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(DRAFT)

Delaying Artemisinin Resistance in India
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Delivering Artemisinin Resistance in India

Report of a consultation convened by the National Institute of Malaria Research and the Public Health Foundation of India

24-25 March 2014
INTRODUCTION

Artemisinin resistance has been called the greatest threat to malaria control, and could lead to loss of the hard-won gains of the last decade. That success has been dramatic: since 2000, malaria deaths have been halved, due in no small part to the widespread use of artemisinins in artemisinin-combination therapies (ACTs).

India, thus far, has detected no cases of artemisinin resistance within its borders, but occupies a strategic position in its potential spread when arrives or arises. Artemisinin resistance has arisen in the Greater Mekong Subregion (GMS), documented first in Cambodia near the border with Thailand in 2007. Since then, resistance has been confirmed in Thailand, Vietnam, Laos and Myanmar.

With the world’s largest population at risk of malaria, India could see the current burden of malaria in India increase if the current first line treatments that depend on artemisinin fail. But malaria treatment and artemisinin containment policies in India could have consequences for Africa. They could either slow the movement of resistance genes from spreading to Africa and beyond, or serve as the gateway for that spread, as was the case for spread in the 1970s of pfcrt mutations that conferred chloroquine resistance. If resistance were to spread to sub-Saharan Africa, the gains made against malaria in the last decade could be lost.

Global and regional scientists and malaria control representatives met in New Delhi on 24-25 March 2014 under the auspices of the Public Health Foundation of India (PHFI) and the National Institute of Malaria Research (NIMR) to take stock of the regional artemisinin resistance situation and to make course corrections to the Indian response, as needed.

This report summarizes the two days of deliberations, organized in the following sections:

1. THE IMPORTANCE OF ARTEMISININ COMPOUNDS TO MALARIA CONTROL AND THE THREAT OF ARTEMISININ RESISTANCE
2. FOCUS ON INDIA: MALARIA, ANTIMALARIAL RESISTANCE AND TREATMENT POLICY
3. REPORTS FROM OTHER COUNTRIES IN SOUTH AND SOUTHEAST ASIA
4. WORLD HEALTH ORGANIZATION ACTIVITIES RELATED TO ARTEMISININ RESISTANCE IN THE SOUTH EAST ASIA REGION
5. TOOLS FOR ARTEMISININ CONTAINMENT
6. SUMMARY AND CONCLUSIONS
1. THE IMPORTANCE OF ARTEMISININ COMPOUNDS TO MALARIA CONTROL AND THE THREAT OF ARTEMISININ RESISTANCE

Introduction

Presented by Dr. Nel Druce

Artemisinin resistance in South East Asia is the single greatest threat to global malaria control. Right now, resistance is limited to the Greater Mekong Subregion (GMS), but there is a risk of spreading to Bangladesh, India and onwards. Early containment efforts did not stop an increase in resistance, but given successes all over the world in reducing the malaria burden, containment must still be possible, if the right steps are taken. Artemisinins have already saved millions of people from dying of falciparum malaria and there are no other drugs available today or in the late stages of development that are nearly as effective.

Artemisinins entered into routine use in the GMS much earlier than in other regions, mainly as monotherapy. Those facts alone might be enough to explain why resistance also arose there first, but other factors may be at play. Resistance to the last mainly of treatment, chloroquine, also arose in the region (and was not first used there) as did resistance to pyrimethamine (figure 1).

FIGURE 1

SOURCE: Druce 2014

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1 Sources refer to the meeting presentation from which the illustration is drawn
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The UK Department for International Development (DfID) perspective is that artemisinin resistance containment is a global and regional responsibility, for the collective good. Momentum has been growing since WHO developed its plan for containment (see below) in 2011 and an assessment by many partners, including DfID, in 2012, led to the WHO’s further emergency plan for the region. Increased funding is now enabling countries and technical agencies to step up efforts, though more needs to be done. Artemisinin resistance containment depends upon regional collaboration, research, effective national control programs, elimination of monotherapy and private sector engagement.

DfID is supporting many of these activities through global and bilateral commitments, as well as funding for various independent research groups.

A new entrant to the field is the Asia Pacific Leaders Malaria Alliance (APLMA), formed in late 2013 by the Asian Development Bank. APLMA has taken artemisinin resistance containment as one of its main goals. India and Australia co-chair the APLMA task force on Access to Quality Medicines and Other Technologies, which can be influential in the containment effort. India has a big contribution in the leadership of this Task Force and in supplying the market with high-quality ACTs and rapid diagnostic tests (RDTs).

APLMA is funded through the newly established Regional Malaria and Other Communicable Disease Threats Trust Fund, a multidonor fund that includes contributions from development partner agencies, the private sector, and foundations. DfID has contributed a significant sum to the fund and endorses the work of APLMA.

Overview

Presented by Professor Arjen Dondorp

Artemisinins paired with other antimalarials in oral artemisinin-combination therapies (ACTs) have replaced older monotherapies as first-line treatments for uncomplicated malaria all over the world. Injectable artesunate, the artemisinin derivative in most of the ACTs, is also the WHO-recommended first-line therapy for severe malaria and has been adopted in most endemic countries.

Artemisinin, an extract from the annual plant Artemisia annua, was identified in the 1970s as an effective antimalarial. Several derivatives (which end up as the same active moiety in vivo) have been developed and are in use as ACT components. A small number of unrelated compounds are in late phase development (the most advanced in phase 2 trials) as antimalarials, but no other drug is now available to succeed the artemisinins should they fail.

Artemisinins as monotherapy have been used in South East Asia since the 1980s, a practice that continued exclusively until the early 2000s. Now, combination drugs (ACTs) are the recommended treatments and are used in public programs, but monotherapies are still available and used widely by people buying malaria treatment in the private sector (a large proportion of malaria treatment seekers in most countries).
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A point to remember is that each drug in the ACT combination plays an important role. Currently, ACT regimens are 3 days, but it takes 7 days for all the parasites at a given time to mature and be eliminated by the drug. The artemisinin acts quickly and reduces the parasite load by about 10,000 fold, but has a short half-life, leaving the partner drug to “mop up” the remaining parasites. Because all current partner drugs have long half-lives, parasites are exposed to them at ever-declining levels, which is favorable for the selection of drug-resistant strains. For this reason, although the emphasis is on artemisinin resistance, attention also must be paid to resistance to partner drugs. Taking this scenario out farther, if malaria parasites become resistant to a partner drug, the artemisinin component will be exposed with no back-up, leading to treatment failures and the risk of artemisinin resistance, as the artemisinin will effectively be monotherapy.

Artemisinin Resistance

Partial resistance to artemisinins first manifested as delayed parasite clearance time after treatment—parasites disappeared completely, but only after several days longer than usual. This was observed anecdotally in the early 2000s in Cambodia near the border with Thailand—the same area that has been identified as the epicenter of chloroquine resistance emergence. It was reported decisively in 2009 in a study that compared the clearance times in 2007-2008 in patients in Pailin, Cambodia, where delay had been observed, with patients in Wang Pha, Thailand, where no delay in parasitological cure had been seen (figure 2).

FIGURE 2

Artemisinin resistance = delayed clearance

![Graph showing parasite clearance times](image)

2007-2008 (p=0.0001 for Δ slopes between sites)


SOURCE: Dondorp 2014
High failure rates were reported from the Myanmar side of the Thai-Myanmar border beginning in about 2009 (figure 3).

FIGURE 3

**High failure rates MAS3 Thailand –Myanmar border**

![Graph showing failure rates over years](image)

SOURCE: Dondorp 2014

The lesson from the Cambodia and Myanmar experience is that partial artemisinin resistance has proven to be a prelude to ACT failure, and that resistance to the partner drug is as much a concern as is resistance to the artemisinin.

**In Vitro Testing for Artemisinin Resistance**

One of the reasons that artemisinins are so effective is that they kill parasites at many (though not all) stages in their development—a wider range than any other current antimalarial. Although the mechanism of artemisinin resistance in falciparum parasites is not known, it is known, through observation, that the failure in resistant organisms is concentrated in the trophozoite (also known as the ring stage) of parasite development. This has led to development of in vitro tests specific to the ring stage. The trophozoite-specific test is much more sensitive than the conventional test, which measures inhibition of the schizont stage (figures 4 and 5).

FIGURE 4
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**Ring-stage specific in-vitro sensitivity tests (1)**

Schizont maturation inhibition (WHO)  
Trophozoite maturation inhibition (TMI)

SOURCE: Dondorp 2014

FIGURE 5

SOURCE: Dondorp 2014

**Ring-stage specific in-vitro sensitivity tests (2)**

DHA 700nM exposure for 6 hours; Second generation survivors

SOURCE: Dondorp 2014
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Tracking Artemisinin Resistance—The TRAC Study

TRAC began in 2011, a project funded by the U.K. Department for International Development (DfID), to conduct clinical research, assess demand factors for artemisinin combinations (in a series of different types of study), and design and test new approaches to vector control. It is coordinated by the Mahidol University Research Unit (a Wellcome Trust site) and involves researchers around the world. The aim is to halt or slow the spread of artemisinin resistance.

The first clinical study was completed in 2013, involving 12 sites in 10 countries in Southeast and South Asia, and 3 in Africa. One site in India, in West Bengal, was included. The aim was to determine the extent of existing artemisinin resistance as defined by parasite clearance time (figure 6). Slow parasite clearance was found in western and northern Cambodia, on the Thai-Cambodia and Thai-Myanmar borders, in southern Myanmar, and in southern Viet Nam. Signs of emerging resistance were found in Laos and eastern Cambodia. In the remaining sites, artemisinin appeared to be fully effective. Data are being reanalyzed in light of the availability of a genetic resistance marker that had not yet been identified when the study was ongoing.

FIGURE 6

Mapping Artemisinin resistance

Some studies in the “demand factors” category are completed and others are under way. A study of malaria patients from the parts of Cambodia with the greatest artemisinin resistance problem found that they were more likely to be migrants or part of the mobile population, recently arrived, and likely

SOURCE: Dondorp 2014
to have taken antimalarials recently for symptomatic disease. Further follow-up pinpointed a few foci of likely transmission of artemisinin-resistant strains.

Drug quality was studied, with encouraging results. No counterfeits were found in Cambodia, in contrast to the situation a few years ago. Measures taken to secure the drug supply appear to be working. Quality is still an issue, however, with about 30 percent of the drugs having significantly lower or higher concentrations of active ingredients.

Other studies address the effect of Village Malaria Workers in Cambodia, more on the migrant and mobile populations, and other aspects of demand.

Vector control studies have focused on the specific vectors that are important in Asia and their biting behaviors. Most of the vector control strategies in use around the world have been developed for African vectors, which have different biting behaviors than those in Asia.

TRAC continues, with major results now in preparation for release.

**Near-Term and Medium-Term Priorities**

When resistance was first acknowledged, the “firewall” concept was adopted. However, we now know that we are not dealing with one emergent mutation that has spread, but many founder mutations. If the firewall could have worked at all, it is now too late for it. The highest priority is eliminating falciparum malaria from the areas where resistance has already emerged as quickly as possible. This means eliminating the entire falciparum malaria reservoir through some form of mass treatment campaign. Control leading even to low-level transmission may not be good enough: the small the pool of parasites, the higher the percentage likely to be resistant. This is the “last man standing” argument. There is also an assumption that the more recent the mutations associated with resistance, the higher the fitness cost they impose. As time passes, compensatory mutations may occur, reducing fitness costs.

In the meantime, treatment policies can be changed to recommend longer ACT regimens, e.g., lengthening from three to five days. This might require drug repackaging (blister packs of an entire course are the norm). In some cases, drug rotation can buy time. All changes should be treated as research with adequate tracking of results.

In the longer term, new drugs can help define better strategies. For instance, we would like to use entirely different drugs for symptomatic and asymptomatic individuals, but there is no good alternative to an artemisinin.

**A Molecular Marker of Artemisinin Resistance**

*Presented by Professor Christopher Plowe*

The biggest news in malaria research is the identification of a molecular marker for artemisinin resistance. Ever since prolonged clearance times were observed as a possible sign of resistance, the hunt has been on for a telltale molecular marker in the parasite genome. True resistance always has a
genetic basis and markers for resistance to all other important antimalarials were known. Without such markers, parasite clearance time remains the only way to know whether a drug is working as expected. With a marker, the parasite itself can be analyzed and typed, eliminating other reasons for slow clearance (e.g., poor absorption, poor quality drugs, inadvertent underdosing).

In January of this year, the first definitive molecular marker—actually any of a number of mutations in a single gene—was announced in a paper describing a remarkable, methodical 5-year quest. Frederic Ariey from the Pasteur Institute led the research team. The mutations are on *P. falciparum* chromosome 13 in a gene that encodes “kelch protein 13,” or in shorthand, “K13-propeller,” named for the pinwheel shape of the protein encoded by the gene.

The method of identifying the mutations (single nucleotide polymorphisms, or SNPs) involved subjecting successive generations of a *P. falciparum* clone from Tanzania to repeated exposures to artemisinins over 5 years—125 cycles of escalating doses of artemisinins. The researchers then examined the gene mutations detected in whole-genome sequencing (compared with the same clone cultured without artemisinin exposure), eliminated some for pre-specified reasons, and then compared the remaining polymorphisms—in seven genes—with the full genomes of strains from Cambodia known clinically to be partially resistant to artemisinins. Six genes dropped out, leaving just K13. To confirm this finding, the researchers also analyzed parasite genomes from all over Cambodia, which had a range of sensitivity to resistant clinical characteristics and found a very good correlation: the mutations were present where clinical resistance was present and were absent where artemisinin was still very effective.

There may well be other genes involved in artemisinin resistance, but for now, the identification of the K13-propeller represents a huge advance. Researchers at the Mahidol University Research Unit have developed a relatively quick PCR method to identify the K13-propeller mutations and are applying it to samples from TRAC participants.

### Multiple “Founder” Clones

Resistance has arisen not once but several times in Cambodia alone (figure 7). This is perhaps the most surprising and worrisome finding of the analyses of K13 proteins. It means that—unlike resistance to chloroquine and some other antimalarials—the main threat comes not just due to spread of resistant parasites from one epicenter (or a very small number of points), but from *de novo* resistance emerging and spreading from many points. This has relevance for India, with its wide variation in malaria ecologies. There may well be areas with conditions conducive to the emergence of new clones. One of the current research priorities is to study the populations where founder clones have emerged to identify common characteristics that might be used to map the likelihood of *de novo* emergence. The potential for cross-border spread of resistance from surrounding countries is also very real.

FIGURE 7
Further analysis presented at the conference documented founder clones in Vietnam and Myanmar that also correlate with delayed parasite clearance.

The identification of K13 opens the field for many types of studies that will be likely to be more efficient than studies relying on phenotypic characteristics, especially parasite clearance time. Immediate needs are for validation studies to clarify the roles of specific mutations.

### The Role of Asymptomatic Parasitemia

Many more people are infected with malaria parasites than show clinical symptoms and seek treatment. The ratio of asymptomatic to symptomatic individuals rises with the endemicity level. In other words, the more intense is malaria transmission, the greater will be the proportion of individuals who remain asymptomatic most of the time. The reason is related to transient immunity that is maintained with exposure to infection. In much of the Greater Mekong Subregion, including some areas where artemisinin resistance has emerged, endemicity levels are low and a high proportion of infected individuals develop clinical malaria and are treated. Everywhere, however, a reservoir of parasites exists in untreated individuals.

In areas of lower endemicity, where people are more likely to be infected from a single exposure, meaning they may harbor a single of parasite strain, whereas in areas of high endemicity, people may be infected with multiple strains. This is relevant to the emergence and spread of resistance because the lack of competition among strains in areas of low endemicity may favor resistant strains, while any
“fitness cost” imposed by the mutation may make it vulnerable where competition is higher, especially in areas of intense transmission.

The identification of the K13 propeller mutations and the PCR assays for it will enable studies of the geography of resistance among the all-important asymptomatic parasite carriers, who are considered a major source of transmission, despite their usually low parasitemias and lack of symptoms. It is important in designing intervention strategies to characterize these populations accurately, to know, for example, whether they are largely migratory (as is the case for many border-region inhabitants) or stable residents.

Professor Plowe proposed the plan of action in Box 1 for next steps in working toward elimination of resistant strains—meaning elimination of malaria in the region.

BOX 1: Suggested Plan of Action

- Map the true prevalence and distribution of malaria infection, including sub-patent, asymptomatic parasitemia
- Map the current prevalence and distribution of artemisinin resistance, using K13 SNPs
- Improve the designation of “Tier 2” areas at risk of artemisinin resistance, using gene flow to estimate parasite migration rates
- With this information, collected and analyzed by local scientists and public health workers, make informed decisions about pilot-testing Targeted Malaria Elimination and other elimination interventions

SOURCE: Plowe, 2014

2. **FOCUS ON INDIA: MALARIA, ANTIMALARIAL RESISTANCE AND TREATMENT POLICY**

*Presented by Dr. Neena Valecha*

About one million cases of malaria are reported each year in India, including infections with both *P. vivax* and *P. falciparum*. This figure is an acknowledged gross underestimate of the actual burden, representing only reports from the public sector.

Since 1953, when the National Malaria Control Programme was established, the mainstays of control have, until recently, been treatment with chloroquine or amodiaquine and mosquito control using DDT. All three interventions were highly effective at that time and by 1965, the caseload had been brought down to 100,000 cases (figure 8).

FIGURE 8
The success was short-lived, however, with a resurgence beginning in the late 1960s. In 1976, 6.4 million cases were reported. That setback extended to all Southeast Asian countries except the Maldives. Another phenomenon that can be seen in figure 8 is the growth of falciparum as a proportion of total cases. From less than 10 percent in 1960, it has risen to about 50 percent today.

It was during this period of resurgence that chloroquine resistance was first reported in India, in Karbi Anglong, Assam, in the northeast. In 1977, drug resistance monitoring was initiated and the spread of chloroquine resistance to all endemic areas was documented (figure 9).

FIGURE 9
The spread could be seen as resistance moved region to region (figure 10). Failure to contain it in the northeast led to the nationwide failure of chloroquine against *P. falciparum*. It still retains full efficacy against *P. vivax*.

FIGURE 10
India Malaria Control Programme

Presented by Dr. A.C. Dhariwal

The current objective of the India Malaria Control Programme is to prevent malaria morbidity and mortality and to contribute to the ongoing socioeconomic development of the country. Specifically, the aim is to bring down annual parasite incidence (API) to <1 in all districts by 2017—“pre-elimination” status. The malaria MDG, to halt and reverse malaria incidence by 2015, has already been achieved.

The India malaria map has “shrunk” between 2000 and 2012 (figure 11). The number of districts with an API greater than 10 has been halved and the number with API less than 1 has grown by 40 percent.

FIGURE 11
The control programme includes interventions at all levels, from national down to sub-district, and collaborates with global and local partners. Drug and insecticide resistance are continual challenges, met with monitoring 419 sentinel sites around the country (for drug resistance) and making sure drug and insecticide policies are consistent with current evidence. The programme also monitors the quality of microscopy and RDT use and interpretation.

Other challenges include procurement of drugs, diagnostics and LLINs, ensuring that the essential medicines list is in line with current evidence and ensuring the quality of all malaria commodities. An ever-present challenge is the large burden of vivax malaria in India.

On the positive side, many global and national partners are participating in malaria control and results of the efforts are substantial. The gains already made must be maintained toward eventual elimination of falciparum malaria from India.

**Odisha**

*Presented by Dr. M.M. Pradhan*

Odisha is a large state in eastern India, with about one-quarter of the country’s malaria cases. Malaria is seasonal, with somewhat different patterns overall and in forested tribal districts (figure 12).
Since 2009, control has been strengthened, with increases in insecticide-treated (and long-lasting) nets, indoor residual spraying (IRS), RDTs (bivalent, able to detect and distinguish between *P. falciparum* and *P. vivax*), provision of ACTs, and capacity building of workers at all levels (including ASHA community health workers). As a result, both malaria incidence and deaths from malaria have declined. All the new efforts have been accompanied by strong evaluation components.

The new efforts have yielded dramatic results. For example, the “M0-MASHARI” Programme to distribute long-lasting insecticide-treated nets (LLIN, has reached a large proportion of high-endemicity sites, including tribal residential schools and prisons in addition to traditional households.

Going forward, comprehensive case management will continue in Odisha, with impact assessment. The overall plan for the state includes activity in all areas, according to endemicity level.

**Treatment Policy and Patterns**

*Presented by Dr. Anup Anvikar*

The full range of older antimalarials are registered in India. Among the ACTs, those registered are:

- AS+SP blister pack
- Artemether-lumefantrine
- AS+MQ blister pack and fixed-dose combination (FDC)
- ASAQ FDC
- Arterolane-piperaquine FDC

Artesunate monotherapy is restricted to the injectable form for severe malaria.
National policy has evolved with antimalarial resistance and recommendations from WHO, with input from the NVBDCP, NIMR and other expert groups (figure 16).

**FIGURE 16**

**Evolution of antimalarial drug policy**

As is the case in most countries, compliance with the drug policy can be mandated only in public sector facilities, which treat the minority of cases in India. The strengths of the current policy include:

- Banning of oral artemisinin monotherapy in 2009
- Antimalarial therapy only after parasitological diagnosis
- Robust National Drug Resistance Monitoring System: widespread and longitudinal measurement of the treatments
- The current first-line therapies for *P. falciparum* (AS+SP and AL) and for *P. vivax* (CQ) are efficacious
- Policy process well-defined, consultative, and evidence based
- The frequency of drug policy updates has increased
- Policy translated into easy-to-follow case management guidelines for use by clinicians

Weaknesses include:

- AS+SP is a blister pack and not a fixed-dose formulation (FDC), leading to poorer adherence and the potential for monotherapy use
- Poor access to the public sector delivery systems leads to high levels of self-treatment through the private sector, which is growing
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- Many ineffective (irrational) malaria treatments are on offer in the private sector
- There has been an increase in the use of injectable artesunate monotherapy for uncomplicated malaria, which is entirely inappropriate
- Lack of awareness of the national drug policy among the private sector
- Wide variation in treatment choice along with dose, duration, and co-administered drugs, such as antibiotics
- Physician and patient compliance with primaquine use is poor

Concerns for the near future include the potential for artemisinin resistance, either from cross-border spread, particularly from nearby Thai-Myanmar and Thai-Cambodia borders; or from de novo resistance in India, possibly because of failure of SP placing additional pressure on artemisinins. The possibility that resistance to chloroquine might emerge in *P. vivax* would immensely complicate malaria control. Thus far, no signs of this are apparent.

**Surveillance of Antimalarial Drugs in India**

*Presented by Dr. Neelima Mishra*

AS-SP was established as first-line treatment of falciparum malaria in 2005. Efficacy monitoring in sentinel sites began in 2009, by NVBDCP and NIMR. Through 2011, 34 studies found 94 to 100 percent efficacy, but molecular markers to pyrimethamine resistance were increasing in prevalence. Eventually, in three studies in the northeast region, treatment failure was above the 10 percent failure threshold for policy change, due to resistance of parasites to pyrimethamine.

The efficacy monitoring that began in 2009 was a new paradigm. The two institutions (NVBDCP and NIMR) began to work together, the sentinel sites had widespread and longitudinal coverage, though a system of alternating sites (figure 17). Both falciparum and vivax were included, and there was PCR support for genotyping and analyzing for molecular markers.

FIGURE 17
Surveillance and monitoring will continue. Two sites in the northeast are proposed for the next round of TRAC studies. The K13 mutations will be included in new studies, and the samples already collected...
in previous studies are being analyzed for these. Cross-border studies are also planned to monitor the efficacy of AL in northeast states. Artemisinin monotherapy is an additional focus of NIMR study. A study in 2008 provided evidence for the ban on oral artemisinin monotherapy. In that study, about 15 percent of patients across all settings (drug shops, small clinics, hospitals, private practitioners) received artemisinin monotherapy, and the biggest contributor was the private sector (figure 18). Monotherapy was available in 75 percent of chemist shops and were sold without prescription by 42 percent of chemists. A follow-up study, to determine the effect of the ban, is planned for this year.

FIGURE 18

**Artemisinin monotherapy in India (2008)**

Multiple responses were given by the doctors for antimalarial prescription
Majority of the Clinicians prescribe Chloroquine, Artemisinin or SP monotherapy

NIMR plans a number of activities going forward to contribute to artemisinin resistance containment. These include continued sentinel site monitoring; training in use of the treatment guidelines, treatment efficacy study procedures and ethics; and follow up on artemisinin monotherapy.

3. REPORTS FROM OTHER COUNTRIES IN SOUTH AND SOUTHEAST ASIA

Nepal

*Presented by Dr. B.R. Marasini*

*Malaria Burden*
About half the population of Nepal lives in an area with some risk of malaria, mostly low risk (<0.5 annual parasite incidence). High risk (comprising about 4 percent of the population) and low risk (comprising about 10 percent of the population) areas are concentrated in the south, along the border with India (figure 19). Much of the remainder of the country is malaria-free or very low endemicity.

In 2012, about 2100 cases of malaria were reported, about 75 percent of them *P. vivax* and 25 percent falciparum malaria. Half of the vivax cases were imported and half acquired within Nepal. No deaths occurred among the reported cases. Various malaria indices have fluctuated over the past half century, but levels are relatively low at present (figure 20).

The Nepal Malaria Control Programme has entered the “pre-elimination phase,” with a goal of zero indigenous transmission by 2025. The malaria MDG was met in 2010.

Challenges remaining include highland malaria, malaria in labor migrants, financing for malaria control and antimalarial resistance. Cross-border collaboration remains a critical need.

**Antimalarial Resistance**

Testing for chloroquine resistance started in 1978 and was first detected in imported *P. falciparum* cases in 1979 and in indigenous cases in 1984. Resistance subsequently spread to seven districts.
Resistance to SP was first reported as early and late treatment failure in 1996-1997 in the same area where chloroquine resistance had first been detected. In 2000, late treatment failure occurred in about 57 percent of cases in one district (Dhanusha). In 2002, late treatment failure was common in two more districts. All of these results are from studies conducted according contemporaneous WHO guidelines.

Monitoring treatment with ACTs began in 2007 and continues in four sentinel sites. Before 2013, no signs of resistance were seen. However, one case of delayed failure was recorded out of just 17 enrolled between April and December 2013. This reinforces the need to maintain surveillance in Nepal, though, overall, malaria control is good and elimination targets are being met.

FIGURE 20

API: Annual parasite incidence: annual confirmed cases/population under surveillance x 1000.
AFI: Annual falciparum index—total positive Pf in a year x 1000 /total population
Pf: Plasmodium falciparum
BER: Blood examination rate—number of slides examined/population x 100
SFR: Slide falciparum rate—percentage falciparum of all positive slides
SPR: Slide positivity rate
SOURCE: Marasini 2014

Myanmar (Burma)
Presented by Professor Myaing Nyunt
Conditions that favor malaria transmission and make malaria difficult to control coincide in Myanmar. The rural and remote populations, especially in forested areas, have little access to healthcare. Mobile populations support gold and gem mining, timber extraction, rubber tapping and agriculture; and
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political instability causes further population movements. Self-treatment without diagnosis is common, with antimalarials purchased in the private sector, which is largely unregulated.

The reported incidence of malaria has declined since 1990 (figure 21), but most reported cases are a minority of all cases. *P. falciparum* causes about three-quarters of reported cases and *P. vivax*, most of the remainder. *P. malariae* and *P. ovale* are present at very low levels.

FIGURE 21

![Malaria case load in Myanmar 1990–2012](image)

![Malaria species (2006–2012)](image)

SOURCE: Nyunt 2014

ACT efficacy monitoring was begun in 2004, including artesunate-amodiaquine, artestunate-mefloquine and artemether-lumefantrine. With declining efficacy noted in 2009-2010, the “Myanmar Artemisinin Resistance Containment” (MARC) plan was developed in consultation with WHO and other partners in 2010 and endorsed in 2011. The objectives are:

- To improve diagnosis and treatment
  - Emphasis on high-risk populations (migrants)
  - Subsidizing ACT and RDT in private sector
  - Social marketing of ACT
- To stop the use of monotherapy and substandard drugs
  - Revitalization of FDA activities
- Vector control (ITN, IRS)
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- Operational research to guide & promote behavioral change (personal protection, ITN use)
- Sentinel surveillance of ACT response (Therapeutic Efficacy Studies), using persistent parasitemia on day 3 as the measure of efficacy

MARC activities are planned according to the three tiers defined by WHO (figure 22).

FIGURE 22

Tier division: Strength of suspicion (2011)

SOURCE: Nyunt 2014

The importance of artemisinin containment in Myanmar is recognized by the global community, resulting in a large international donor commitment and a wide range of partners implementing MARC.

Baseline surveys were conducted in 2011 in Tier 1 and 2 areas, including a household and health facility survey and a drug outlet survey. Training in malaria reporting, and report monitoring were prioritized, and the migrant populations were mapped.

The efforts have paid off in declining malaria morbidity and mortality (figure 23).
**ACT Therapeutic Efficacy Studies**

MARC has involved clinical trials of the three main ACTs in use in Myanmar against *P. falciparum*—AL, AM, and DHA-PQ—using PCR-corrected day 3 parasitemia to define treatment failure. Similar studies have been conducted with chloroquine against *P. vivax*. Studies have been conducted on the eastern and western borders and in limited areas on the central regions.

The day 3 positivity rate ranged from 2 to 4 percent, with the highest levels in states bordering Thailand and low to no positives on the Bangladesh and Indian borders.

Treatment may fail for reasons other than artemisinin resistance. An artesunate monotherapy study was conducted in 52 adults, from a tier 1 area in the south, with uncomplicated falciparum malaria to rule out the role of pharmacokinetics in treatment failure. In about 30 percent of patients, parasitemia persisted on day 3; in about 35 percent, clearance was slow.

In Thailand, along the Myanmar border, outcomes for 3200 patients treated from 2001 through 2010 were analyzed. The percentage of slow-clearing infections increased from 0.6 percent to 20 percent over that time. The researchers concluded that resistance rates would match those in western Cambodia in 2 to 6 years.

The thinking in Myanmar (as elsewhere) is that eliminating artemisinin resistance will probably require eliminating malaria. Toward that end, Myanmar must intensify malaria control, including ensuring quality ACTs, possibly using primaquine, eliminating artemisinin monotherapy, increasing vector control and personal protection, behavioral interventions with migrant populations, and training for a range of
workers in the public and private sectors. Another part of the strategy involves dealing with the large reservoir of asymptomatic infections.

Bangladesh

*Presented by Professor Abul Faiz*

Malaria is at a low ebb in Bangladesh, with significant progress since 2007 (figure 24). Before that time, cases and deaths had been rising steadily.

FIGURE 24

**Reported Malaria Cases in Bangladesh, 1964-2007**

![Chart showing reported malaria cases in Bangladesh from 1964 to 2007. The chart illustrates the reduction in cases and deaths from 2007 onwards.](chart)

SOURCE: Faiz 2014

The highest endemicity areas are on the borders with northeast India and Myanmar (figure 25). About 27,000 cases (mostly falciparum) and 15 deaths were reported in 2013.

FIGURE 25
Sites in Bangladesh have been included in a number of recent studies, including TRAC. In that study, no evidence was found of slow clearance in Ramu, the Bangladesh site. The single patient with a long clearance time vomited the first dose of the drug and probably did not get a full treatment course. No K14 mutations were later found in the parasites causing her infection.

Bangladesh intends to continue conducting monitoring and surveillance to quickly identify artemisinin should it arise de novo or arrive from across the border, particularly making using of K13 analysis.

4. WORLD HEALTH ORGANIZATION ACTIVITIES RELATED TO ARTEMISININ RESISTANCE IN THE SOUTHEAST ASIA REGION

Presented by Dr. Leonard Ortega

WHO’s 2013 World Malaria Report documents the progress that has been made since 2000, when malaria control efforts began to be stepped up in the recent assault on the disease. Between 2000 and 2012, global malaria incidence rates decreased by 29 percent and the global malaria mortality rate decreased by 45 percent. An estimated 3.3 million lives were saved as a result of scale-up of malaria interventions; 90 percent—3 million—of them children in sub-Saharan Africa. Worldwide, 52 countries are on track to reduce malaria case incidence rates by 75 percent, in line with World Health Assembly and Roll Back Malaria targets for 2015.

In the South East Asia region, about 2 million cases were confirmed and 1200 deaths were reported in 2012. WHO estimates that this translates to 27 million cases and 42,000 death, 99 percent of them from
India, Indonesia and Myanmar. One country in the region—Sri Lanka—is malaria free, reporting no indigenous cases since November 2012.

Drug resistance is one of several challenges threatening to unravel the accumulated gains. WHO has provided normative standards for defining antimalarial resistance during the recent era (box 2).

**BOX 2: WHO Working Definition of Artemisinin Resistance**

**Suspected resistance:** an increase in parasite clearance time, as evidenced by greater than 10 percent of cases with parasites detectable on day 3 following treatment with an ACT.

**Confirmed resistance:** a treatment failure as evidenced by presence of parasites at day 3 and either persistence of parasites on day 7 or recrudescence after day 7 of parasites within 28/42 days, after treatment with an oral artemisinin-based monotherapy, with adequate blood concentration.

SOURCE: Ortega 2014

WHO has tracked artemisinin resistance in the Greater Mekong Subregion with a nod to the history of resistance to other antimalarials. Resistance to most other antimalarials has arisen in this region early in the evolution and spread of resistance. This is not to say that the Greater Mekong Subregion is the only area where resistance arises—it has happened elsewhere, the number of times varying with the individual drug. Currently, containment activities have been started in the five countries where resistance has been confirmed (figures 26 and 27).

**FIGURE 26**

**Summary of the status of artemisinin resistance in the Greater Mekong Subregion**

<table>
<thead>
<tr>
<th>Country</th>
<th>Year of emergence</th>
<th>Detected</th>
<th>Year of containment activities</th>
<th>AL D3+</th>
<th>AS-MQ D3+</th>
<th>DHA-PPQ D3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>2001*</td>
<td>2006</td>
<td>2009</td>
<td>♦</td>
<td>♦</td>
<td>♦</td>
</tr>
<tr>
<td>Laos</td>
<td>2013</td>
<td>2013</td>
<td>2014</td>
<td>♦</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Myanmar</td>
<td>2001*</td>
<td>2008</td>
<td>2011</td>
<td>♦</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thailand</td>
<td>2001*</td>
<td>2008</td>
<td>2009</td>
<td>♦</td>
<td>♦</td>
<td>–</td>
</tr>
<tr>
<td>Viet Nam</td>
<td>2009</td>
<td>2009</td>
<td>2011</td>
<td>♦</td>
<td>♦</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**
- first-line treatment; * detected retrospectively using molecular markers or retrospective data;
- ♦ observed to be > 10%; – observed to be < 10%; blank = undetermined

[Image of World Health Organization and Global Malaria Programme logos]
WHO’s response to artemisinin resistance in the GMS was first, the *Global Action Plan for Artemisinin Resistance Containment* (GPARC) with its five pillars (figure 28).
When it became clear that artemisinin resistance was increasing despite containment efforts, WHO issued its *Emergency Response to Artemisinin Resistance in the GMS* (ERAR). ERAR’s four focus areas are:

1. **Full coverage of quality interventions in priority areas**
   Includes working with health and non-health sectors to reach high-risk populations
2. **Tighter coordination and management of field operations**
   Includes increasing monitoring of staff performance and supportive supervision
3. **Better information for resistance containment**
   Includes advancing priority research and refining tools for containment and elimination
4. **Strengthen regional oversight and support**
   Includes support to improve cross-border coordination

The objectives are:

1. Strengthen leadership, coordination and oversight mechanism
2. Maintain and expand drug efficacy surveillance networks and accelerate priority research
3. Improve access for migrant and mobile populations to quality services
4. Facilitate the full implementation of the Myanmar Artemisinin Resistance Containment (MARC) framework
5. Strengthen the response to artemisinin resistance in Viet Nam
6. Limit the availability of oral artemisinin-based monotherapy, substandard and counterfeit antimalarial medicine while improving quality of artemisinin-based combination therapies
WHO has played a key role in coordinating global support for artemisinin resistance containment in the Greater Mekong Subregion. To date, high-level commitments have been made in the region, particularly through the Asia Pacific Leaders Malaria Alliance, with its secretariat at the Asian Development Bank.

Strategic objectives for malaria control and eventual elimination in the South East Asia region, through 2020 are:

1. To scale up key interventions in countries and areas with high burden of malaria.
2. To re-orient national malaria control programmes towards pre-elimination / elimination in countries with very low burden of malaria.
3. To prevent the emergence of artemisinin-resistance and to contain it in areas where it has already emerged.
4. To strengthen managerial and technical capacities for malaria control and malaria elimination.
5. To strengthen partnership, multi-sector participation and international collaboration in malaria control and elimination.
6. To generate evidence and strategic information for policy and strategy development, operational planning and decision making.

5. TOOLS FOR ARTEMISININ CONTAINMENT

The Worldwide Antimalarial Resistance Network

Presented by Professor Carol Hopkins Sibley

The Worldwide Antimalarial Resistance Network (WWARN) is a collaboration among 230 partners to track antimalarial resistance to all drugs and to provide reliable evidence for decisions about malaria control. By pooling data on drug efficacy from a large number of sites, WWARN seeks to identify risks to efficacy at the earliest stages.

In the past, the world chronicled the failure of antimalarial drugs (Figure 29). The result was widespread resistance to chloroquine and SP—familiar stories. The route of resistant parasites was well worn (figure 29).

FIGURE 29
In the past, as drugs failed, we kept track

% CURE RATE (falciparum malaria) NW Thailand

WHITE, 1999

SOURCE: Sibley 2014

FIGURE 30

Well-warn route of resistant parasites

Su, Kirkman, Fujioka & Wellems. Cell, 1997

SOURCE: Sibley 2014
However, antimalarial failure does not happen instantaneously. In past instances of resistance, e.g., resistance to SP, several steps toward clinical failure have been documented (figure 31).

**FIGURE 31**

Many changes before clinical failure is obvious

![Data from Sibley 2014](image)

**EARLY WARNING BEFORE CLINICAL FAILURE**

SOURCE: Sibley 2014

This recognition has led to a new paradigm, that of early warning signs of resistance. We need tools and methods to detect the earliest signs of resistance, including delays in the speed of parasite clearance, molecular markers of parasite resistance, and a progressive decrease in *in vitro* susceptibility.

WWARN collates data sets from many contributors. All data must be individual patient (or parasite) records, not summary data from studies. This allows researchers to query the data and form large, pooled data sets of individuals.

**FIGURE 32**

WWARN Explorer allows a range of queries.
For example, how are the current ACTs doing in Africa? (figure 33)

**FIGURE 33**

*How are current ACTs doing?*

<table>
<thead>
<tr>
<th></th>
<th>AL</th>
<th>DHA-PQP</th>
<th>AS-AQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>66</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>15,000</td>
<td>7,000</td>
<td>5,400</td>
</tr>
<tr>
<td></td>
<td>299</td>
<td>127</td>
<td>240</td>
</tr>
</tbody>
</table>
By using pooled data, common factors in failures after ACT treatment have been identified. These are young age (less immunity and higher parasitemia), low dose of drug, and certain subgroups. This has led to the recognition that pregnant women and infants, for instance, tend to be underdosed. This is potentially a potent driver of parasite resistance and can represent a significant proportion of the patient population.

WWARN, with its interactive format, can provide several tools in addition to pooled data. It can predict where resource would be best deployed, e.g., for active surveillance (figure 34) or for efficient sampling (figure 35).

**FIGURE 34**

**Modelling to target active surveillance**

- Guide surveillance to hotspots
- Concentrate effort and investment in high risk areas
- Proof of concept with SP-AQ
  - seasonal malaria chemoprevention

**SOURCE:** Sibley 2014

**FIGURE 35**
WWARN provides tools to help avoid pitfalls of the past, when antimalarial resistance was observed rather than contained.

**Mathematical Modeling to Aid Resistance Surveillance and Containment**

*Presented by Dr. Lisa White*

Mathematical models are especially useful for simplifying complex dynamic systems involving infectious disease transmission. Research in artemisinin resistance is an area that modeling can help understand and make predictions about, and can be used as an aid to decisionmaking. Current models (developed by researchers at the Mahidol Oxford Research Unit in Bangkok) predict that:

- Low to intermediate transmission settings with intermediate to high treatment coverage of clinical cases have the best conditions for the spread of resistance
- Containment must take the form of local elimination of all falciparum malaria (sensitive and resistant alike)

The models allow analysis of how interventions are likely to work in different conditions, and to develop the appropriate strategies (figure 36).

**FIGURE 36**
All available information was used to develop a model for Cambodia, where resistance first was documented and is the most widespread (figure 37).

FIGURE 37

A model for Cambodia
Delaying Artemisinin Resistance in India

SOURCE: White 2014

As more data become available on the parameters included in the model, their inclusion is likely to make the results more precise. However, this model has predicted current outcomes well based on earlier inputs. It now is being used to develop strategies for malaria elimination in Cambodia.

Modeling has confirmed that there is no “one size fits all” intervention for artemisinin containment because of the wide spectrum of conditions in which malaria exists, including both the natural environment and the varied characteristics of populations at risk. Therefore, the answer to the question “which intervention is best?” will be different for every country and from every perspective.

6. SUMMARY AND CONCLUSIONS

Artemisinin-resistant malaria has been documented in five countries in the Greater Mekong Subregion: Cambodia, Thailand, Vietnam, Myanmar and Laos. It was assumed by knowledgeable scientists that the chloroquine story was replaying—spread from the epicenter in Cambodia. Containment plans have been developed around the idea of stopping the spread. But new and surprising results from analyses of molecular markers that have just been identified demonstrate clearly that resistance has arisen many times in the region.

To date, no early signals of resistance have been recognized in India (and countries in the region besides those named above) or in all of Africa. Cross-border spread is a clear and present danger, but preventing de novo emergence now deserves at least as much attention. Further analysis of the sites where resistance has already emerged in the region should provide clues about the conditions that promote it, and this will guide types and locations of interventions to prevent it.

In the meantime, however, action must be taken based on the rich pool of existing information.

The current regional strategy is based on good practices for malaria control everywhere and intensive focal efforts in areas with documented resistance. This was based on the assumption that new foci were the result of spread. The choice of strategy among the wide range of stakeholders must be revisited in light of the identification of the K13 propeller mutations. This information may or may not change the current direction. Discussion at the meeting leaned toward organizing a much more intensive effort over the next few years to eliminate malaria, at least in the countries with documented resistance. More than once, the concept of the “last man standing” was invoked, meaning that as malaria declines to ever lower levels, the most resistant parasites become a larger proportion of the entire parasite pool, so elimination is the only logical endpoint.

A second line of defense must be to create a surveillance system to quickly identify new areas of resistance emergence. The characteristics of areas where resistance is likely to emerge should become clearer from analysis of the areas where we now know that it has emerged. However, it is possible that we will not have this information for some years, and yet devising appropriate strategies must begin immediately.
Implications for India

The entire spectrum of malaria endemicity and transmission can be found within India, including areas of exclusive *P. falciparum* or *P. vivax* and places where mixed infections are common. It has, as yet, no evidence of artemisinin resistance, but resistance to other drugs is common. Most importantly, the ACT in widest current use is artesunate+SP, which historically, and still is predominantly, given as a loose combination. Resistance to SP (specifically, to the pyrimethamine component) has reduced the efficacy of the ACT and makes it more likely that parasites resistant to artesunate will survive and be transmitted. The first-line ACT in areas with known pyrimethamine resistance has been changed to artemether-lumefantrine (AL; Coartem branded), but first-line treatment in the rest of the country is still artesunate+SP. Other ACTs (fixed-dose combinations, in particular) are effective in India and should be considered as first-line therapy. Of possibly much greater long-term efficacy is adopting a policy of multiple first-line therapies (MFTs).

India has responsibility to prevent as much malaria as possible within its borders and to treat every case effectively. It also bears responsibility to prevent artemisinin resistance from escaping over its borders, should it arise within India or arrive from a neighboring country. India carries the dubious distinction of being the gateway to Africa for the pfcrt mutation associated with chloroquine resistance (although it would have arrived there eventually by another route). Nonetheless, India must mount effective surveillance to identify and then control resistance in border areas.

Implications for the South and Southeast Asia Region

Through the efforts of WHO and others, there already is a framework for collaboration in research and cross-border surveillance. There is a clear need to continue and expand the TRAC study, incorporating the new molecular marker in the K13 gene. New types of streamlined studies may be made possible by this marker, and any that will provide information directly relevant to control and elimination strategies should be prioritized.

Documenting the Current Situation

Agreement was reached at the meeting that set of five papers would be written by teams of authors, led by meeting attendees but including a wide range of regional and international experts. Dr. Valecha agreed that the papers would be published in a special issue of the *Journal of Vector Borne Diseases*.

The topics are:

1. Antimalarial resistance in the subcontinent
2. The potential for artemisinin resistance in India under current circumstances
3. Potential burden, costs and consequences of artemisinin resistance in India and the subcontinent and interventions to reduce the probability of its development
4. Operational and regulatory priorities in relation to malaria control in India
5. Research priorities to aid artemisinin resistance containment

Collectively, the papers will lay the groundwork for India assuming a more prominent role in malaria control, and in measures to meet the challenge of artemisinin resistance, in the region. Papers 1 and 2
**Delaying Artemisinin Resistance in India**

will characterize the current status of artemisinin resistance and the existing conditions that favor its arising *de novo* and/or spreading in India and its neighbors. The third paper will describe the consequences of an inadequate response and outline preemptive strategies to avert or delay resistance (e.g., longer courses of effective drugs, multiple first-line therapies, etc.). Paper 4, more India-specific than the others, will lay out the national action priorities for control and actions the government can take to ensure their implementation (through regulation or other means). The final paper will outline an operational research agenda for the region specifically aimed at averting artemisinin resistance and at eliminating malaria.

The papers will be harmonized with WHO priorities and activities and those of neighboring countries.

**Opportunities for India**

Malaria in Southeast and Southern Asia has become a clear focus of global concern and activity in the last few years, mainly because of the appearance of artemisinin resistance in the region. With this concern comes the potential to act swiftly and decisively, and India can play a major role in this, both within its own borders and within the region.

*Domestic and cross-border artemisinin resistance surveillance.* India can take the lead with its smaller neighbors in initiating and/or strengthening ongoing or frequent periodic surveillance. NIMR is well placed to lead these efforts. India can initiate this with bilateral discussions between research and/or control programs in each bordering country, concluding formal agreements to collaborate, share information, share costs and develop contingency plans should artemisinin resistance or significant changes in resistance patterns be detected.

Within India, the current surveillance plan should be reviewed and revised as needed. In the next several years, more information will come to light from the four GMS countries where artemisinin resistance has already been detected, elucidating the conditions conducive to emergence. When this occurs, India—which has examples of most, if not all, the Asian malaria ecologies—can target potential problems areas.

*Supplying commodities.* India is in the best position in the region to supply high-quality ACTs, RDTs and other commodities. The existing generic pharmaceutical companies should be primed to quickly ramp up production of these commodities. India’s co-chairmanship of the APLMA Task Force on Access to Quality Medicines and Other Technologies places India in a leadership role in this arena. At the same time, the Ministry of Health and Family Welfare has been strengthening the role of the Central Drugs Standard Control Organization (CDSCO) in promoting public health and quality in medicines as a global public good. CDSCO could play more of a regional role, including sample drug analysis and setting regulatory standards.
ACKNOWLEDGMENTS

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