

Malaria in the Asia-Pacific: Challenges and opportunities for access to quality malaria medicines and other technologies

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The Australian Government is hosting the Malaria 2012: Saving Lives in the Asia-Pacific conference in Sydney, Australia from 31 October to 2 November 2012. The conference aims to reinvigorate progress in malaria control and elimination in the Asia-Pacific region and to agree actions to urgently tackle resistance to artemisinin. The Australian Agency for International Development (AusAID) has commissioned five thematic papers to inform presentations and discussions during the conference.

The analysis in these papers examines progress to, and efforts needed to achieve the goals set by the global malaria community including the long term aim of malaria elimination. The papers look at how and what is needed to accelerate progress to achieve a 75 per cent reduction in malaria deaths and cases by 2015 over a 2000 baseline, agreed by the World Health Assembly in 2005 and re-confirmed in 2007.

The five papers in the series are:

1. ***Malaria in the Asia-Pacific: burden, success and challenges*** which summarises the current burden, successes and challenges in malaria control and elimination in the Asia-Pacific region and discusses the major policy implications for countries and regional development partners.
2. ***Malaria in the Asia-Pacific: Challenges and opportunities for sustainable financing*** describes some of the challenges facing the region as it moves towards greater regional self-sufficiency in financing malaria control and elimination.
3. ***Malaria in the Asia-Pacific: Challenges and opportunities for access to quality malaria medicines and other technologies*** summarises the key issues and challenges to improving quality and access to malaria medicines and commodities in the Asia-Pacific region, and highlights reducing the risk of artemisinin resistance.
4. ***Malaria in the Asia-Pacific: Modelling the current and potential impact of artemisinin resistance and its containment*** describes the global impact of artemisinin resistance should artemisinin combination therapies and artemisinin monotherapies lose their effectiveness. The paper also focuses on the health, economic and development impact of increased levels of artemisinin resistance in the Asia-Pacific region.
5. ***Malaria in the Asia-Pacific: The role of the private sector in ensuring equity and access to services*** provides an overview of the private sector operating in malaria in the Asia-Pacific region and describes key challenges and opportunities for engaging the private sector, including best practice from the region and elsewhere.

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Acronyms

A2S2	Assured Artemisinin Supply System	NEPAD	New Partnership for Africa's Development
ACCSQ	ASEAN Consultative Committee for Standards and Quality	NDRA	National drug regulatory authority
ACTs	Artemisinin-based combination therapies	NGO	Non government organisation
ADDO	Accredited Drug Dispensing Outlets	PAHO	Pan American Health Organisation
AMFm	Affordable Medicines Facility for malaria	PQ	Pre-qualified/pre-qualification
AMRH	African Medicines Regulatory Harmonisation	PSI	Population Services International
AMTs	Artemisinin-based monotherapies	RDT	Rapid diagnostic test
ASEAN	Association of Southeast Asian Nations	SP	Sulphadoxine-pyrimethamine
CQ	Chloroquine	SRA	Stringent regulatory authority
DDT	Dichlorodiphenyltrichloroethane	USP	United States Pharmacopeia
FIND	Foundation for Innovative New Diagnostics	VMW	Village malaria worker
G6PD	Glucose-6-phosphate dehydrogenase	WHO	World Health Organization
GPARC	Global Plan for Artemisinin Resistance Containment		
GPIRM	Global Plan for Insecticide Resistance Management		
HIV	Human immunodeficiency virus		
IFFIm	International Finance Facility for Immunisation		
IRS	Indoor residual spraying		
ITN	Insecticide treated nets		
LLIN	Long lasting insecticide treated net		
MMV	Medicines for Malaria Venture		

Executive Summary

Key messages

1. High quality, affordable medicines and other technologies are a critical element of the fight against malaria and are key to accelerating progress towards the global target to reduce malaria cases and deaths by 2015. The most effective medicines are artemisinin-based combination therapies (ACTs). Other key technologies include insecticides, mosquito nets and diagnostic tests.
2. The Asia-Pacific region is already a major manufacturer of malaria medicines and other technologies—for example 80 per cent of the global supply of the plant source of artemisinin is produced in the region, mainly in China and Vietnam. Even so, much untapped potential remains: both the volume and the quality of production could be increased, bringing economic and health benefits to the region.
3. Getting medicines and other technologies to the right people, at the right time and in the right quantities remains a challenge across the Asia-Pacific region.
4. A key reason for this 'market failure' is the way that malaria medicines and other technologies are financed. At present, most money comes directly from the individual users at point-of-sale. This financing model favours those producing cheap (and often sub-standard) products. Equally, high-quality manufacturers may be discouraged from entering the market.
5. A related issue is that in many countries, the institutions regulating the manufacture and sale of medicines and other technologies are weak, resulting in poor control of medicines and the availability of fake or substandard products.
6. Poor supply and delivery channels are also a challenge, especially in remote areas. This can lead to health centres running out of medicines, or shopkeepers selling insecticide-treated nets that are out of date and thus less effective.
7. Even when medicines and other technologies are available, they may be too expensive, especially for the poor and so people may choose to not take the full course of treatment. Equally, health workers may not be properly trained to administer treatment correctly. Where malaria medicines are not taken properly, or when poor quality medicines are used, drug resistance can emerge.
8. Economic integration and high levels of labour mobility mean that regional solutions are needed: drug resistant parasites do not respect borders, and the cost of technologies in one country can impact on supply in its neighbour. Countries should continue working together to address these challenges, building on existing efforts. Recommendations set out in this paper include:
 - **Create a high level multi-sectoral working group on access to malaria medicines and products** to facilitate inter-country coordination to improve access to medicines in the region.
 - **Establish a regional initiative to strengthen national capacity to regulate medicines** and

support under-resourced regulatory authorities.

- **Work through markets to build demand and incentivise manufacturers to improve the quality of the processes for medicines and other technologies.** Experience from other medicine markets shows this is possible.
- **Build the capacity of malaria program staff** so that countries can better anticipate patterns of supply and demand of medicines and other technologies, and so better manage the ‘supply chain’ from manufacturers to users.
- **Develop robust financing mechanisms** which use public policy to steer the market towards high quality outputs, and ensure access for the very poor. The pros and cons of a regional financing mechanism for malaria medicines for a subset of countries in the region should be explored.
- **Ban the use of oral artemisinin-based monotherapy** in the countries of the region where it is still available to contain artemisinin resistance. This will require coordination across the region to take a common approach; strong political commitment to de-register the medicines and repeal importation and marketing licenses; and human and financial resources to enforce the ban.

Overview

This paper describes the challenges of increasing equitable access to quality malaria medicines and other technologies in the Asia-Pacific region. It also outlines the links between their manufacture, supply, regulation and use and the emergence of antimalarial drug resistance.

Access rests not only on the *availability* of a product (enabled by rules and regulations, and production and distribution systems) but also on *affordability*, *awareness* among users that it exists, and *acceptance* (i.e. people are willing to use it). Regional cooperation—both political and technical—will be paramount in addressing these challenges. This includes, for example, pooling

financial and technical resources to support activities such as quality testing medicines manufactured in the region, and building regional capacity for regulation. Harmonising registration processes for medicines and other technologies could also help to reduce costs for manufacturers and facilitate trade between countries in the region.

Opportunities

The Asia-Pacific region is well positioned to continue progress towards the global target of reducing the number of malaria cases and deaths by 75 per cent by 2015. The region drives global production of malaria medicines and other technologies. Approximately 90 per cent of the active ingredients for malaria medicines originate from China, India, and South Korea. Similarly, the textile raw materials used in long lasting insecticide treated nets (LLINs) are increasingly manufactured in the region. Producers of these technologies are increasingly attracting global financial investment, and there is further potential to expand the industry and increase the output of high quality medicines. This should bring both economic and health benefits to the region.

Key challenges

Despite a diversity of contexts, there are common problems in access to medicines across the region. These include weak regulatory capacity; substandard medicines; fragmented markets; ineffective delivery channels; low affordability; and misuse of medicines.

Although manufacturers in the region provide a significant proportion of the global output of malaria medicines and other technologies, some struggle to match supply with demand. Similarly, many countries have limited capacity to ensure medicines meet global quality criteria, leading to the proliferation of substandard medicines.

Other challenges relate to the timely distribution

of medicines and other technologies to users. In particular, it can be hard to reach those living in remote areas and mobile populations such as migrants. Many countries experience regular ‘stock-outs’ of medicines and other technologies in their public distribution channels. The private sector plays a critical role in filling these gaps, but the goods it sells may be unaffordable for the poor and of unknown quality.

When prices are too high, people often turn to cheaper, sub-optimal therapies or do not take all the medicines required. Conversely, over-diagnosis of malaria—and provision of treatment when it is not needed—is common across the region, despite the availability of good quality diagnostic technologies in many countries. All these behaviours can encourage drug resistance.

Impact on resistance

The Asia-Pacific region has the highest rates of anti-malarial drug resistance in the world. There is widespread resistance to certain medicines used to treat *P. falciparum* malaria (chloroquine and sulphadoxine-pyrimethamine). Indonesia, Papua New Guinea and India have also reported resistance to chloroquine used to treat *P. vivax* malaria. Most worrying of all is the emergence of resistance to artemisinin—currently the most effective malaria medicine when taken as part of

artemisinin-based combination therapies (ACTs).

The first cases of artemisinin resistance were confirmed in Cambodia in 2007¹. Since then, suspected resistance has been detected in remote areas along international borders within the Greater Mekong sub-region, specifically Myanmar, Thailand and Vietnam.² The loss of artemisinin-based medicines to full-blown resistance would be a global disaster—undermining gains in malaria control not only in the Asia-Pacific region, but across all endemic countries.

Promoting access to quality malaria medicines and other technologies in both the public and private sectors is essential in the fight against resistance. The cost of not taking action is immense, and the window of opportunity for containing it limited.

¹ Noedl, H., et al., ‘Artemisinin Resistance in Cambodia 1 (ARC1) Study Consortium. Evidence of artemisinin-resistant malaria in western Cambodia’, *N Engl J Med*, 359(24) (2008), 2619-20.

² Dondorp, A. M., et al., ‘Artemisinin resistance: current status and scenarios for containment’, *Nature*, 8 (2010), 272-280.

1. Introduction and background

Over several decades, the Asia-Pacific region has achieved successes in reducing and in some cases even eliminating the malaria burden within its countries' borders. Improving access to malaria medicines and the other technologies which prevent, diagnose and treat malaria has been a key driver of this success. In Sri Lanka, for example, the widespread use of a range of technologies, including the use of insecticides, the distribution of mosquito nets and a scale up of diagnosis and treatment, has had significant results on malaria cases and deaths. With increased financial support from external donors and domestic sources over the last decade for improving access to malaria medicines and other technologies, malaria elimination has been achieved and sustained by several countries, and it is a goal being pursued by 13 other countries in the region.³ However, despite these achievements, malaria is an enormous health and development problem in the Asia-Pacific region.

With continued progress and additional targeted initiatives, the Asia-Pacific region would be very well positioned to accelerate progress towards the global target of a 75 per cent reduction in cases and deaths from malaria by 2015. The region is home to major global manufacturers of malaria medicines, active pharmaceutical ingredients,

long lasting insecticide treated nets (LLINs), and other technologies used for malaria control and prevention, bringing wide economic and health benefits.

This paper is part of a series commissioned for the Malaria 2012 Conference *Saving Lives in the Asia-Pacific* in Australia. It focuses on the role of access to medicines and other health technologies used to prevent, treat and diagnose malaria; to sustain and build on achievements made in malaria control and elimination in the Asia-Pacific region; and to contain the spread of resistance to the antimalarial medicine artemisinin.

1.1 The Asia-Pacific region: malaria landscape

The Asia-Pacific region is characterised by its varied malaria landscape. Malaria in the region is transmitted by a notably high number of vector species in a variety of transmission settings, ranging from forested areas along international borders in Thailand to urban areas in India.^{4,5} Unlike sub-Saharan Africa, the outdoor biting nature of some species of mosquitoes in the Asia-Pacific region means that vector control measures which are only focused on domestic settings—such as use of insecticide treated nets (ITNs) and indoor

³ Asia Pacific Malaria Elimination Network, 'Vietnam to Tackle Ending Malaria with Asia Pacific Malaria Elimination Network. Asia Pacific Malaria Elimination Network' *Asia-Pacific Malaria Elimination Network* [web document] (2012), <<http://apmen.org/storage/newsmedia/Vietnam%20joins%20APMEN%20%20media%20release%2020%20August%202012.pdf>>.

⁴ Rijken, M. J., et al., 'Malaria in pregnancy in the Asia-Pacific region', *Lancet Infect Dis*, 12 (2012), 75-88.

⁵ Sinka, M., et al., 'The dominant *Anopheles* vectors of human malaria in the Asia-Pacific region: occurrence data, distribution maps and bionomic précis', *Parasites & Vectors*, 4 (2011), 89.

residual spraying (IRS)—may not be adequate in malaria control and elimination efforts. More targeted approaches that take local epidemiology into account are required. Additionally, both *P. vivax* and *P. falciparum* malaria co-exist in Asia-Pacific countries. All of these variations have important implications on malaria strategies implemented in the region.

1.2 Antimalarial drug resistance in the Asia-Pacific region

The Asia-Pacific region has the highest rates of antimalarial drug resistance in the world. *P. falciparum* resistance to chloroquine (CQ) and

sulphadoxine-pyrimethamine (SP) is widespread throughout Asia, and CQ-resistant *P. vivax* has also been reported in Indonesia, Papua New Guinea, and India. In 2007, the first signs of resistance to the antimalarial medicine artemisinin were identified in western Cambodia.⁶ Suspected resistance has since been detected in remote areas along international borders within the Greater Mekong sub-region, specifically in Myanmar, Thailand and Vietnam (see Box 1 for a definition of artemisinin resistance).⁷ The populations at risk are often ethnic minorities in remote areas and seasonal, migrant workers who move frequently, sometimes across international borders, and have limited access to the formal channels of health care.

Box 1: Defining artemisinin resistance

- The World Health Organization (WHO) working definition of suspected resistance is an increase in parasite clearance time, as evidenced by ≥ 10 per cent of cases with parasites detectable on day three after treatment with an artemisinin-based combination therapy (ACT).
- Confirmed resistance is treatment failure after treatment with an oral artemisinin-based monotherapy (AMT) (4mg/kg/day over seven days) with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for seven days, or the presence of parasites at day three and recrudescence within 28/42 days.

The emergence of drug resistance is not a well-understood phenomenon, but experts theorise that the first signs of artemisinin resistance in the Asia-Pacific region have emerged from a long history of artemisinin usage, administration of dosages at levels below the threshold where it is effective (sub-therapeutic) and by a large number of patients in a community; the widespread availability of AMTs; unavailability of quality assured ACTs, and the proliferation of medicines of substandard quality.

Resistance to artemisinin is problematic not only for the Asia-Pacific region but for the global community.

Currently, no other antimalarial medicine is as effective and well tolerated as ACTs, and promising new medicines are years away from entering the global market. Therefore, preserving the efficacy of artemisinin and its partner medicines is critical to sustaining the achievements made in global malaria control and elimination. In response to emerging resistance, WHO has laid out a strategy to protect ACTs as an effective treatment regimen against *P. falciparum* malaria in the Global Plan for Artemisinin Resistance Containment (GPARC). One of the pillars to achieve this objective is to improve

⁶ Noedl, H., et al., 'Artemisinin Resistance in Cambodia 1 (ARC1) Study Consortium. Evidence of artemisinin-resistant malaria in western Cambodia', *N Engl J Med*, 359(24) (2008), 2619-20.

⁷ Dondorp, A. M., et al., 'Artemisinin resistance: current status and scenarios for containment', *Nature*, 8 (2010), 272-280.

access to diagnostics and rational treatment with ACTs.⁸ Improving access to quality malaria medicines and other technologies is essential to addressing drug resistance and meeting malaria control targets, and will be examined in the subsequent sections.

1.3 The Asia-Pacific region's role in malaria medicine and health technology production

The global scale up in the use of ACTs since 2004 and the unprecedented scale up of LLINs in 2009–2010 have highlighted the importance of global supply chains for these products, which very often originate in the Asia-Pacific region. In 2011, more than 42 per cent of reported expenditures on all malaria technologies, including medicines and LLINs, by the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) benefited manufacturers in Asia while approximately 80 per cent of the global supply of the plant source for artemisinin was cultivated in Asia, mainly China and Vietnam.⁹ Beyond its central role in medicine supply chains, the Asia-Pacific region is also home to four of the ten WHO-approved LLIN manufacturers. It is clear that the region is a key engine for the production of malaria medicines and other technologies, not only for countries in the Asia-Pacific region but for the world. Strengthening the links between manufacturers in the region and the global market for malaria technologies has the potential to bring economic benefits to the region while addressing the global gap in commodity availability.

1.4 Why this paper? Why now?

Well designed policies, programs, and projects can help the Asia-Pacific region accelerate progress towards the target of a 75 per cent reduction in malaria cases and deaths by 2015. Countries in the region that are in the pre-elimination phase can achieve and sustain those targets if political and economic commitment is maintained. There is a limited timeframe for containing artemisinin resistance which is emerging in some parts of the Asia-Pacific region. The loss of artemisinin-based medicines to full-blown resistance would be a global disaster, undermining gains made in recent malaria control efforts across endemic countries. Similarly, the potential economic benefits to the region from the production of higher quality malaria medicines and other technologies are very large. The costs of not taking action are immense. Thus, regional political and technical cooperation is paramount to containing drug resistance and ensuring equitable access to high-quality malaria technologies. These efforts will save lives and bring about greater economic benefits to the region.

⁸ WHO, *Global Plan for Artemisinin Resistance Containment* (GPARC), (Geneva: WHO, 2011b).

⁹ Global Fund, 'Price and Quality Reporting Tool', *Global Fund* [web page] <<http://www.theglobalfund.org/en/procurement/pqr/>>

2. Understanding access to quality malaria medicines and other health technologies

Access to health technologies is a multi-dimensional concept that is defined here as the ability to obtain and appropriately use a quality health technology for prevention, treatment, or diagnosis.¹⁰ A supportive ecosystem enables access and includes: access-promoting rules and regulations; capacity to produce high quality medicines and other technologies; and effective distribution channels that facilitate availability to those who need them. Availability alone, however,

does not always translate into use—affordability, awareness, and acceptance of health technologies are key concepts that also need to be considered as part of a system that promotes access. Figure 1 highlights some of the key access challenges in the Asia-Pacific region and their market and public health impact. Addressing these challenges can therefore have important health and economic benefits for the region. These issues are explored in more detail below.

Figure 1: Market and public health impact of access challenges in the Asia-Pacific region

MARKET IMPACT	CHALLENGES	PUBLIC HEALTH IMPACT
Low-priced, substandard medicines thrive in the market threatening the viability and reducing the market size those manufacturers that produce high quality medicines.	Weak regulatory capacity	Delayed access to safe and efficacious novel drugs of high quality due to long registration process. Substandard drugs thrive in the market with consequences on malaria morbidity and mortality.
Segmentation leads to two-tiered market with differing quality standards.	Fragmented pharmaceutical and health technology market	Limits access to high quality medicines and technologies drives drug resistance and poor patient health outcomes.
Limits growth of manufacturers as product cannot reach more people who could have benefitted from them. Exacerbates demand uncertainty.	Ineffective delivery channels	Limits access to those in need. Limited access to high quality medicines drives drug resistance and poor patient health outcomes.
Lower volumes of medicines produced; economies of scale not achieved by some manufacturers.	Low affordability of medicines	Limits access to the poorest. Can lead to partial treatment dose purchases which drive drug resistance and poor patient health outcomes.
Wastage of scarce resources for non-malaria related illness.	Irrational use of malaria medicines	Drives drug resistance and poor patient health outcomes.

¹⁰ Frost, L. J., and Reich, M., 'The access framework. In Access: How do good health technologies get to poor people in poor countries?' Cambridge: Harvard Center for Population and Development Studies, (2008), 15-38.

2.1 Regulation

Well-functioning medicine regulatory systems that can carry out key functions to ensure the availability of safe, effective and high quality health technologies are essential for promoting access to quality medicines. However, many countries in the Asia-Pacific region face limitations in the availability of skilled human resources and funding. This leads to poor mechanisms for surveillance and manufacturers not conforming to globally agreed quality standards. This in turn leads to a proliferation of substandard medicines.

Drug registration

National drug regulatory authorities (NDRAs) in many countries in the region do not have sufficient expertise or funding to conduct the technical evaluations required for approving the entry of new medicines. Currently, Indonesia and Malaysia are the only malaria-endemic countries in the Asia-Pacific region with globally recognised stringent regulatory authorities (SRAs). In order to address these limitations, the WHO drug pre-qualification (PQ) program was established to evaluate a manufacturer's ability to consistently produce a quality medicinal product in accordance with international standards. This PQ process provides surrogate regulatory approval on which developing countries can rely, allowing them to access a faster review process.

However, WHO PQ status does not always lead to immediate in-country registration, and manufacturers are often required to submit documents separately to each NDRA to seek approval and registration. This resource-draining duplication in small markets could be addressed through regional harmonisation of medicine quality standards and the creation of regional quality-testing facilities. This could efficiently accelerate the entry of high-quality products in

new markets without compromising quality, safety and efficacy.^{11,12}

In Africa, the African Medicines Regulatory Harmonisation (AMRH) program of the New Partnership for Africa's Development (NEPAD) works with regional economic communities, including the Southern African Development Community, East African Community, and West African Health Organisation, to harmonise medicine regulations in their member countries, effectively pooling technical and financial resources across NDRAs and reducing the time taken to register essential medicines for the treatment of diseases like malaria. The AMRH program also provides a platform for international donors to finance activities such as training and best practice workshops for regulators and supporting regulatory agencies, improving the efficiency with which limited resources are used. Regionally harmonised processes for registration also decrease the registration costs for manufacturers, which can lead to increased competition.

Efforts have been ongoing in South East Asia over the last decade through the Association of Southeast Asian Nations' (ASEAN) Consultative Committee for Standards and Quality (ACCSQ). This group has been working to harmonise pharmaceutical regulations for ASEAN member countries to complement and facilitate trade in the region. These groups can be engaged to think about creating platforms to harmonise pharmaceutical and health-related technology regulation for the broader region.

Monitoring and enforcement capacity

Ineffective monitoring and surveillance networks for detecting substandard malaria medicines and other technologies also threaten patient health outcomes in the region. In Cambodia and Myanmar, unregulated private medicine shops

¹¹ McCabe, A., et al., *Private Sector Pharmaceutical Supply and Distribution Channels in Africa: A focus on Ghana, Malawi and Mali*, (World Bank, 2011).

¹² Christophel, E., et al., 'Joint Assessment of the Response to Artemisinin Resistance in the Greater Mekong Sub-Region', (2012).

were found to be the major source of sub-standard antimalarial medicines. The widespread availability and use of ineffective malaria treatment has also been reported in the private sector in Laos.¹³

The monitoring and enforcement capacity of the private sector can be enhanced through both increased financial investment in regulation and effective deterrent legislation. These steps may help to decrease access to sub-standard medicines. Formalising or upgrading the quality of private sector outlets is also an area which could be considered. In Tanzania, small community-based medicine shops, popularly known as *duka la dawa baridi*, provide essential health services to remote, rural populations living far from formal health facilities. These medicine shops, however, face challenges with poor dispensing and storage practices and the sale of sub-standard, unregistered or expired medicines. In response, the government of Tanzania, supported by Management Sciences for Health and the Bill and Melinda Gates Foundation, established an accreditation program providing rigorous training on storage and dispensing practices, to convert these medicine shops into a network of Accredited Drug Dispensing Outlets (ADDOs). The initiative has achieved remarkable success in improving access to malaria treatments through the private sector.¹⁴ Networks similar to these medicine shops already exist in some countries in the Asia-Pacific region—for example, the Village Drugs Post (Pos Obat Desa/POD) in remote areas of Indonesia. Initiatives such as these which strengthen existing networks with additional training and access to capital could be further explored by countries in the Asia-Pacific region.

It is challenging for resource-constrained governments to monitor all aspects of health technology supply chains. Many of the countries

in the Asia-Pacific region do not require regulatory approvals or cannot enforce regulatory standards for medicines or diagnostic products like RDTs and so work with international agencies to build the capacity of their regulatory program. For example, WHO provide NDRA with support such as biolabs to test medicine quality. Because RDTs are produced in small manufacturing setups, there is significant variation in quality by batch or lot. The Foundation for Innovative New Diagnostics (FIND) runs a testing program to help countries verify the quality of each lot of RDTs, while WHO has a product testing program for RDTs that conducts laboratory evaluations by comparing performance using a standardised panel of specimens and procedures. WHO has also recently started a PQ program for malaria diagnostics. Options for harnessing and scaling up these existing initiatives within the Asia-Pacific region could be explored at the national or regional level.

Strengthening technical coordination and enforcement capacity at both regional and national levels is critical for accelerating progress towards and sustaining malaria control and elimination targets and ensuring the quality and safety of products in the market. In the face of emerging resistance, these coordinated efforts are particularly important to curb the promotion, sale, and use of therapies that threaten the effectiveness of ACTs such as sub-standard medicines and oral AMTs—which can encourage drug resistance. Without this collaboration, neighbouring countries' efforts to sustain malaria control may be undermined. Commitment from global donors to provide financial and technical support to NDRA and manufacturers that comply with regional agreements on banning the production of oral AMTs may encourage wider adoption of this policy.

¹³ Sengaloundeth, S., et al., 'A stratified random survey of the proportion of poor quality oral artesunate sold at medicine outlets in the Lao PDR—implications for therapeutic failure and drug resistance', *Malar J*, 8 (2009) 172.

¹⁴ Rutta, E., et al., 'Creating a New Class of Pharmaceutical Services Provider for Underserved Areas: The Tanzania Accredited Drug Dispensing Outlet Experience', *Progress in Community Health Partnerships: Research, Education, and Action*, 3(2) (2009), 145–52.

2.2 Production

The Asia-Pacific region is a major and growing contributor to the global supply of malaria technologies, including many of the technologies' starting materials. *Artemisia annua*, the plant source for the antimalarial medicine artemisinin, is cultivated mainly in China and Vietnam—accounting for approximately 80 per cent of global production.¹⁵ The basic textile raw materials for LLIN manufacturing (polyester, polyethylene, and polypropylene) are also increasingly manufactured in the Asia-Pacific region. The one exception to the region's role as a supply source is the key raw material for RDTs (mono-clonal antibody) which is produced by a single manufacturer: National Bioproducts Institute, in South Africa.¹⁶

The region also has an important and expanding role in the production of finished malaria technologies. The production of malaria medicines like ACTs, as well as diagnostics, has grown remarkably over the past few years. The number of ACTs procured increased from 11 million in 2005 to 181 million in 2010. Similarly, the production of RDTs has increased markedly from 45 million tests delivered in 2008 to an estimated 88 million in 2010.¹⁷ Despite its size, the market for ACTs and malaria RDTs is fragmented and consists of many manufacturers. However, of the dozen or so manufacturers dominating the market for ACTs and RDTs in international and public sector tenders, five of the ACT manufacturers and two of the RDT manufacturers are located in the Asia-Pacific region.^{18,19} Additionally, four among the ten LLIN manufacturers approved by the WHO Pesticide Evaluation Scheme are located in Asia.²⁰ While manufacturers in the Asia-Pacific region

have a significant share of the global market for malaria technologies, the region faces challenges in producing them at international standards and matching supply with demand due to low capacity and resource levels. These issues will be explored in more detail below.

Many finished-product manufacturers in the region have not obtained WHO PQ or SRA approval. For example, only five manufacturers of ACTs in the region satisfy internationally recognised quality standards, leaving a large market of ACTs with quality that is not guaranteed by WHO. This presents a huge opportunity to improve quality and access to global markets if manufacturers were encouraged to improve quality to international standards. Additionally, while intravenous artesunate is recommended as a first line treatment for severe malaria in both adults and children, only a single WHO PQ manufacturer (Guilin Pharmaceuticals in China) exists in the region. In order to accelerate progress towards a 75 per cent reduction in deaths in the Asia-Pacific region, creating a healthier medicines market may be necessary—in which more manufacturers of malaria medicines achieve SRA or WHO PQ status. This would bring not only substantial health gains but greater economic benefits to the region.

Some countries in the Asia-Pacific region operate with dual quality standards—one for medicines produced for domestic use and one for export medicines that are typically PQ or approved by an SRA. The purpose of PQ is to make quality medicines available to those in need, but for developing country manufacturers the process can appear to be long, slow and prohibitively expensive, with success not guaranteed.²¹ Therefore, the

¹⁵ Shretta, and Yadav, *Stabilising Supply of Artemisinin and Artemisinin Based Combination Therapies in an Era of Widespread Scale-up, Working Paper*, (Virginia: Management Sciences for Health, 2012).

¹⁶ UNITAID, *Malaria Landscape Report*, (UNITAID, 2012).

¹⁷ WHO, *World Malaria Report*, (Geneva: WHO, 2011a).

¹⁸ Guilin in China and Ajanta, Cipla, Ipca, and Strides Arcolab in India.

¹⁹ Orchid Biomedical and Span Diagnostics, both in India.

²⁰ Tana Netting Co. Ltd. of Thailand; Yorkool International Co. of China; Sumitomo Chemical Co. of Japan and VKA Polymers of India.

²¹ Investments required for manufacturing facilities to comply with good manufacturing practice standards can range in the hundreds of thousands to millions of dollars.

region needs to consider how to incentivise lower quality producers in this two-tier market to participate more actively in the larger global market. This participation could increase competition and encourage the consolidation across the two market segments, potentially decreasing prices. Achieving this requires innovative thinking and new market-based approaches. Best practices and tools for intervention can be learned from organisations such as UNITAID, which addresses market inefficiencies that contribute to low access to quality assured medicines, diagnostics and preventive technologies. Highlighting the size of the high quality market to existing manufacturers and reducing transaction costs for participating in the high quality market are strategies that have worked well. The GAVI Alliance has also achieved successes using highly innovative tools, such as Advanced Market Commitments, to ensure global access to high quality vaccines that are procured from both developed and developing country manufacturers.

Another key challenge faced by manufacturers is matching supply and demand. Forecasts, underpinned by quality data that are reviewed periodically and matched with predictable, long-term funding, help manufacturers to plan appropriately and ensure that supplies are available when needed. In the ACT market, this is complicated by the long lead-time—typically 14–18 months—between the planting of *Artemisia annua* seed and completion of the final manufacture of ACTs. This implies that the planting of artemisinin has to be planned on ACT demand forecasts developed at least 24 months in advance. In a rapidly growing market with multiple confounding factors, an accurate 24-month forecast is difficult to obtain. In the RDT market, while there are efforts to provide technical assistance to countries for better forecasting and quantification for RDTs, a clear architecture for creating a global forecast for RDTs is still needed.

Ensuring a continuous supply of malaria medicines and other technologies requires that forecasts are not only created at national and global levels, but

that they are also shared with relevant stakeholders. Since the launch of ACTs in 2004, the artemisinin market has been fraught with uncertainties in both price and supply, with periods of shortage and high prices experienced every few years. In 2008, UNITAID created the Assured Artemisinin Supply System (A2S2), a US\$8 million loan facility for artemisinin extractors to ensure adequate planting in advance of growing needs. This initiative, however, contributed only marginally to improved artemisinin supply and problems persist in the market. One of the problems is that extractors and growers do not receive clear demand information and market intelligence in a timely manner. To be effective, mechanisms to improve the regularity of sharing market information along the entire ACT value chain are needed.

Greater efforts to address artemisinin market volatility are required. The need for long-term, predictable malaria funding cannot be understated. Predictable funding allows for long-term planning and also provides more negotiating power in contracting with manufacturers, allowing countries to achieve lower prices. Lessons in this regard from the non-malaria sector can be taken from successes of the GAVI Alliance whose contracting with vaccine suppliers has contributed to established, predictable, long-term funding through the International Finance Facility for Immunisation (IFFIm). Donor commitments to IFFIm are for a period of ten to twenty years and are legally binding, which reduces the demand uncertainties and risk faced by manufacturers—allowing them to plan production better and to achieve economies of scale with important benefits on price and availability of products.

Innovation of new medicines and other technologies are also needed. Efforts supported by the Bill and Melinda Gates Foundation and the Medicines for Malaria Venture (MMV) are seeking to discover new medicines and other technologies to improve access to high quality, affordable malaria technologies. India's Ranbaxy

Pharmaceutical Limited, for example, has produced a combination malaria medicine, highlighting the need for joint efforts between industry and organisations like MMV to create novel medicines with synthetic sources that are not exposed to the vagaries of the plant-based artemisinin market.

Additional efforts to bring better medicines to market for the radical cure of *P. vivax* malaria are also needed. In South East Asia, 50–60 per cent of *P. vivax* malaria cases relapse, which has important public health consequences. WHO recommends primaquine for the radical cure of *P. vivax* malaria; however, primaquine is not recommended among groups such as pregnant women and populations with a certain severe enzyme deficiency. In addition, screening for this enzyme deficiency—which is found in some populations in the Asia-Pacific region—is generally not available outside of hospitals. Treating patients with the enzyme deficiency with primaquine can have dire consequences on health outcomes. Therefore, efforts to accelerate access to affordable, reliable RDTs to determine whether individuals are enzyme deficient (already under development) are required to ensure that medicines administered have an impact on eliminating *P. vivax*.²²

2.3 Distribution

The timely supply and distribution of medicines is vital. Efficient channels that can consistently deliver high quality malaria medicines even in remote areas are critical to achieving the global targets of reduced malaria cases and deaths. Distribution occurs through three main channels: the public sector, the formal private sector and the informal private sector. Each channel faces unique challenges to ensure the availability of quality ACTs and other malaria technologies but strengthening them has

the potential to improve the supply of technologies, not just for malaria, but also for other diseases such as tuberculosis and HIV.

Public sector distribution channels in the region are often characterised by chronic or periodic shortages of essential health technologies. Such stock-outs result from problems in procurement, distribution, and disbursement as well as shortfalls in financing. Cambodia, for example, experienced stock-outs of ACTs lasting over 18 months due to delays in funding procurement and disbursement. Poor access to life saving medicines, particularly in a region with burgeoning drug resistance, undoubtedly has dire health consequences. Efforts to promote the continuous supply of health technologies through regional collaboration have had some success, such as through the Pan American Health Organization revolving fund, which serves as a mechanism for the joint procurement of immunin-related technologies and supplies. Member countries contribute 3.5 per cent of the net purchase price to a common fund, the majority of which is used as working capital to offer credit lines for member states requiring assistance.²³ Examples like these can be explored for their potential to be applied in the Asia-Pacific region.

Limited human resources and difficult terrain also impede the reach of supply chains to remote areas in countries like Papua New Guinea and East Timor, as well as hard to reach, migrant populations in the Greater Mekong Sub-region. Some successful strategies to increase access to remote populations in the Asia-Pacific region have employed the use of community health workers. In Cambodia, the village malaria worker (VMW) program has improved accessibility to both diagnosis and treatment in remote provinces.²⁴ In Myanmar and Cambodia, mobile malaria workers—often members of the

²² WHO, *Guidelines for the treatment of malaria*, (2nd ed.; Geneva: WHO, 2010).

²³ Pan American Health Organization (PAHO), 'The Revolving Fund as a Cooperation Mechanism for Immunization Programs in the Americas: FAQs', PAHO [web document] (2012), < http://new.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=8643&Itemid=>.

²⁴ Littrell, M., et al., 'Case management of malaria fever in Cambodia: results from national anti-malarial outlet and household surveys' *Malaria Journal*, 10 (2011), 328.

migrant communities they serve—are trained to specifically help migrants and offer effective malaria case management. While the use of community health workers can contribute to the delivery of health interventions, the feasibility of employing this cadre needs to be assessed, considering issues such as costs of training and retention, envisaged functions and numbers required.

The private sector delivery channel plays a critical role in filling public sector gaps, but also faces limitations around quality and affordability. In countries like Afghanistan, where the majority of patients seek treatment in the private sector, high out of pocket payments and user fees can limit access to health services. Terminating user fees is sometimes not a viable option for governments, therefore efforts to improve access to health services and lessen the burden of out of pocket fees are required. India, for example, has implemented price controls to make essential medicines more affordable, while Cambodia has worked to reduce the burden of health care costs on low-income households through health equity funds, which reimburse poor patients for transport and food costs and health facilities for foregone user fees. Countries with user fees can consider a range of options for improving access to health care services including increased government contribution to health expenditures, community-based health financing, social health insurance programs, or a combination of these.

2.4 Pricing

Price can be a major obstacle deterring access to quality health technologies. Particularly in countries like Afghanistan, Pakistan, India, Nepal, Bangladesh, Cambodia, Laos, and Myanmar, where over 60 per cent of total health expenditures are out of pocket. This lack of affordability of high quality ACTs drives demand for cheaper, sub-optimal therapies such as AMTs, substandard ACTs, and other non-artemisinin-based medicines, and can also lead to patients choosing not to take

a full course of treatment and preclude purchase of malaria technologies such as LLINs. These behaviours are problematic not only in terms of patient health outcomes, but also because they can lead to the development of drug resistant parasites. This problem is detailed in the sections that follow.

Between 2004 and 2011, the prices of ACTs decreased due to economies of scale for existing manufacturers and the entry of several new manufacturers, which increased competition. However, increases in the price of artemisinin, the key starting material for ACTs, continue to exert upward pressure on price of ACTs. Stabilising the artemisinin market is key to containing the price of ACTs and in establishing further decreases from production efficiencies and economies of scale. As described earlier, this can be achieved through more predictable funding and binding contracts which can help manufacturers with better production planning. Innovative processes for the development of cheaper sources of artemisinin, either through higher yielding crops or synthetic production sources, are also key to increasing the affordability of ACTs. Manufacturers of ACTs in the Asia-Pacific region have an important role to play in this endeavour.

While the global LLIN market has grown rapidly, coverage remains variable in the Asia-Pacific region. Some estimates place the LLIN coverage in the region at approximately 44 per cent, although there are significant variations between countries. A barrier to wider use is the high up front cost of LLINs (which are effective for three to five years) relative to simple ITNs (which are only effective for approximately one year). While volumes have increased, the LLIN market in the Asia-Pacific region remains highly concentrated among a few suppliers. Prices have decreased, but only marginally, compared to the increase in volume. Most countries and international agencies award their LLIN tenders on the basis of lowest price rather than cost per effective years

of net coverage, and thus ignore the fact that net durability varies from one supplier to another. WHO and other partners are working to create guidance to help countries determine how long LLINs last in the field and incorporate this into their procurement decisions. In addition, benefits could come from more standardisation in LLINs, which currently have a large range of specifications across colour, shape, size, packaging, labelling and accessories. While global agencies are working to address this issue, countries in the Asia-Pacific region could consider creating procurement structures and specifications that will help create a healthier market for LLINs on a region wide basis.

2.5 Rational use

WHO defines rational use of medicines as when “patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.”²⁵ It is estimated, however, that the majority of dispensed medicines are administered inappropriately, leading to misuse of essential medicines and other technologies and wastage of scarce resources.²⁶ For example, non-malaria fevers are often treated with antimalarial medicines, which is problematic both for the patient and for overall public health.

Over-diagnosis and mistreatment of malaria in Central and South Asia is widespread.²⁷ While good quality microscopy to diagnose malaria is available in many countries (such as Thailand, Bhutan, Philippines, and Sri Lanka) and RDTs have been scaled up in several countries (including Cambodia, Indonesia, Sri Lanka, and Thailand), the overall appropriate use of diagnosis is still very limited. In places such as Cambodia, “cocktail treatment” for suspected malaria cases is highly prevalent, where patients with suspected malaria are given one or more tablets of various medicines including antipyretics, vitamins, antimalarial medicines, antihistamines, and antibiotics. According to a recent study in Cambodia among all people with “malaria fever,” just 15 per cent received only an antimalarial treatment (without acquiring cocktail treatment). Increased access to accurate diagnosis coupled with provider and patient education about rational treatment would help to ensure better targeting of patients with malaria and appropriate use of medicines. LLINs are also sometimes improperly used. Repurposing of nets for activities including fishing and protecting crops is commonly reported in many countries in the Asia-Pacific region.

²⁵ WHO, *Promoting the rational use of medicines: core components-WHO policy perspectives on medicines*, No. 005. (Geneva: WHO, 2002).

²⁶ WHO, *WHO Medicines: rational use of medicines, Fact sheet No. 338*, (Geneva: WHO, 2010a).

²⁷ Leslie, T., et al., ‘Overdiagnosis and mistreatment of malaria among febrile patients at primary healthcare level in Afghanistan: observational study’ *BMJ*, 345 (2012), e4389.

3. Understanding the main drivers for drug resistance in the Asia-Pacific region

A discussion of access to malaria medicines in the Asia-Pacific region is incomplete without a discussion of evolving resistance to malaria medicines in the region and its likely causes. Resistance can result when a patient is exposed to sub-therapeutic levels of a medicine, leading to the selection, persistence, and spread of resistant parasites. The current challenges to accessing malaria technologies plays an important role in the emergence and spread of drug resistance. Awareness of the drivers of artemisinin resistance at all levels is critical to designing appropriate context specific interventions and is explored in more details below.

3.1 Diagnosis: presumptive treatment and lack of diagnosis

WHO recommends that all suspected cases of malaria be confirmed with a diagnostic test prior to treatment; however, use of antimalarial medicines without confirmed diagnosis of the malaria parasite is still common in some countries of the Asia-Pacific region, particularly in the private sector. Administration of ACTs to a person who does not have malaria does not cause drug resistance in itself. The problem of drug resistance has typically developed in relatively low-transmission areas, but is often of greatest concern in high transmission settings, where there is a greater likelihood that

an uninfected individual (who has taken ACTs) is bitten by an infected mosquito in the days after they have begun treatment. If malaria parasites are exposed to sub-therapeutic levels of the medicine still present in the bloodstream, sensitive parasites are eliminated but resistant parasites can survive and reproduce.²⁸ In consequence, increased access to diagnostic testing is critical to improving health outcomes, and for slowing the onset of full-blown drug resistance. Prompt access to diagnosis with appropriate action taken based on the results, on the other hand, ensures appropriate patient care and prevents unnecessary use of antimalarial medicines, which in turn limits resource wastage and decreases opportunities for resistance emergence in artemisinin and its partner medicines.²⁹

Many challenges prevent more widespread adoption of diagnostics in the region. On the global supply-side, the existence of over 200 RDT manufacturers with tests of variable quality and performance makes it difficult for countries to determine which test is appropriate for their specific setting. RDTs for mixed transmission settings are not very effective in detecting which parasite is causing illness. Inability to correctly detect the cause of illness can have deleterious consequences on patient health outcomes, because the recommended treatments for *P. vivax* and *P. falciparum* malaria are different (see Box 2).

²⁸ Newton, P. N., et al., 'Poor quality vital anti-malarials in Africa— an urgent neglected public health priority', *Malaria Journal*, 10 (2011), 352.

²⁹ WHO, *Universal Access To Malaria Diagnostic Testing*, (Geneva: WHO, 2011).

FIND has pioneered the development of a web-based interactive guide to help with the selection of appropriate malaria RDTs for a particular setting

based on parameters such as malaria species and malaria transmission intensity.³⁰

Box 2: Treatment of uncomplicated malaria

P. falciparum: ACTs

P. vivax: CQ combined with 14 days of treatment with primaquine. (In places where there is no proven CQ resistance; radical cure with primaquine is contraindicated for pregnant women, children under four years, and in those with severe G6PD deficiency.)

Mixed infection (where *P. vivax* and *P. falciparum* co-exist): ACTs completed by primaquine.

Weak and costly delivery channels to areas with populations in need, particularly remote areas, also inhibit greater use of malaria diagnosis technologies in the Asia-Pacific region. There are examples of initiatives to address these barriers such as a program in Cambodia which offers subsidised RDTs and malaria treatment in the private sector through social marketing. While often cited as a best practice, such examples take time and significant financial and political commitment to establish.

Another factor prohibiting rational use of diagnostics is provider adherence to test results—ensuring that providers are not supplying an antimalarial medicine when the test is negative. This problem is partly due to lack of clarity about how to handle negative RDT results. Comprehensive training and communication strategies are needed to improve patient and provider awareness. Such strategies should include job aids which can be disseminated through all levels of the health system. These job aids would improve overall case management of febrile illness, improve the accuracy of RDT administration and provide normative guidance on dealing with negative test results.

The scale up of RDTs in the public sector in Senegal demonstrates that high adherence to RDT results and appropriate use of antimalarial medicines are achievable on a national scale through well planned implementation, with both health and economic benefits.³¹ Over the three-year period of implementation in Senegal, parasite-based diagnosis increased nationally from 3.9 per cent of reported malaria-like febrile illness to 86 per cent, and led to a more than 50 per cent reduction in ACT prescription (from 72 per cent to 31.5 per cent) for malaria-like febrile illness. Considerable cost-savings were achieved from averting the inappropriate prescription of approximately 516 576 courses of ACTs. However, operational research studies in western Kenya, Zambia, and Uganda point to challenges of RDT roll-out in the private sector, revealing that the use of RDTs in the private sector is feasible but adherence to negative test results is still poor. The incentives for diagnosis and treatment dispensing are not always well aligned in the private sector; therefore, improving access to diagnostics requires careful consideration of how to appropriately incentivise both patients and providers to adhere to the results. While many

³⁰ WHO Global Malaria Programme, *Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs)*, (Geneva: WHO, 2012).

³¹ Thiam, S., et al., 'Major Reduction in Anti-Malarial Drug Consumption in Senegal after Nation-Wide Introduction of Malaria Rapid Diagnostic Tests' *PLoS ONE*, 6(4) (2011) e18419.

small studies have shown the operational and theoretical feasibility of creating such incentives, very little is understood about the incentive system for a package of treatment and diagnosis. More research is required to understand how to create an appropriate package.

3.2 Quality treatment

Access to quality assured malaria medicines in both the public and private sectors is essential in the global effort to contain artemisinin resistance. Factors impeding access to quality treatment are described below and include under-dosing, proliferation of sub-standard and counterfeit medicines, failure of artemisinin partner medicines and use of oral AMTs.

Under-dosing

Under-dosing occurs when a patient is exposed to a sub-therapeutic level of medicine which does not clear all malaria parasites, and thus encourages the selection of resistant parasites.³² Under-dosing can result from the following:

- lack of patient adherence to a correctly prescribed medicine regimen (i.e. not taking the full course of treatment or not taking both pills in a co-blister pack)
- purchase of an incorrect treatment dose because of:
 - › medicine unaffordability
 - › lack of provider knowledge about correct dosing
 - › lack of awareness about the danger of selling partial doses
- patient consumption of poor quality medicines that do not contain adequate levels of active ingredients

- differing personal absorption rates of artemisinin among sub-populations (e.g. pregnant women and children)

Understanding where problems arise in the patient treatment seeking pathway is important so that interventions to improve medicine usage and adherence can be tailored accordingly.³³ Efforts to create more high quality, user friendly combinations for adults and children may encourage adherence to complete treatment doses. In October 2012, Cipla Pharmaceuticals, with support from the non-profit organisation Drugs for Neglected Diseases, became the first manufacturer to achieve WHO PQ for the fixed-dose combination of artesunate and mefloquine—a first-line treatment for uncomplicated malaria in many Asian countries. The single daily dose of one or two tablets over three days, as well as the fixed-dose two-medicine formulation, will help to ensure that patients are receiving the right proportions of the active ingredients and will encourage compliance, thereby decreasing the risk for drug resistance.

Sub-standard and counterfeit medicines

The proliferation of sub-standard antimalarial therapies is a significant threat to malaria control and elimination efforts, and can lead to the emergence of drug resistance when sub-therapeutic levels of active ingredients are present. Box 3 contains WHO's definition of sub-standard and counterfeit drugs.

Studies conducted over the last decade have pointed to an abundance of sub-standard antimalarial medicines in the Asia-Pacific region. A study conducted in 2006 found a profusion of sub-standard artesunate in mainland South East Asia with between 38 per cent and 52 per cent of

³² White, N. J., 'Antimalarial drug resistance', *Journal of Clinical Investigation*, 113 (2004), 1084-1092.

³³ Yeung, S., White, N.J., 'How do patients use antimalarial drugs? A review of the evidence', *Trop Med Int Health*, 10 (2005), 121-138.

Box 3: WHO definition of sub-standard and counterfeit drugs³⁴

- WHO defines **sub-standard drugs** as “products whose composition and ingredients do not meet the correct scientific specifications and which are consequently ineffective and dangerous to the patient. Active ingredients may be completely absent in sub-standard drugs, which can lead to ineffective treatment, prolonged illness, or death. Alternatively, active ingredients may be present in sub-therapeutic concentrations leading to drug resistance”.
- **Counterfeit medicine** is “one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients, or with fake packaging”.

artesunate blister packs sampled not containing any active ingredient.

Drivers of sub-standard and counterfeit antimalarial medicines include:

- absence of deterrent legislation to apprehend and prosecute counterfeiters
- limited human and financial resources that prevent medicine regulators from conducting technical evaluations and effectively monitoring medicines
- poor compliance of local manufacturers with good manufacturing practice standards
- institutional purchases (public, private, domestic, international) without adequate reference to quality standards
- unaffordability of quality assured ACTs, leading to high demand for cheaper products
- lack of consumer awareness about:
 - › the problem and consequences of substandard or counterfeit antimalarial medicines
 - › how to discern if a medicine is substandard or counterfeit.

Resistance containment will not succeed if a long-term strategy does not include efforts to strengthen national and regional regulatory and

enforcement capacities—to monitor the quality of medicines on the market, shut down sources of poor quality medicines and provide incentives for existing low quality manufacturers to upgrade and participate in the high quality market. Failure to address these issues will have enormous negative public health and economic consequences.

Artemisinin partner medicine selection

Artemisinin and its derivative forms (i.e. artemether, artesunate, dihydroartemisinin) are recommended in combination with another partner medicine (e.g. lumefantrine, piperaquine) in the treatment of uncomplicated *P. falciparum* malaria. The theory of combination therapy, which has been applied in the treatment of tuberculosis, leprosy, and HIV infection, points to the delayed emergence of resistance when medicines with different modes of action are used in combination as opposed to being used alone as monotherapies.³⁵

There are very few suitable partner medicines for artemisinin in Asia. There is some evidence of piperaquine resistance in China, which emerged in the late 1980s after it was used in mass treatment. Mefloquine resistance has been identified along the north-western border of Thailand. Ideally, to ensure the maximum useful therapeutic life, there should be no resistance to the partner medicine

³⁴ WHO, *Counterfeit medicines, Fact sheet No. 275*, (Geneva: WHO, 2006).

³⁵ White, N.J., Pongtavornpinyo, W., ‘The de novo selection of drug-resistant malaria parasites’, *Proc. R. Soc. Lond. B*, 270 (2003), 545–554.

in ACTs—as a failing partner medicine used in combination with artemisinin could eventually leave the artemisinin component inadequately protected.³⁶ More studies are needed to understand the best partner medicines to be used in each country and region, contain resistance and reduce malaria cases and deaths.

Use of monotherapies

It is widely thought that the use of AMTs can lead to the development of artemisinin resistance. Since 2005, WHO has been working with pharmaceutical companies around the world to stop the production of oral AMTs. Countries like Cambodia and Laos have had success in enforcing a ban on AMTs. This progress, however, has not been achieved throughout the region, and use of AMTs is rife in other areas. As of April 2012, the national drug authorities in 16 malaria-endemic countries still allowed marketing of oral AMTs for use in the private sector, with four of them from the Asia-Pacific region.³⁷ Factors that continue to drive the use of AMTs include:^{38,39}

- poor regulation, particularly of the informal private sector
- lack of access to affordable, quality ACTs
- lack of awareness among drug regulatory authorities, providers, and patients about the consequences of the use of oral AMTs
- Confusion due to different policies between the use of oral and injectable forms of AMTs (injectable AMTs still have a role to play in the treatment of severe malaria).

Ensuring access to effective, affordable ACTs in both the public and private sectors, while

progressively removing oral AMTs from the market, is critical in the effort to contain artemisinin resistance.

3.3 Insecticide resistance

Although many countries in the Asia-Pacific region have included LLINs as part of national malaria control strategies, overall coverage in the region remains low, as they have mostly been used for small scale projects. IRS, on the other hand, has been the mainstay of malaria prevention in many countries in the region. Pyrethroid-based LLINs and IRS have been the basis for malaria control programs to date, with the exception of India, which uses dichlorodiphenyltrichloroethane (DDT) for its IRS program. About 75 per cent of global IRS coverage in 2009 was pyrethroid-based. In a 2000–2009 study conducted by WHO, the South East Asia and Western Pacific regions accounted for 30.1 per cent (125 of 414 tons) of the total global use of pyrethroids and 58 per cent of pyrethroid use for the treatment of nets.

Widespread use of a single insecticide class has resulted in a natural cycle of vector resistance. According to the 2011 World Malaria Report, pyrethroid resistance has been reported in 41 countries worldwide, including some countries in the Asia-Pacific region like Vietnam, Cambodia, and India. Resistance against pyrethroids is a particular cause for concern, as no other insecticide class can be used for ITNs.⁴⁰ Effective management of insecticide resistance requires active collaboration between malaria programs and agriculture departments, which is often not easy to achieve.

³⁶ Nosten, F., and White, N. J., 'Artemisinin-Based Combination Treatment of Falciparum Malaria', *Am. J. Trop. Med. Hyg.* 77(6) (2007), 181–192.

³⁷ WHO, *Marketing of oral artemisinin-based monotherapy medicines at country level*, WHO [web document] (2012), <http://www.who.int/malaria/monotherapy_NDRAs.pdf> .

³⁸ Mishra, N., et al., 'Prescription practices and availability of artemisinin monotherapy in India: where do we stand?', *Malaria Journal*, 13(10) (2011), 360.

³⁹ Population Services International (PSI). *Myanmar's private sector antimalarial market in the context of artemisinin drug resistance containment*, Conference Presentation, ACTwatch Advisory Committee Meeting. 2012.

⁴² WHO, *Global Insecticide Use for Vector-Borne Disease Control. A 10-YEAR ASSESSMENT (2000–2009)*. (5th ed.; Geneva: WHO, 2011c).

Many malaria endemic countries in the Asia-Pacific region have large scale IRS programs but do not have a well developed monitoring system for insecticide resistance. The Global Plan for Insecticide Resistance Management (GPIRM) presents a set of steps for countries and regions to address the increasing threat of insecticide resistance. Strategies include monitoring and quickly rotating insecticides when low levels of resistance are detected, mosaic spraying, and the use of two or more compounds from different

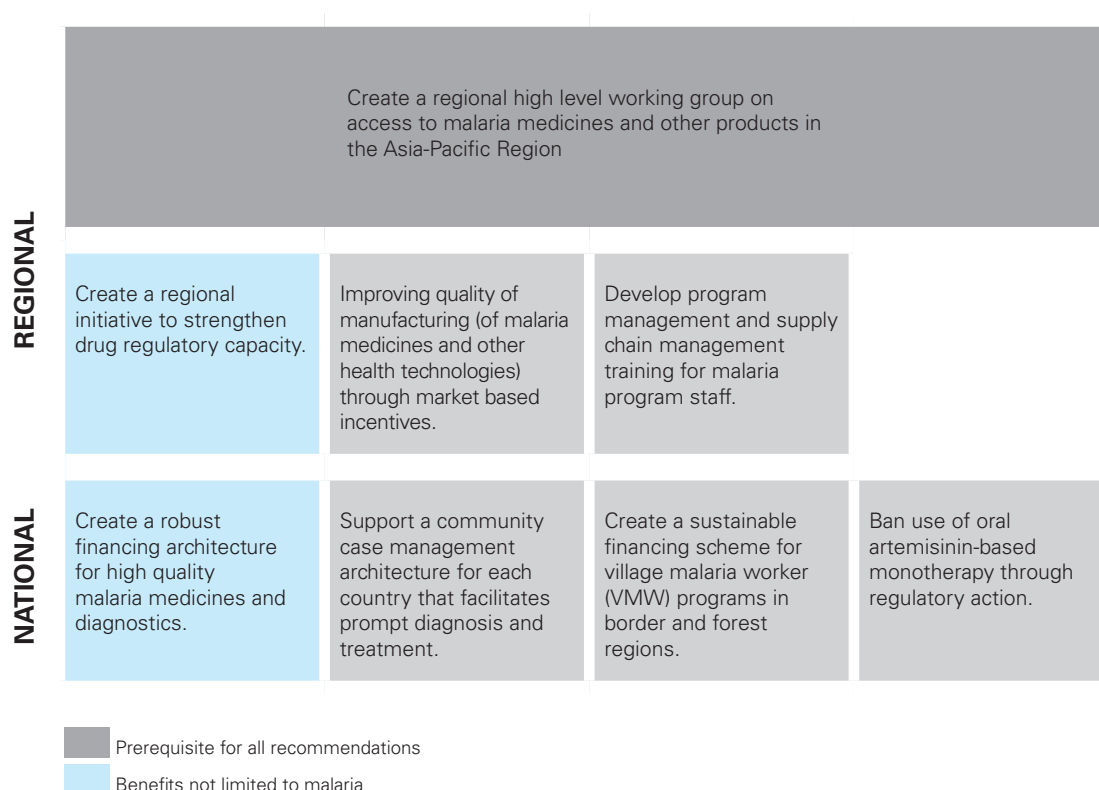
insecticide classes. For example, when low levels of pyrethroid resistance were identified in Surat, India in 2001, pyrethroids were promptly withdrawn from IRS in the villages in 2002. The quick withdrawal while resistance was still low resulted in reversal of resistance within three years (to 98 per cent susceptibility). In contrast, resistance to DDT still persists in Surat, even after its withdrawal from IRS for 30 years, because the withdrawal took place too late, after full scale development of resistance.

4. Recommendations

Improving access to malaria technologies is vital to accelerating progress towards global malaria targets and for containing emerging artemisinin resistance. Simultaneous change is required across the entire ecosystem, across sectors and at all levels in order to improve access to medicines

and other technologies. The region requires both a structured regional coordination process to set a common agenda and shared goals, and stratified approaches at the national level which take account of different epidemiology and treatment-seeking practices.

Figure 2: Regional and national level recommendations



1. Create a regional high level working group on access to malaria medicines and other products in the Asia-Pacific region.

Countries in the Asia-Pacific region have a shared responsibility for improving access to quality malaria technologies—both in the region and globally. Many countries in the region, however, have limited resources, capacity and expertise to encourage an increase in the quantity and quality of the technologies produced. Regional collaboration therefore is vital to the success of any strategy to improve access in the region. These approaches, however, require financial and technical support, in addition to a governance structure which can encourage collaboration and work with countries to implement regional priorities at the national level. Existing malaria control efforts in the Asia-Pacific region have traditionally been under the charge of Ministers of Health who do not usually have a mandate to cover all aspects of malaria technology production or regional engagement. Foreign Ministers tend to be responsible for engaging with other countries in the region while Industry and Commerce Ministers tend to be responsible for industrial policy issues associated with the manufacturing of malaria medicines. Both of these groups, however, have not traditionally regarded malaria as an important priority. Working across sectors is therefore vital.

As a result of this, a key prerequisite for concerted regional action around access to malaria technologies is a high level, multi-sectoral panel or working group nominated by the inter-ministerial group at Malaria 2012 to develop and monitor progress. This working group which could build on existing governance structures in the region would consist of secretaries of health, industry, and other relevant departments from malaria endemic countries in the region, together with international donors. In collaboration with independent experts, the group could develop strategies and assess progress on regional goals to improve access to high quality technologies.

2. Create a regional initiative to strengthen medicine regulatory capacity.

Having robust, well-staffed regulatory authorities to ensure the quality of malaria medicines, diagnostics, and other products should be the cornerstone of any strategy to improve access to malaria technologies in the region. Strengthening the national regulatory system can build confidence in the quality of the products in export markets, bringing economic benefits to the country. Regulatory authorities in many countries of the region, however, are underfunded and understaffed and cannot play their regulatory oversight roles in an effective way. Weak regulatory infrastructure is detrimental to access to medicines in general, but is even more critical in regard to malaria medicines in countries with moderate to high malaria burdens.

Strengthening national level regulatory capacity through regional approaches can allow for sharing of regulatory capacity and expertise, as well as leveraging collective information and buying power. When, for example, quality testing facilities are shared at the regional level, the inefficient duplication of working in small markets can be addressed. In South East Asia for example, ASEAN's Consultative Committee for Standards and Quality is working to harmonise pharmaceutical regulation for member countries. Approaches like this can facilitate the entry of new quality assured products and encourage trade within the region. In addition, because malaria transcends borders, working in a coordinated way is required to ensure that the gains made by one country in the control of malaria and drug resistance are not diminished by a lack of action among its neighbours. The success of these approaches, however, hinges on firm political commitment and financial resources to collectively develop agreed frameworks to assess medicines, and to enact supporting legislation.

3. Improving quality of manufacturing of malaria medicines and related technologies through market based incentives.

There are strong economic and political drivers to build national manufacturing capacity for malaria technologies in the Asia-Pacific region. While India, China, and South Korea have traditionally been the largest producers of malaria technologies in the region, Bangladesh, Indonesia, Thailand and other countries are starting to play an important role. Not all manufacturers adhere to international quality standards or in some cases even to basic good manufacturing practices, and weak regulatory enforcement results in products of non-assured quality circulating in the market. Some manufacturers find it difficult to meet international regulatory standards (such as WHO PQ) because of the capital investment needed to upgrade facilities to international standards.

National governments in the Asia-Pacific region should consider supporting higher technical standards in manufacturing by working closely with international organisations with expertise in this field such as WHO and donor initiatives such as those run by the German Agency for International Cooperation, the United Nations Industrial Development Organization and United States Pharmacopeia (USP). This will facilitate learning from the lessons that their work has generated. It would also be beneficial if organisations like the International Finance Corporation of the World Bank create separate financing windows for manufacturers in the region. This would enable manufacturers to make capital investments in upgrading manufacturing plants to meet global standards. The business case for these decisions cannot be based solely on net returns, but also their social and health benefits which are substantial.

National governments in many of the countries in the region play a significant role in shaping regional and global markets for malaria technologies. These

governments and the international donors that are active in malaria control could consider adapting their conventional approach of procurement and technical assistance. Market based approaches that link market access to quality on a regional level could be leveraged. These approaches have been used by global organisations such as UNITAID and the GAVI Alliance who have many best practice examples that can be adapted and used at a regional level and applied in the Asia-Pacific region.

4. Develop program management and supply chain management training for malaria program staff.

Many malaria endemic countries in the Asia-Pacific region lack planning and management capacity at the national, regional and local level. Training programs, designed by a consortium of universities in the region could increase program management and supply chain management skills. The training modules should be developed to provide hands-on learning for program staff, allowing them to identify and rapidly resolve procurement and supply chain bottlenecks, and improve national demand and supply plans for malaria technologies. Building this capacity will help shorten delays in disbursements from donors and significantly improve the ability of malaria programs to manage commodities. The benefits of this approach include fewer national and sub-national stock-outs and better case management in the public sector. To ensure that the training modules are context specific, it is important that they are designed and imparted by a consortium of universities in the region. This will also lead to a stronger culture of interaction between academia and technical experts on the one hand and national malaria programs on the other. These programs should also include training on effectively contracting the private sector for supply chain services. Building expertise in this area would enable malaria programs to use the private sector to leverage best practices and distribute technologies where appropriate.

5. Create a robust financing architecture for high quality malaria medicines and diagnostics.

Most financing for malaria medicines in the Asia-Pacific region comes from private out of pocket expenditures. Such a market is fraught with failures. Where high quality medicines are unaffordable, patients often end up purchasing low quality medicines which are abundantly sold in the Asia-Pacific region. In addition, high quality manufacturers are discouraged from full participation in the market due to high transaction costs. The use of effective public policy and financing tools, however, could encourage greater access of high quality medicines to the market. The exact nature of a financing model for malaria medicines will vary across countries in the region and the pros and cons of an approach will need to be carefully considered. In middle income countries, social health insurance funds can prioritise payments for high quality malaria medicines and diagnosis. For low income countries, a combination of government and donor funds could provide free or subsidised high quality malaria medicines in both the public and private sectors. The Asia-Pacific region can look to existing models for country specific strategies to improve access to ACTs and other technologies in the private sector. The Affordable Medicines Facility for malaria (AMFm), for example, an innovative subsidy financing mechanism hosted and managed by the Global Fund, improved the availability of affordable, quality assured ACTs in seven African countries during a two-year pilot period.

6. Support a community case management architecture for each country that facilitates prompt diagnosis and treatment.

Effective case management involves early and accurate diagnosis, and for confirmed malaria cases, access to affordable, high quality treatment. It also requires a clear understanding of how to handle negative test results in order to promote rational treatment of malaria, to reduce wastage of

resources and delay the spread of drug resistance. This approach to case management underpins the success of all malaria control and elimination efforts and the appropriate case management architecture needs to take each country's specific contexts into account. This includes the country's malaria profile and the strength of its health care delivery system.

Community based case management and a vibrant private sector are features of many countries in the Asia-Pacific region. The private sector, however, cannot always be relied upon to implement the best practice approach to case management outlined above. It is therefore important for countries in the region to consider innovative solutions which leverage existing community based case management capacity and private sector approaches in order to enhance access to effective and affordable treatment. Private sector care can be substantially improved through training, accreditation and regulation of private sector medicine sellers. Examples such as in the ADDO program in Tanzania provide some important lessons which can be applied to the Asia-Pacific region. Within the region, the experience of Cambodia in increasing the supply of ACTs and RDTs in the private sector; new projects in Myanmar to improve access to ACTs through social franchises, and Indonesia's Village Drugs Post (Pos Obat Desa-POD) provide opportunities for expansion both within the countries and to other countries in the region. Similarly, findings from operational research studies can be used to design programs for community case management using medicines and other technologies.

7. Create a sustainable financing scheme for village malaria worker (VMW) programs in border and forest regions.

Large portions of the population that are at the highest risk of malaria are based in forests or are migrant workers. These groups tend to live in isolation or in camps on the fringes or outside established villages and are often not served by

traditional village health volunteers. Improving access to high quality medicines and diagnostics for highly mobile migrant workers and forest workers through special interventions is imperative to both contain the spread of artemisinin resistance and to reduce malaria cases and deaths in the region. It can also lead to significant economic advantages to the region. The reach of formal health care networks and government run clinics is poor in areas where migrant workers live and work. Community based case management through a network of VMWs and community volunteers is therefore the most effective means of reaching these population groups. Current activities in Myanmar, Cambodia and Thailand include mobile malaria workers/migrant health volunteers trained specifically to help migrants. The workers are often selected from among the semi-permanent migrants themselves. Other ongoing activities include the active detection of malaria among migrants, migrant screening points, migrant liaison officers in malaria-endemic villages and the distribution of LLINs in work camps. All of these activities can help to prevent, treat, diagnose and raise awareness of malaria among these difficult to reach groups. While these VMW programs exist, there is no regional financing operation for significantly scaling up their role. The Asia-Pacific region would benefit from creating a platform for VMW schemes that provides: financing; cross country learning from existing initiatives; and best practice sharing. This could encourage the scaling up of diagnosis and treatment for malaria and other febrile illnesses in migrant populations.

8. Effectively ban the use of oral artemisinin-based monotherapies through regulatory action.

Oral AMTs threaten to accelerate resistance to the most effective antimalarial treatment available, ACTs. In the absence of novel medicines that are as well tolerated and effective, the reduced effectiveness of ACTs has dire implications on malaria related cases and deaths. Despite WHO's

recommendation for manufacturers worldwide to stop the production and sale of oral AMTs, they continue to persist in the market in some countries of the Asia-Pacific region.

Coordination across the region is required to put pressure on the countries that continue to allow production of oral AMTs, as the consequences are felt beyond the borders of those countries. Banning the use of oral AMTs requires high levels of political commitment to de-register the medicines and repeal importation and marketing licenses. This commitment needs to be backed by dedicated human and financial resources to enforce these efforts and prevent the entry of oral AMTs and other substandard products across borders. These efforts will help to preserve the efficacy of ACTs.

Annex 1: Summary of best practices in the region and in other regions

BEST PRACTICES		
	THE ASIA-PACIFIC REGION	OTHER REGIONS
Market shaping at global level.	<p>FIND and WHO product testing and lot testing programs help improve quality of RDTs.</p> <p>A2S2 and global ACTs forecasting lead to more reliable and affordable ACTs supplies.</p> <p>ACTwatch collects systematic data about ACT use in eight countries to inform better designed market interventions.</p> <p>Technical guidance from WHO on LLIN durability to be incorporated into procurement decisions.</p> <p>Streamlined product specifications/stock-keeping units as rationalisation for LLINs.</p>	
Market shaping at local level.	<p>Population Services International (PSI) Cambodia's ACTs and RDTs provision creates a healthier market for quality ACTs and RDTs in Cambodia.</p>	<p>AMFm leads to increased distribution reach and availability of ACTs.</p>
Monitoring and surveillance.	<p>APMEN connects 12 countries in the region— Bhutan, Cambodia, China, Democratic People's Republic of Korea, Indonesia, Malaysia, Philippines, Republic of Korea, Solomon Islands, Sri Lanka, Thailand and Vanuatu—in an effort to learn from each other's malaria program approaches, translate research into action and consider optimal program implementation. Its efforts also include coordinated monitoring and surveillance.</p>	<p>The Worldwide Antimalarial Resistance Network provides a global platform for exchanging scientific and public health information on malaria drug resistance.</p>
Access to quality ACTs.	<p>Subsidised ACTs through PSI model allow Cambodians to access affordable, high quality antimalarial treatment.</p> <p>Price controls in India make essential medicines (including malaria medicines) more affordable to a population that pays for most health expenditures out of pocket.</p>	<p>The AMFm makes affordable, quality assured ACTs available in both private and public sectors in seven sub-Saharan African countries.</p> <p>Strengthening the public sector supply chain for ACTs reduced stock-outs and improved availability of ACTs.</p>

BEST PRACTICES		
	THE ASIA-PACIFIC REGION	OTHER REGIONS
Regional coordinated training, best practice sharing and communication.	The Asian Collaborative Training Network for Malaria is an inter-country training and communication network that includes Bangladesh, Cambodia, PR China, Republic of Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, East Timor, and Vietnam. The collaborative network organises joint training programs for member countries and improves communication across the countries.	
Access and adherence to diagnostics.	VMW program reaches remote communities with diagnosis and treatment in Cambodia.	Roll out of RDTs in Senegal's public sector led to successful adherence to test results and subsequent reduction in consumption of ACTs.
Stricter quality regulation.	Cambodian Health Ministry closes unlicensed medicine shops where substandard and counterfeit medicines proliferate.	Madagascar and Zanzibar remove over the counter status of ACTs and restrict its sales to specific outlets only.
Regional quality improvement initiatives.		Countries within the East Africa community are harmonising drug registration to facilitate the availability of high quality medicines.
Local manufacturers move toward higher quality.		African Leaders Malaria Alliance (ALMA) initiative promotes improving quality standards of local manufacturers. USP Pharma maintains manufacturing best practice transfer centre in Accra, Ghana. Relationships and technology transfers between manufacturers located in the Asia-Pacific region and manufacturers in Africa (e.g., CIPLA-Quality Chemicals Ltd, Sumitomo-A to Z Textile).

BEST PRACTICES		
	THE ASIA-PACIFIC REGION	OTHER REGIONS
Scientific studies to understand good partner medicines.	Therapeutic efficacy surveys conducted by countries in the region with technical support of WHO.	
Role of innovation and technology in countering drug resistance.	<p>Cambodian VMW use pre-coded SMS to report malaria transmission.</p> <p>eMIS in Thailand captures near real time data for case detection, monitoring drug compliance etc.</p> <p>eMIS in Thailand captures near real time data for case detection, monitoring drug compliance etc.</p>	Sproxil and Mpedigree allow consumers in several African countries to detect counterfeit products via SMS.
Enhancing technical capacity of regulatory enforcement.	<p>USP in collaboration with WHO conducts training workshops to strengthen national capacity to detect counterfeit and sub-standard antimalarial medicines.</p> <p>Provision of GPHF-Minilab®, a simple, portable, easy to use mini-laboratory for detection of counterfeit and sub-standard pharmaceuticals, by USP to countries in the region.</p>	
Public-private partnerships in health technology distribution.	The government of Bangladesh and a BRAC-led non government organisation (NGO) consortium consisting of 20 smaller partner NGOs run a successful program for the free distribution of ITNs/LLINs.	AngloGold Ashanti in Ghana carries out IRS and case management as a principal recipient of the Global Fund grant on malaria.

BEST PRACTICES		
	THE ASIA-PACIFIC REGION	OTHER REGIONS
Improving malaria case management through social franchises and accredited retailer networks.	Sun Franchise in Myanmar provides ACT access to segments of the population that do not seek treatment in the government sector.	The ADDO program in Tanzania helps small businesses provide access to effective malaria treatment.
Quick rotation and change of insecticide when resistance is detected.	When low levels of pyrethroid resistance were identified in Surat, India in 2001, pyrethroids were promptly withdrawn from IRS in the villages in 2002. The quick withdrawal while resistance was still low, resulted in reversal of resistance within three years (to 98 per cent susceptibility)	In 2005–2006, resistance to pyrethroids and DDT was identified in some parts of Colombia. A decision was quickly made to change to fenitrothion, an organophosphate with a different mode of action, for IRS. Rapid implementation of this alternative reduced the frequency of resistance to levels below the level of detection.

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Notes

