges of information with neighbouring provinces, including: entomological data, epidemiological data, approaches for reaching high-risk and hard-to-reach populations, engagement with the community and the private sector, screening migrant and other mobile populations and behaviour change communication strategies. 	<ul style="list-style-type: none"> • Participate in cross-border plans for malaria control and elimination and containment of artemisinin resistance. • Share and promote exchanges of information with neighbouring countries, including: entomological data, epidemiological data, approaches for reaching high-risk and hard-to-reach populations, engagement with the community and the private sector, screening migrant and other mobile populations and behaviour change communication strategies. 	<ul style="list-style-type: none"> • Convene cross-border meetings between central and subnational officials and staff. • Facilitate cross-border plans for malaria control and elimination and containment of artemisinin resistance. • Facilitate exchanges of information on epidemiology, policies and strategies. • Help ensure that plans and proposals take into account the malaria situation in bordering areas.



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