Introduction

Every year more than 200 million cases of Malaria occur and nearly 600,000 deaths are estimated globally. Global efforts to control and eliminate malaria have saved an estimated 3.3 million lives since 2000, reducing malaria mortality 42 percent globally and 49 percent in Africa.

Developments in anti-malaria therapies have contributed significantly in reducing deaths. Artemisinin and its derivatives are highly effective in treating malaria. They rapidly eliminate asexual parasite stages and early sexual forms of falciparum malaria, producing a clinical and parasitological response. 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).

Artemisinin derivatives are highly potent, rapidly eliminated antimalarial drugs with a broad stage specificity of action. They clear parasitemia more rapidly than all other currently available antimalarial agents. In the 1990s, resistance to available antimalarial drugs such as chloroquine and Sulfadoxine–Pyrimethamine worsened across areas of the world where malaria is endemic.

With the world’s largest population at risk of malaria, India could see the current burden of malaria increase if the current first line treatments that depend on artemisinin fail. 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),

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documented first in Cambodia near the border with Thailand in 2007.2

The latest study published in the New England Journal of Medicine, confirms that resistance to the current frontline antimalarial, artemisinin, is now present in Eastern Myanmar, Thailand and Southern Vietnam, as well as Western Cambodia. The paper also provides worrying indications of emerging resistance in Central Myanmar, Southern Laos and North-eastern Cambodia. Reassuringly the study results do not identify the spread or emergence of drug resistance in the three African study sites in Democratic Republic of the Congo, Nigeria and Kenya.

Resistance to artemisinin has not been contained and has now emerged or spread across Southeast Asia. The spread of artemisinin resistance and the consequent emergence of resistance to the increasingly unprotected partner drugs in artemisinin-based combination regimens may well reverse the substantial recent gains in malaria control. New antimalarial drugs are under development but will not be available for several years. Radical measures will be necessary in Southeast Asia to prevent resistance to artemisinins and their partner drugs from spreading to the Indian subcontinent and then to Africa.

**Evolution of Artemisinin Resistance**

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The ACTs were introduced in mid 1990s when there was an imminent prospect of untreatable malaria in South East Asia, where resistance to all anti malarial drugs had developed. In 2005, WHO recommended ACTs to be used a as a first line therapy in all countries where malaria is endemic. Recently with marked increases in availability and use of ACTs along with widespread use of insecticide treated bed nets, global morbidity and mortality is substantially reduced. These gains are now threatened with emergence of atreminisn resistance to falciparum. Atreminsin resistance is characterized by slow parasite clearance , which reflects reduced susceptibility of ring stage parasites. It has recently been linked with point mutations in the propeller region of a p falciparum kelch protein.

P. falciparum resistance to artemisinins has been detected in four countries in the Greater Mekong sub-region: Cambodia, Myanmar, Thailand and Viet Nam. Containment activities were started in 2008 on the Cambodia–Thailand border and are now being conducted in all four countries. 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

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patients in Wang Pha, Thailand, where no delay in parasitological cure had been seen.

**Policy frameworks and Responses**

Soon after it became clear that artemisinin resistance was increasing despite containment efforts, the WHO formulated the Emergency Response to Artemisinin Resistance (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. This calls for greater coordination amongst all stakeholders at regional level to check its spread.

The Global Plan for Artemisinin Resistance Containment (GPARC) was developed in consultation with members of each of the constituencies of the Roll Back Malaria Partnership. The GPARC goals and recommendations are: (i) stop the spread of resistant parasites (ii) increase monitoring and surveillance to evaluate the threat of artemisinin resistance. (iii) Improve access to diagnostics and rational treatment with ACTs (iv) Invest in AR related research (v) Motivate action and mobilize resources.

The Worldwide Antimalarial Resistance Network (WWARN) is a collaboration of 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.

The Tracking Artemisinin Resistance (TRAC) Study 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. Supported by multiple institutes, the teams mapped the extent of artmeinsin resistance across 15 research sites in 10 countries across in Asia and Africa.

"Should drug resistance continue to spread or emerge in Africa, thousands if not millions more lives will be at risk, years of effort and investment could be lost. It may still be possible to prevent the spread of artemisinin resistant malaria parasites by eliminating them, but that window of opportunity is closing fast,” said Prof Nicholas White, senior author of the study and Chairman of the Bangkok-based Mahidol Oxford Tropical Medicine Research Unit (MORU), Professor of Tropical Medicine at the University of Oxford, and Chair of WWARN.

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4 http://www.wwarn.org/

5 http://www.wwarn.org/partnerships/projects/trac
The Indian Context

As per the Indian Antimalarial Drug policy, Oral Artemisinin monotherapy has been banned since 2009. Artesunate monotherapy is restricted to the injectable form for severe malaria. The National policy has evolved keeping in mind patterns of antimalarial resistance and recommendations from WHO, with input from the National Vector Borne Disease Control Programme, National Institute of Malaria Research and other expert groups. 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.

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. 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 from the start 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.

The Workshop

It is with this backdrop, global and regional scientists and malaria control experts met in New Delhi on 24-25 March 2014 under the auspices of the National Institute of Malaria Research (NIMR) and the Public Health Foundation of India (PHFI) to take stock of the regional artemisinin resistance situation and to help shape the ongoing Indian response to national and South Asian needs. The meeting was sponsored by the U.K. Department for International Development (DfID) within framework of Knowledge Partnership Programme managed by IPE Global Pvt Ltd New Delhi.

There is also a risk of resistance developing independently in India and other countries, which is greater than had been assumed—although how much greater is still unknown. When resistance was first confirmed in Cambodia, the assumption was that resistance arose once and was spreading from a single epicenter—the story of chloroquine resistance in the last decades of the 20th century. A startling and worrisome new finding, however, is that artemisinin resistance has arisen not once but several times in Cambodia alone. The highest global malaria priority is eliminating falciparum malaria entirely from the areas where resistance has already emerged, and equally important, establishing efficient surveillance for newly emergent resistance.

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6 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2814%2960700-5/fulltext

7 http://www.ipekpp.com/work_streams.php
This new understanding of the multiple foci of resistance comes from analysis of malaria strains using the first definitive molecular marker for artemisinin resistance—actually any of a number of mutations in a single gene. The mutations are on P. falciparum chromosome 13 in a gene that encodes “kelch protein 13.”

There is no accurate count of the numbers of cases and deaths from malaria in India. The one million cases reported annually in recent years represents a small proportion of actual cases. P. vivax has historically been the predominant species, but the P. falciparum proportion has increased steadily. In 2012, the two species represented equal shares of reported cases. Although artemisinin resistance has not been detected in India, the history of chloroquine resistance spreading across the country stands as a reminder of the potential damage that could be wrought, should resistant strains of P. falciparum cross the border or arise de novo. The failure of ACTs could reverse the substantial gains made since 2000 through the India Malaria Control Programme, which includes halving the number of districts with annual parasite incidence >10 and early achievement of the malaria Millennium Development Goal of halting and reversing malaria incidence by 2015.

One of concern is that the ACT in widest current use in India is artesunate+SP, which is distributed predominantly 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. India is in a particularly strong position to aid in the pushback against artemisinin resistance in neighboring countries and continuing to forge ahead with reducing malaria incidence and mortality within its borders. Partnership with countries in the region is critical and has been facilitated by the World Health Organization (WHO) South East Asia Regional Office (SEARO). SEARO has developed a plan for tackling artemisinin resistance in the region, and regularly convenes country partners to advance the needed work. Technical partners, such as the Worldwide Antimalarial Resistance Network (WWARN) and the Mahidol-Oxford Tropical Medicine Unit (MORU), represented at the consultation, are also potential collaborators, with specialized tools that they have developed for surveillance, modeling and other types of research. India has also assumed a leadership role in the Asia Pacific Leaders Malaria Alliance (APLMA), which has given high priority to dealing with artemisinin resistance.

The workshop participants reached a consensus about India taking a leadership role with its neighbors in establishing and coordinating cross-border Artemisinin resistance surveillance, in supplying high-quality malaria control commodities, in ACT quality testing and in harmonizing regulatory standards throughout the region. The National Institute of Malaria Research (NIMR), National Vector Borne Disease Programme (NVBDP), the Central Drugs Standard Control Organization (CDSCO) and the Public Health Foundation of India (PHFI) will be involved in follow-up activities identified at the consultation. These activities include:
• Documenting the current situation in the region through a dedicated section of an early 2015 issue of the Journal of Vector Borne Diseases

• In consultation with the Asian Development Bank, developing a consolidated work plan joining the four APLMA priority areas for the region, which are:
  
  • Ensuring that regional preventive and therapeutic evidence-based practices are aligned with international standards and guidelines,
  
  • Cutting off the supply of oral artemisinin monotherapies, fake and substandard antimalarial medicines in the region,
  
  • Encouraging collaboration and cooperation among countries in the region to strengthen regulatory capacity, and
  
  • Improving access to commodities for malaria prevention and treatment, particularly for high-risk groups.

• Planning collaborative work with MORU to build capacity in malaria modeling in India and other South Asian countries

• Exploring a role for the Central Drugs Standard Control Organization (CDSCO) in drug analysis and in harmonizing regional regulatory standards.

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 pfcrtn 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.

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Knowledge Partnership Programme (KPP) is a South – South cooperation programme promoting knowledge sharing in the areas of Climate Change, Resource Scarcity and Food Security; Health and Disease Control; Trade and Investment; and Women and Girls. KPP is supported by DFID, UK.

The detailed report of the AR Workshop for India and SE Asia Region is available at KPP Website: www.ipekpp.com

Disclaimer: This material has been funded by UK aid from UK Government’s Department for International Development, however the views expressed do not necessarily reflect the UK Government’s official policies.