

## Mitigating the threat of artemisinin resistance in Africa: improvement of drug-resistance surveillance and response systems

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Artemisinin-resistant *Plasmodium falciparum* malaria has emerged in western Cambodia and has been detected in western Thailand. The situation is ominously reminiscent of the emergence of resistance to chloroquine and to sulfadoxine–pyrimethamine several decades ago. Artemisinin resistance is a major threat to global public health, with the most severe potential effects in sub-Saharan Africa, where the disease burden is highest and systems for monitoring and containment of resistance are inadequate. The mechanisms that underlie artemisinin resistance are not fully understood. The main phenotypic trait associated with resistance is a substantial delay in parasite clearance, so far reported in southeast Asia but not in Africa. One of the pillars of the WHO global plan for artemisinin resistance containment is to increase monitoring and surveillance. In this Personal View, we propose strategies that should be adopted by malaria-endemic countries in Africa: resource mobilisation to reactivate regional surveillance networks, establishment of baseline parasite clearance profiles to serve as benchmarks to track emerging artemisinin resistance, improved data sharing to allow pooled analyses to identify rare events, modelling of risk factors for drug resistance, and development and validation of new approaches to monitor resistance.

### Introduction

Malaria mostly affects the poorest populations of the world, with the largest disease burden in sub-Saharan Africa.<sup>1,2</sup> Early diagnosis and prompt effective treatment—key components of all national malaria control strategies—were seriously compromised during the early 1990s by resistance to widely used monotherapies,<sup>3–5</sup> which led to a public health disaster as earlier predicted.<sup>6</sup> To tackle the threat of drug-resistant malaria, WHO in 2001 recommended the adoption of artemisinin-based combination therapy for treatment of uncomplicated malaria.<sup>7</sup> However, the adoption and implementation of this policy recommendation was slow until, in 2004, research and control communities called for urgent action.<sup>8</sup> All sub-Saharan African countries now recommend artemisinin-based combination therapy as the first-line regimen for uncomplicated malaria.<sup>9</sup> This transition necessitated a huge commitment and concerted efforts from national malaria control programmes and donors. A focused strategy was needed to change standard treatment guidelines, retrain front-line health workers, secure funding for more expensive replacement drugs, and to tender, procure, and distribute them to the peripheries of health systems.<sup>10–17</sup>

One unfortunate consequence of this new policy was the demise of systematic malaria drug-resistance surveillance in Africa. Three reasons account for this outcome. First, there was a controversial belief that artemisinin-based combination therapies would remain unchallenged by resistance for decades.<sup>18</sup> Second, the technical needs for monitoring of resistance to artemisinin or partner drugs are substantially more complicated than the sampling methods used in Africa before 1996.<sup>19,20</sup> For example, the study designs used before 1996 had a 14-day follow-up that did not require

genotyping. Additionally, the sampling method was based on lot quality assurance sampling, which needed very few patients (as few as 16 in some studies). Such research could be done by national control programmes without the need to collaborate with research institutes or universities. However, studies into the efficacy of artemisinin-based combination therapies need a long duration of follow-up and require genotyping to differentiate recrudescence from new infection, and such capacity is usually not available in national programmes. Moreover, to detect emerging artemisinin resistance, frequent parasite-density sampling and pharmacokinetic studies might be needed, which will necessitate close collaboration between national malaria control programmes and academics. Finally, funding for drug efficacy surveillance from bilateral and multilateral agencies has been reduced.

Reports suggest that artemisinin resistance is threatening global malaria control and elimination efforts.<sup>21–23</sup> A consensus has not been reached about whether artemisinin resistance should be declared a public health emergency of international concern, in accordance with the revised international health regulations.<sup>24</sup> The reasons advanced by those against such a declaration are largely political and economic rather than technical. We believe artemisinin resistance fits the definition of a public health emergency of international concern—serious, unusual or unexpected, and with a substantial risk of spreading internationally.<sup>24</sup>

One of the pillars of WHO's global plan for artemisinin resistance containment is monitoring and surveillance to assess the threat of emerging resistance.<sup>25</sup> Nowhere are these efforts more important than in Africa, where the malaria burden remains highest and where the loss of effectiveness of artemisinin-based combination therapies

would have disastrous public health consequences. We believe that what is needed is the renewal of the collaborative effort to predict, detect, and mitigate the threat of antimalarial drug resistance in Africa during the next decade.

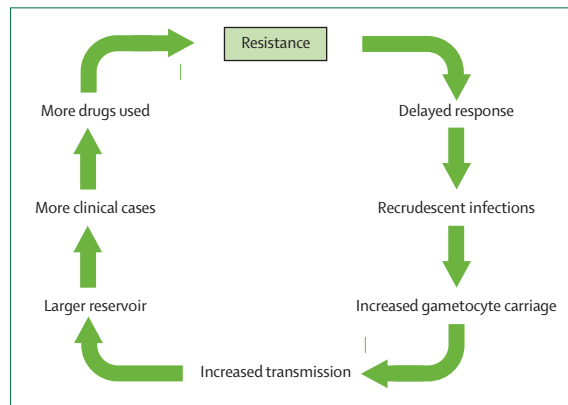
### Parasite resistance

For artemisinin to be effective, the drug has to access the parasites in the infected red blood cells for the time necessary for its normal action.<sup>26</sup> Parasite resistance is the ability of a parasite strain to survive or multiply despite the administration and absorption of a drug in doses equal to or higher than those usually recommended, but within limits of host tolerability.<sup>27</sup>

Parasite resistance to antimalarial drugs has previously started with a delay in the time taken to clear parasites (tolerance). As drug resistance progresses, recrudescence infections develop several weeks after treatment (figure 1). Although high-grade resistance has not yet been seen in southeast Asia, the artemisinin-resistant phenotype (delayed parasite clearance and treatment failure after several weeks) has been confirmed in several locations.<sup>21,22</sup>

In the past, high-grade parasite resistance has often been used interchangeably for both the parasite phenotype, as characterised *in vitro* by its confirmed ability to survive a threshold concentration of the drug in standard conditions of continuous culture, and in reference to therapeutic failure after the administration of a standard dose of a drug. Therapeutic failure is used in the WHO standard *in-vivo* test protocol.<sup>28</sup> Although the WHO protocol remains the gold standard for the update of malaria treatment policies, in most *in-vivo* tests serum drug concentrations are not usually measured and the reported therapeutic failure could be due to poor drug absorption or unusual pharmacokinetics. Therefore, *in-vitro* tests, molecular markers, or pharmacological studies might be needed to confirm whether treatment failure is caused by intrinsic resistance. The *in-vitro* definition reflects biological resistance to the drug, but true parasite resistance requires demonstration of the ability of parasites to survive *in vivo* in the presence of a usually adequate serum concentration of the drug or drugs.

Parasite resistance can also be detected by use of molecular markers; these have gained substantial prominence in the study of epidemiology of resistant malaria during the past two to three decades. After the molecular mechanisms for parasite resistance to the antifolates and chloroquine were elucidated, a proliferation of field studies followed that investigated the use of molecular markers for the detection of drug resistance in Africa.<sup>29–34</sup> However, the challenge now is that neither molecular markers nor *in-vitro* assays for artemisinin resistance are well established.<sup>35</sup> For example, *in-vitro* drug sensitivity tests of samples from Cambodia produced inconsistent results with respect to identification of the *in-vivo* resistant phenotype, and no molecular



**Figure 1: Evolution of antimalarial drug resistance**

Drug resistance first appears as delayed parasite clearance, which progresses to recrudescence infections and increased gametocyte carriage, which in turn leads to enhanced malaria transmission and an increased reservoir of infection. Increased numbers of infections leads to increases in drug use, which intensifies the selection pressure that drives drug resistance in the population.

markers have been reported in the genes (*pfmdr1*, *pfcr1*, and *pfserca*) thought to be associated with resistance to other antimalarials or putatively associated with artemisinin resistance.<sup>36</sup> Furthermore, the relation between resistant genotypes and most drug-resistant parasite phenotypes and clinical outcomes is not always straightforward.<sup>37,38</sup> Another difficulty is that the results from *in-vitro* assays after the use of *ex-vivo* techniques, such as SYBR-green-based protocols or isotope incorporation assays, are very difficult to compare between different sites because of differences in methods.

Parasite resistance for any antimalarial drug can emerge *de novo* through mutations and changes in gene expression that occur spontaneously in parasite populations without any selective pressure.<sup>39</sup> However, the establishment and subsequent rate of spread of resistance is dependent on drug selection pressure.<sup>40</sup> Drug use in much of rural Africa is strongly associated with the spread of resistant mutations in the parasite population.<sup>41</sup> Other factors, including host immunity, human migration, and malaria transmission intensity, play complex parts in the moderation of the emergence and geographical spread of resistance.<sup>42–49</sup> A repeatedly noted circumstance of the first emergence of drug-resistant *Plasmodium falciparum* was widespread inadequate dosing, often caused by poor quality medicines, self treatment, or by mass drug administration in the 1950s that often used subtherapeutic drug concentrations that create potent selection pressure for partly resistant parasites—the first evolutionary step towards complete resistance.<sup>50–55</sup>

In the past, drug-use patterns in Africa readily fostered partly resistant parasites, but high-grade resistance originated from Asia.<sup>56,57</sup> Drug-use patterns in Africa have changed substantially in the past decade and much investment has been made to improve availability of drugs

and provision of chemoprevention for vulnerable groups. De-novo emergence of resistance is most likely to occur in areas of low transmission, low immunity, and high parasite load in infected individuals, where a high proportion of infected people have symptoms and seek treatment. Africa is witnessing an epidemiological transition—some areas have very low transmission, and an increased likelihood of de-novo emergence of high-grade resistance exists in the continent. Nevertheless, since artemisinin-resistant parasites are already circulating in southeast Asia, the greatest danger to the efficacy of artemisinin-based combination therapy in Africa is from importation.

### An improved model for drug-resistance surveillance and response

#### Components of surveillance and response

In 1998, the WHO Regional Office for Africa adopted the integrated disease surveillance strategy, with the intention to create district-focused, action-oriented, and integrated surveillance systems.<sup>58,59</sup> Because of the importance of linking surveillance to public health action, the strategy was later renamed as integrated disease surveillance and response. Action thresholds were then defined for the common epidemic-prone infectious diseases, so that epidemic investigation and response could be triggered in settings where the thresholds were exceeded. Epidemics are substantial increases in the incidence of a disease in a population during a specific time.<sup>60</sup> Protocols for forecasting, early warning, and early detection of malaria epidemics have been developed to provide signals (with increasing precision), from long-term projections to real-time early detection.<sup>61–63</sup> Emerging drug-resistant malaria is an epidemic threat, and we believe that similar principles of forecasting, detection, and surveillance should therefore be applied. Such a surveillance model should have five connected components: forecasting; simplified, wide-coverage, early warning and detection systems; targeted, intensive clinical investigations in hotspots; routine sentinel surveillance at representative sites; and rigorous, continuous approaches to mitigation and containment.

#### Risk factor analysis to identify high-risk areas

Assessment of appropriate drug use, the frequency of drug–parasite contacts (which is dependent on malaria transmission intensity and drug pharmacodynamics), and movement of drug-resistant infected hosts to areas receptive to transmission have not been adequately defined numerically, but can be conceptualised as shown in figure 2. Furthermore, to quantify drug selective pressure, we also need improved ways to assess adherence and characterise the pharmacokinetic properties of the drugs in the target groups. Understanding of these interactions and their effect sizes is necessary for prioritisation and optimisation of future malaria drug-resistance surveillance in Africa. Endemic countries should embrace an empirical analysis of these risk factors, starting with historical data for the temporal and spatial emergence of resistance to

chloroquine and sulfadoxine–pyrimethamine, to examine the mapped rates of spread of drug resistance alleles in populations exposed to diverse treatments and malaria transmission intensities.<sup>64–66</sup> Assembling these data will be difficult, but not impossible. Africa is witnessing a renaissance of malaria transmission-intensity mapping, and data for drug-use patterns are expanding.

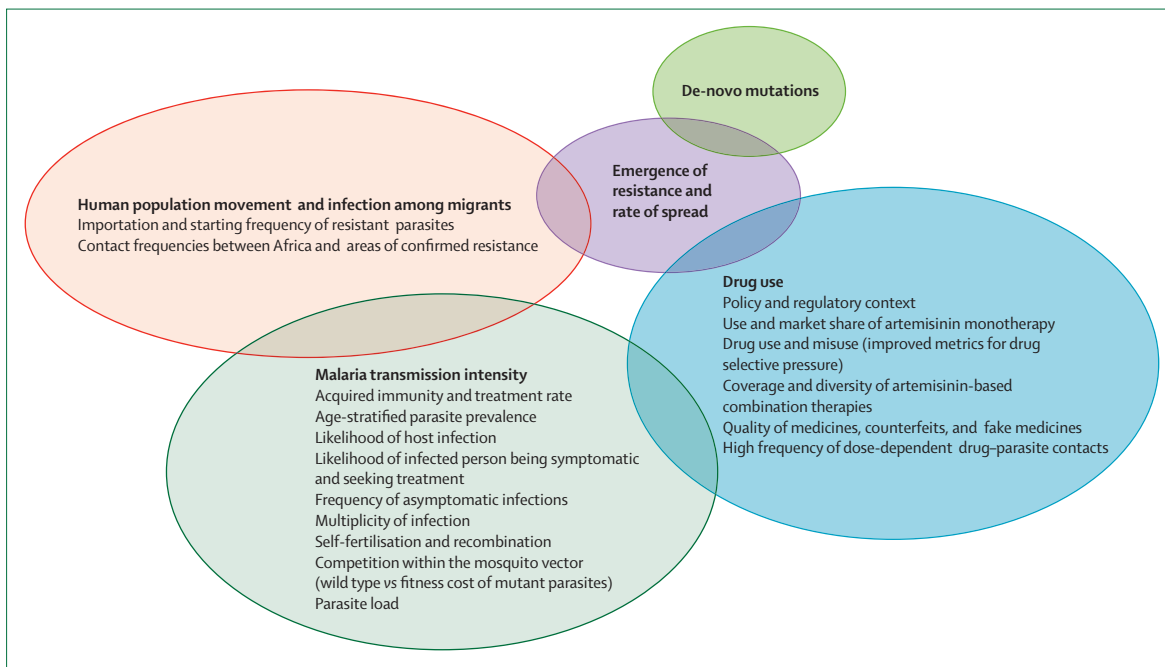
Geographical characterisation of antimalarial drug use is complex and demands innovative ways to quantify drug selective pressure and assess the quality of medicines on the market, use of medicines in different parts of the health sector, and policy and regulatory environments and how they have changed with time. This information has not been systematically collated in a way that would allow for straightforward analysis, and more work is needed to standardise metrics and assemble these data. New ways to model drug use based on the temporal and spatial diversity of artemisinin-based-combination-therapy use—as an indicator of the parasite biomass<sup>67</sup> that comes into contact with different artemisinin-based combinations—will be needed. Such developments will necessitate the combination of data for formal-sector and informal-sector drug use, and data for the use of poor quality drugs, such as fake antimalarials and artemisinin monotherapy.

Data for international, national, and subnational human population movements are either unavailable, difficult to obtain, or rarely used in the context of the spread of drug resistance. Large-scale international movement of human populations is key to the prediction of contact frequencies between Africa and areas of confirmed resistance (tier 1 areas as defined by the WHO global plan for artemisinin resistance containment).<sup>25</sup> Once artemisinin resistance emerges in Africa, monitoring its movement will be crucial. We need to be prepared with new and improved-resolution data for human population movement, with information from censuses, immigration services, and government departments with responsibility for population.

Analysis of the complex interplay of factors for emergence and spread of resistance (figure 2) might provide evidence of a confluence in areas that we might regard as hotspots, which could serve as sentinel sites for surveillance or be targeted for comprehensive clinical trials that include pharmacological measurement and molecular surveillance, if molecular markers for artemisinin resistance become well established.

#### Early warning and investigation

Slow parasite clearance (longer than 72 h), often called tolerance, was the first signal of emerging resistance to sulfadoxine–pyrimethamine.<sup>68</sup> Tolerance, and now resistance, has been confirmed for the artemisinin class of drugs in southeast Asia.<sup>21,22</sup> WHO recommends that 10% of patients remaining parasite-positive after 3 days should serve as a definition for suspected resistance.<sup>25</sup> A review<sup>69</sup> of parasite-clearance data (from more than 18 000 clinical trial patients), mostly from southeast Asia,



**Figure 2: Risk-factor analysis for emergence of drug-resistant malaria**

On the basis of the framework shown in this figure and our proposition that artemisinin resistance fits the definition of a public health emergency of international concern (in accordance with the revised international health regulations),<sup>24</sup> clear policies for travellers from areas of confirmed artemisinin resistance (tier 1 areas as defined by the WHO global plan for artemisinin resistance containment)<sup>25</sup> are urgently needed. Such policies could include the screening and treatment of all travellers from tier 1 areas to malaria-endemic regions of Africa with a highly effective gametocytocidal drug (such as primaquine) and revision of guidelines for prophylaxis.

suggests that the expected frequency of parasite positivity at 72 h after treatment with a 3 day artemisinin-based combination therapy regimen in patients with initial parasitaemia between 10 000 and 100 000 per  $\mu\text{L}$  of blood is less than 3%. This frequency could be regarded as a threshold for ruling out resistance. However, the proportion of patients who remain parasitaemic after 3 days will largely depend on initial parasitaemia and the minimum number of patients studied, since cases of slow parasite clearance can occur sporadically and at low frequency in any malaria setting.<sup>69</sup> These proposed action thresholds (the rule-out threshold of 3% and the WHO suspected-resistance threshold of 10%) need to be validated or modelled in settings in Africa where transmission of malaria is different, with very different age-specific patterns of host immunity. Research is therefore urgently needed to refine parasite clearance thresholds that might serve as early warning signals for artemisinin resistance in Africa.

WHO guidelines for malaria treatment recommend universal parasite-based diagnostic tests for all suspected cases of malaria.<sup>9</sup> Moving away from presumptive to parasite-based diagnosis and treatment offers an opportunity to validate early-warning methods that might be incorporated into routine health information systems. Operational research should be developed around simple models of detecting treatment failure, including institutional collection and reporting of post-treatment review

outcomes, if feasible. Additionally, health workers should strive to bring back increased numbers of patients for post-treatment review, with parasite-density measurements on days 2 and 3, since this will offer enhanced opportunities to measure parasite clearance. However, such follow-up is rare in most African settings, and innovative ways to promote this practice are needed. Improvement of patients' awareness about the need to confirm a malaria-free status after treatment might be achieved through the use of innovative approaches, such as mobile phone text messages with reminders to attend follow-up sessions.<sup>70,71</sup> Another metric worthy of increased attention during intensive malaria surveillance is the proportion of patients who need rescue therapy. These adaptations, together with new ways to document treatment successes, could form the basis of pragmatic early warning systems that allow further investigation. Such a system is achievable, as has been shown in the INDEPTH effectiveness and safety studies of anti-malarial drugs in Africa (INESS), a platform for multicentre, phase 4 trials in Tanzania and Ghana (B Ogotu, unpublished).

Early warning signals would prompt detailed investigations in addition to routine surveillance, including *in vivo* efficacy tests with parasite-density sampling every 6–8 h at locations where delayed parasite clearance is suspected. The drug regimens to investigate in such studies include 7 day artesunate compared with the first-line and second-line artemisinin-based combination

For more on the parasite clearance estimator see <http://www.wvwarn.org/research/parasite-clearance-estimator>

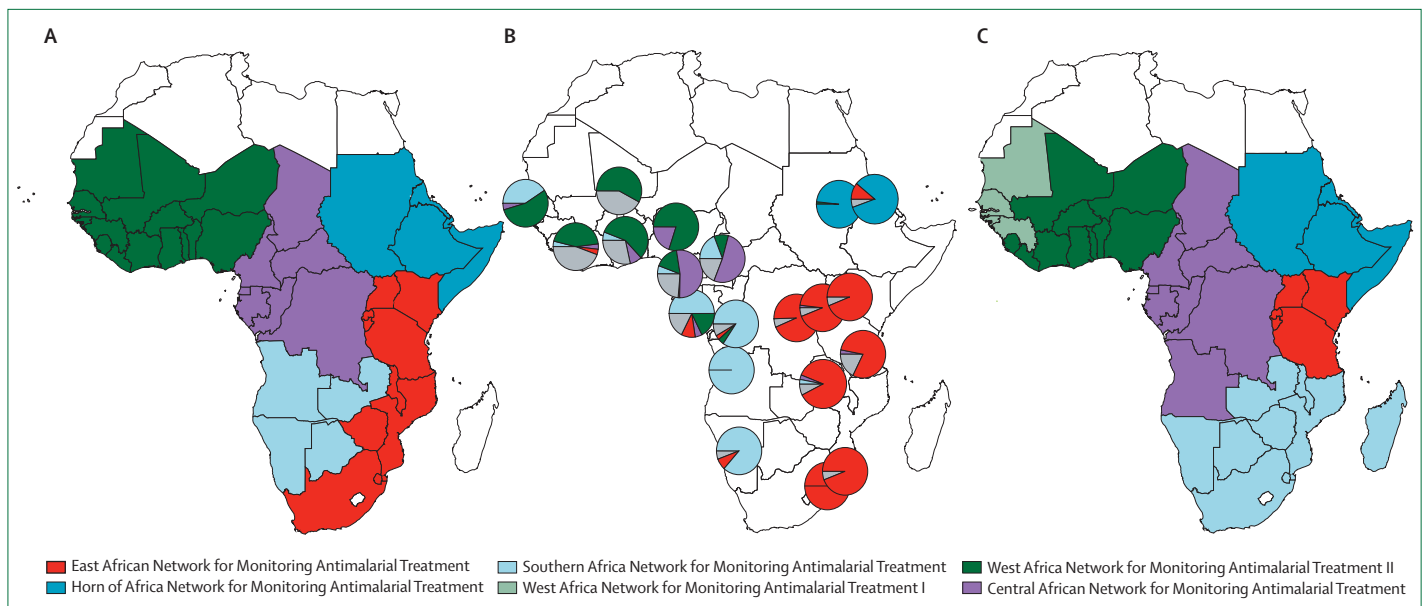
therapy regimens. The aims of such clinical studies would be to confirm whether there is delayed parasite clearance by use of standard measures such as the parasite clearance estimator or other standard measures of parasite clearance;<sup>72</sup> document the predictors and profile of parasite clearance, recrudescence, and rescue therapy in patients who present to clinics at the suspected epidemic locations; generate benchmarks for normal distribution of clinical response and deviations from it; initiate investigation of molecular markers linked to artemisinin resistance, once such markers have become available and have been validated, and initiate in-vitro testing (which could require systematic storage of samples to enable retrospective analysis of the emergence of resistant parasites once suitable molecular markers have been identified); and, if suggested from the investigations, initiate mitigation strategies such as local investigation of drug quality, awareness raising for clinical staff, and improved adherence strategies for patients.

### National and regional routine sentinel surveillance networks

During the era of failing monotherapy, regional and subregional networks were established to routinely monitor efficacy of antimalarial treatment in Africa. These networks were useful for the development of standard approaches, maintenance of cross-country quality assurance, and provision of a platform for dialogue between national malaria control programmes and regional research groups (with a focus on drug resistance and its monitoring) to effectively change

policy. For example, the East African Network for Monitoring Antimalarial Treatment, with support from the UK Department for International Development, established a standard system for monitoring of drug sensitivity between 1998 and 2004. More than 173 efficacy studies were done, at 40 representative sentinel sites, for eight different drugs or drug combinations. The data generated provided important evidence for the regional policy change from monotherapy to combination therapy. The networks were instrumental in bringing researchers and programme managers together with a collective sense of common purpose,<sup>73</sup> but after adoption of the policy in favour of artemisinin-based combination therapy, monitoring of drug efficacy became a reduced priority. Although the governance and management structures for most of the networks were large, led by individuals rather than institutions, and heavily dependent on donors, the objectives of these historical networks are still valid. The national groupings adopted by African surveillance networks have subsequently been vindicated by studies into malaria migration<sup>74</sup> and drug-resistance dispersal patterns (figure 3).<sup>65</sup> Results of both of these studies show the regional character of malaria populations and reflect the strong economic, political, and cultural linkages between countries. These networks offer a framework for surveillance and future management of artemisinin resistance in Africa that is both pragmatic and underpinned by good scientific evidence.

In November, 2011, delegates from national malaria control programmes and research institutions of the



**Figure 3: Malaria migration, drug resistance, and surveillance networks in Africa**

Malaria migration (A) and dispersal of drug resistance (B) both reflect the regional affiliations between neighbouring countries that were also apparent in the first surveillance networks (C). Countries connected by relatively high *Plasmodium falciparum* malaria migration can be divided into regional blocks (A). Lineages are each derived from one ancestral mutant. Relative abundance of resistant lineages in each population are shown by pie charts (B) in which each colour represents one resistant lineage. Country membership of previous African drug-resistance surveillance networks (C). (A) is reproduced from reference 74, by permission of *Proceedings of the National Academy of Sciences of the United States of America*. (B) is reproduced from reference 65, by permission of *PLoS Medicine*.

former East African Network for Monitoring Antimalarial Treatment countries (Burundi, Kenya, Rwanda, Tanzania, and Uganda), along with delegates from Ethiopia and the Democratic Republic of the Congo, and other partners in malaria control, met in Kigali, Rwanda. The meeting was organised by the WHO Global Malaria Programme and the Regional Office for Africa, and resolved, in what has been termed the Kigali Call for Action, to revive the regional drug-resistance surveillance network to coordinate implementation of rational and evidence-based malaria-treatment policies. The plan is to ensure that the network has a permanent secretariat hosted by a neutral institution with a regional presence. The proposed core objectives of the revived regional network were also agreed upon (panel).

Crucial to the success of drug-resistance surveillance is communication between national control programmes and research groups. Such communication was perceived as an important part of the East African Network for Monitoring Antimalarial Treatment before 2004, because it allowed for the rapid translation of research into policy. The changing technical needs of efficacy studies include the use of molecular techniques to distinguish recrudescence from new infections, which in most settings necessitates a technical partnership between regional or national research groups and ministry of health staff, either as a long-term sustained relationship or as a provisional step towards building modern epidemiological competencies within ministries of health. New methods are needed for forecasting, early warning, and detection of artemisinin resistance, and these must be developed in partnership with various stakeholders and experiences must be shared across a network of countries. Detection of emergent artemisinin resistance will inevitably need complex studies, new techniques, and improved collaboration globally, regionally, and nationally and between universities, research institutes, and ministries of health.

Many stakeholders in Africa agree that malaria drug-resistance surveillance should be a long-term, national commitment with common national and international goals.<sup>75</sup> Regional activities should be coordinated by a central body, located at a regional institution so as to provide regional ownership. Furthermore, investment in technology to enable increased numbers of studies with pharmacokinetic and pharmacodynamic components is needed. Such investment will need a long-term vision and should be integrated with capacity improvements, particularly of human resource, diagnostic, and infrastructural capacities. Regional priorities could include: articulation of surveillance strategies for risk factors for resistance and for the monitoring of drug resistance and drug quality; formulation of a capacity building plan; development of a resource mobilisation strategy and a mechanism for network coordination (preferably a light steering committee); standardisation and harmonisation of data collection, collation,

#### Panel: Objectives of the revived East African Network for Monitoring Antimalarial Treatment

- Rationalise the distribution of surveillance sites on the basis of up-to-date malaria risk mapping
- Do regular standardised therapeutic efficacy studies and encourage capacity building for antimalarial drug-resistance surveillance
- Establish a mechanism for exchange of data, sharing of expertise and best practices, and dissemination of results of therapeutic efficacy studies and their implications
- Identify and promote important research, support the collation of research evidence, and disseminate results to inform policy and practice
- Collectively address transnational issues and harmonise efforts within and between countries
- Collaborate with other regional and subregional groups and wider global networks

management, and analysis; collaborative phase 4 clinical trials; and knowledge management and regional analytical projects.

Artemisinin resistance in Africa is initially likely to occur as a rare event, and individual patient-level pooled analysis across several sites could greatly increase the chances of detection. This method is frequently used in epidemiology when single studies are too small to allow any definite conclusion. In an endeavour to encourage pooled analysis, the Worldwide Antimalarial Resistance Network has called for the formation of study groups.

Five such study groups have been formed so far: the artemisinin-based combination therapy Africa baseline study group (to collect and collate baseline information about parasitological response to artemisinin-based combination therapies in Africa); the artemisinin-based combination therapy dosing impact study group (to assess the effect of dosing strategies on risk of treatment failure in patients given recommended artemisinin-based combination therapies); the amodiaquine pharmacokinetic and pharmacodynamic study group (to investigate how often treatment failures are attributable to inadequate drug exposure rather than drug resistance); the artesunate–amodiaquine and artemether–lumefantrine molecular marker study group (to investigate candidate molecular markers for prediction of clinical outcomes for artemisinin-based combination therapies, with lumefantrine and amodiaquine as the partner drugs); and finally, a pooled analysis of parasite clearance profiles is under way for the few available studies that have frequent (every 6–8 h) parasite-density sampling. However, individual patient-level pooled analysis will not be possible unless scientists share data. As recommended by the key leading health agencies,<sup>76</sup> all stakeholders (donors, researchers, national control programmes, and surveillance networks) should support data sharing.

For more on study groups for pooled analyses see <http://www.warn.org/partnerships/study-groups>

## Conclusions

Although we currently have no evidence that artemisinin resistance has emerged in Africa, routine monitoring and surveillance, as recommended by the WHO global plan for artemisinin resistance containment, needs substantial strengthening, since we do not know where or when artemisinin resistance will first emerge in the continent. Whereas chloroquine resistance, which emerged in only a few independent locations, took 20 years to spread from its site of origin in southeast Asia to east Africa,<sup>77,78</sup> increased population movement between Asia and Africa is likely to shorten this time period. Worryingly, if artemisinin resistance has the capacity to emerge de novo at several locations, wherever the drug is used (as with low-grade resistance to pyrimethamine), then containment efforts will be almost impossible.

In the failing monotherapy era, the practice was to routinely do conventional efficacy studies at representative sentinel sites every 2 years. Such routine studies are best practice and should be done continuously. Furthermore, Africa urgently needs good quality clinical trials, with standardised study design and data collection, and frequent parasite-density sampling—preferably every 6–8 h—to provide baseline benchmarks for the parasite-clearance profile of artemisinin monotherapy and artemisinin-based combination therapy. However, such intensive studies are expensive and can only be done at a few sites, which could be inadequate for the detection of the subtle signs of emergent artemisinin resistance, which will likely necessitate wide-coverage surveillance. The improved surveillance model that we propose would allow the strengthening of routine health information systems and would increase the value of surveillance. It would also allow the targeting of additional clinical investigations to complement sentinel surveillance, on the basis of either analysis of surrogate markers or risk factors, or pragmatic early warning methods.

### Contributors

AOT, RWS, and UD'A shaped the ideas and approaches proposed, and drafted and revised the report. CK contributed to writing the report and organised and participated in the meeting in Kigali, Rwanda on efforts to revive the East African Network for Monitoring Antimalarial Treatment. EJ, AN, BO, and JL reviewed the report and were part of the Kigali meeting. MM, WFM, and PJG reviewed the report. CR took part in the original discussions of the ideas proposed, helped to revise the report, and contributed to figure 3.

### Conflicts of interest

AOT and RWS have been invited speakers at scientific symposia organised by Novartis, Pfizer, Sigma Tau, and Sanofi. AOT has received a research grant from Sanofi and RWS has received research grants from Pfizer and Novartis. RWS and AOT have been co-chairpersons of best-practice workshops in regional and national malaria control programmes sponsored by Novartis, for which they received honoraria. UD'A has been an invited speaker at symposia organised by Sigma Tau and Novartis, and has received a research grant from Sigma Tau. BO has been an invited speaker at scientific symposia organised by Novartis, Sanofi, and Pfizer and has received research grants from the same companies. All the other authors declare that they have no conflicts of interest.

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