Published in final edited form as:
Lancet Infect Dis. 2012 November ; 12(11): 888–896. doi:10.1016/S1473-3099(12)70241-4.

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

Ambrose O Talisuna, PhD,
Malaria Public Health and Epidemiology Group, University of Oxford and KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya; Centre for Tropical Medicine, University of Oxford, Oxford, UK; Worldwide Antimalarial Resistance Network, Oxford, UK

Corine Karema,
Malaria and Other Parasitic Diseases Division, Rwanda Biomedical Center, Ministry of Health, Kigali, Rwanda

Bernhards Ogutu, PhD,
Walter Reed Project, Kenya Medical Research Institute, Kisumu, Kenya

Elizabeth Juma, MD,
Kenya Medical Research Institute, Nairobi, Kenya

John Logedi, MD,
Division of Malaria Control, Ministry of Health, Nairobi, Kenya

Andrew Nyandigisi, BPharm,
Division of Malaria Control, Ministry of Health, Nairobi, Kenya

Modest Mulenga, PhD,
Tropical Disease Research Centre, Ndola, Zambia

Wilfred F Mbacham, ScD,
Biotechnology Centre, University of Yaoundé I, Yaoundé, Cameroon

Cally Roper, PhD,
Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK

Correspondence to: Dr Ambrose O Talisuna, Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford OX3 7LJ, UK ambrose.talisuna@wwarn.org.

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. 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.

Conflicts of interest:
All the other authors declare that they have no conflicts of interest.

For more on the **parasite clearance estimator** see http://www.wwarn.org/research/parasite-clearance-estimator

For more on **study groups for pooled analyses** see http://www.wwarn.org/partnerships/study-groups

Europe PMC Funders Author Manuscripts

Philippe J Guerin, PhD,
Centre for Tropical Medicine, University of Oxford, Oxford, UK; Worldwide Antimalarial Resistance Network, Oxford, UK

Prof Umberto D'Alessandro, PhD, and
Medical Research Council Unit, Fajara, The Gambia; Institute of Tropical Medicine, Antwerp, Belgium

Prof Robert W Snow, FMedSci
Malaria Public Health and Epidemiology Group, University of Oxford and KEMRI-Wellcome Trust Research Programme, Nairobi, Kenya; Centre for Tropical Medicine, University of Oxford, Oxford, UK

Abstract

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.[1,2] 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,[3-5] which led to a public health disaster as earlier predicted.[6] To tackle the threat of drug-resistant malaria, WHO in 2001 recommended the adoption of artemisinin-based combination therapy for treatment of uncomplicated malaria.[7] However, the adoption and implementation of this policy recommendation was slow until, in 2004, research and control communities called for urgent action.[8] All sub-Saharan African countries now recommend artemisinin-based combination therapy as the first-line regimen for uncomplicated malaria.[9] 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.[10-17]

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.[18] 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.[19,20] For example, the study designs used

Europe PMC Funders Author Manuscripts

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.[21-23] 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.[24] 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.[24]

One of the pillars of WHO's global plan for artemisinin resistance containment is monitoring and surveillance to assess the threat of emerging resistance.[25] 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.[26] 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.[27]

Parasite resistance to antimalarial drugs has previously started with a delay in the time taken to clear parasites (tolerance). As drug resistance progresses, recrudescent 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.[21,22]

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.[28] 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.[29-34] However, the challenge now is that neither molecular markers nor in-vitro assays for artemisinin resistance are well established.[35] 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 markers have been reported in the genes (*pfmdr1, pfcrt*, and *pfserca*) thought to be associated with resistance to other antimalarials or putatively associated with artemisinin resistance.[36] Furthermore, the relation between resistant genotypes and most drug-resistant parasite phenotypes and clinical outcomes is not always straightforward.[37,38] 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.[39] However, the establishment and subsequent rate of spread of resistance is dependent on drug selection pressure.[40] Drug use in much of rural Africa is strongly associated with the spread of resistant mutations in the parasite population.[41] 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.[42-49] 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 suboptimum doses. All of these practices can lead to subtherapeutic drug concentrations that create potent selection pressure for partly resistant parasites—the first evolutionary step towards complete resistance.[50-55]

In the past, drug-use patterns in Africa readily fostered partly resistant parasites, but high-grade resistance originated from Asia.[56,57] 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.[58,59] 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.[60] 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.[61-63] 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.[64-66] 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[67] 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).[25] 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.[68] Tolerance, and now resistance, has been confirmed for the artemisinin class of drugs in southeast Asia.[21,22] WHO recommends that 10% of patients remaining parasite-positive after 3 days should serve as a definition for suspected resistance.[25] A review[69] of parasite-clearance data (from more than 18 000 clinical trial patients), mostly from southeast Asia, 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 μL 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.[69] 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.[9] 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.[70,71] 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 Ogutu, 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 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;[72] 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,[73] 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[74] and drug-resistance dispersal patterns (figure 3).[65] 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 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.[75] 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, 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,[76] all stakeholders (donors, researchers, national control programmes, and surveillance networks) should support data sharing.

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,[77,78] 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.

Acknowledgments

AOT is supported by the Worldwide Antimalarial Resistance Network through a grant from the Bill & Melinda Gates Foundation (grant number 48807.01). RWS is supported by the Wellcome Trust as Principal Research Fellow (grant number 079080). AOT and RWS acknowledge support from the Wellcome Trust core grant number 092654/Z/10/A.

References

1. Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. Nature. 2005; 434:214–17. [PubMed: 15759000]
2. WHO. World Malaria Report 2011. World Health Organization; Geneva: 2011. http://www.who.int/malaria/world_malaria_report_2011/9789241564403_eng.pdf
3. Bloland PB, Lackritz EM, Kazembe PN, Were JB, Steketee R, Campbell CC. Beyond chloroquine: implications of drug resistance for evaluating malaria therapy efficacy and treatment policy in Africa. J Infect Dis. 1993; 167:932–37. [PubMed: 8450258]
4. East African Network for Monitoring Antimalarial Treatment (EANMAT). The efficacy of antimalarial monotherapies, sulphadoxine-pyrimethamine and amodiaquine in East Africa: implications for sub-regional policy. Trop Med Int Health. 2003; 8:860–67. [PubMed: 14516296]
5. Talisuna AO, Bloland P, D'Alessandro U. History, dynamics and public health importance of malaria parasite resistance. Clin Microbiol Rev. 2004; 17:235–54. [PubMed: 14726463]
6. White NJ, Nosten F, Looareesuwan S, et al. Averting a malaria disaster. Lancet. 1999; 353:1965–67. [PubMed: 10371589]
7. WHO. Antimalarial drug combination therapy—report of a WHO technical consultation, 4–5 April 2001. World Health Organization; Geneva: 2001. http://www.who.int/malaria/publications/atoz/who_cds_rbm_2001_35/en/index.html
8. Attaran A, Barnes KI, Curtis C, et al. WHO, the Global Fund, and medical malpractice in malaria treatment. Lancet. 2004; 363:237–40. [PubMed: 14738799]
9. WHO. Guidelines for the treatment of malaria. 2nd edn. World Health Organization; Geneva: 2010. http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html
10. Williams HA, Durrheim D, Shretta R. The process of changing national malaria treatment policy: lessons from country-level studies. Health Policy Plan. 2004; 19:356–70. [PubMed: 15459161]
11. Zurovac D, Ndhlovu M, Rowe AK, Hamer DH, Thea DM, Snow RW. Treatment of paediatric malaria during a period of drug transition to artemether-lumefantrine in Zambia: cross sectional study. BMJ. 2005; 331:734. [PubMed: 16195289]
12. Malik EM, Mohamed TA, Elmardi KA, et al. From chloroquine to artemisinin-based combination therapy: the Sudanese experience. Malar J. 2006; 5:65. [PubMed: 16879742]

13. Mulligan JA, Mandike R, Palmer N, et al. The costs of changing national policy: lessons from malaria treatment policy guidelines in Tanzania. Trop Med Int Health. 2006; 11:452–61. [PubMed: 16553928]
14. Amin AA, Zurovac D, Kangwana BB, et al. The challenges of changing national malaria drug policy to artemisinin-based combinations in Kenya. Malar J. 2007; 6:72. [PubMed: 17535417]
15. Sipilanyambe N, Simon JL, Chanda P, Olumese P, Snow RW, Hamer DH. From chloroquine to artemether-lumefantrine: the process of drug policy change in Zambia. Malar J. 2008; 7:25. [PubMed: 18230140]
16. Zurovac D, Tibenderana JK, Nankabirwa J, et al. Malaria case-management under artemether-lumefantrine treatment policy in Uganda. Malar J. 2008; 7:181. [PubMed: 18803833]
17. Tren R, Hess K, Bate R. Drug procurement, the Global Fund and misguided competition policies. Malar J. 2009; 8:305. [PubMed: 20028536]
18. Yeung S, Pongtavornpinyo W, Hastings IM, Mills AJ, White NJ. Antimalarial drug resistance, artemisinin-based combination therapy, and the contribution of modeling to elucidating policy choices. Am J Trop Med Hyg. 2004; 71:179–86. [PubMed: 15331836]
19. Lemeshow S, Taber S. Lot quality assurance sampling: single- and double-sampling plans. World Health Stat Q. 1991; 44:115–32. [PubMed: 1949879]
20. WHO. Assessment of therapeutic efficacy of antimalarial drugs for uncomplicated malaria in areas with intense transmission (WHO/MAL/96.1077). World Health Organization; Geneva and Brazzaville: 1996.
21. Dondorp AM, Yeung S, White L, et al. Artemisinin resistance: current status and scenarios for containment. Nat Rev Microbiol. 2010; 8:272–80. [PubMed: 20208550]
22. Phyo AP, Nkhoma S, Stepniewska K, et al. Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study. Lancet. 2012; 379:1960–66. [PubMed: 22484134]
23. Cheeseman IH, Miller BA, Nair S, et al. A major genome region underlying artemisinin resistance in malaria. Science. 2012; 336:79–82. [PubMed: 22491853]
24. WHO. International Health Regulations (2005). 2nd edn. World Health Organization; Geneva: 2008. http://whqlibdoc.who.int/publications/2008/9789241580410_eng.pdf
25. WHO. Global plan for artemisinin resistance containment (GPARC). World Health Organization; Geneva: 2011. http://www.who.int/entity/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf
26. Bruce-Chwatt, LJ.; Black, RH.; Canfield, CJ.; Clyde, DF.; Peters, W.; Wernsdorfer, W. Chemotherapy of malaria. 2nd edn. World Health Organization; Geneva: 1986. WHO monograph series 27
27. WHO. Resistance of malaria parasites to drugs—report of a WHO scientific group (technical report series 296). World Health Organization; Geneva: 1965.
28. WHO. Assessment and monitoring of antimalarial drug efficacy for the treatment of uncomplicated falciparum malaria (WHO/HTM/RBM/2003.50). World Health Organization; Geneva: 2003.
29. Plowe CV, Djimde A, Wellems TE, Diop S, Kouriba B, Doumbo OK. Community pyrimethamine–sulfadoxine use and prevalence of resistant *Plasmodium falciparum* genotypes in Mali: a model for deterring resistance. Am J Trop Med Hyg. 1996; 55:467–71. [PubMed: 8940973]
30. Nzila AM, Nduati E, Mberu EK, et al. Molecular evidence of greater selective pressure for drug resistance exerted by the long-acting antifolate pyrimethamine/sulfadoxine compared with the shorter-acting chlorproguanil/dapsone on Kenyan *Plasmodium falciparum*. J Infect Dis. 2000; 181:2023–28. [PubMed: 10837185]
31. Djimde A, Doumbo OK, Steketee RW, Plowe CV. Application of a molecular marker for surveillance of chloroquine-resistant falciparum malaria. Lancet. 2001; 358:890–91. [PubMed: 11567708]
32. Dorsey G, Kamya MR, Singh A, Rosenthal PJ. Polymorphisms in the *Plasmodium falciparum* pfcrt and pfmdr-1 genes and clinical response to chloroquine in Kampala, Uganda. J Infect Dis. 2001; 183:1417–20. [PubMed: 11294677]

33. Kublin JG, Dzinjalamala FK, Kamwendo DD, et al. Molecular markers for failure of sulfadoxine–pyrimethamine and chlorproguanil-dapsone treatment of *Plasmodium falciparum* malaria. J Infect Dis. 2002; 185:380–88. [PubMed: 11807721]
34. Talisuna AO, Langi P, Mutabingwa TK, et al. Population-based validation of DHFR gene mutations for the prediction of sulfadoxine–pyrimethamine resistance in Uganda. Trans R Soc Trop Med Hyg. 2003; 97:338–42. [PubMed: 15228255]
35. Imwong M, Dondorp AM, Nosten F, et al. Exploring the contribution of candidate genes to artemisinin resistance in *Plasmodium falciparum*. Antimicrob Agents Chemother. 2010; 54:2886–92. [PubMed: 20421395]
36. Dondorp AM, Nosten F, Yi P, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. N Engl J Med. 2009; 361:455–67. [PubMed: 19641202]
37. Wellems TE, Panton LJ, Gluzman IY, et al. Chloroquine resistance not linked to mdr-like genes in a *Plasmodium falciparum* cross. Nature. 1990; 345:253–55. [PubMed: 1970614]
38. Denis MB, Tsuyuoka R, Lim P, et al. Efficacy of artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in northwest Cambodia. Trop Med Int Health. 2006; 11:1800–07. [PubMed: 17176344]
39. White NJ, Pongtavornpinyo W. The de novo selection of drug-resistant malaria parasites. Proc Biol Sci. 2003; 270:545–54. [PubMed: 12641911]
40. Wernsdorfer WH. Epidemiology of drug resistance in malaria. Acta Trop. 1994; 56:143–56. [PubMed: 8203301]
41. Malisa AL, Pearce RJ, Abdulla S, et al. Drug coverage in treatment of malaria and the consequences for resistance evolution—evidence from the use of sulphadoxine/pyrimethamine. Malar J. 2010; 9:190. [PubMed: 20602754]
42. Hastings IM, D'Alessandro U. Modelling a predictable disaster: the rise and spread of drug-resistant malaria. Parasitol Today. 2000; 16:340–47. [PubMed: 10900482]
43. Hastings IM, Watkins WM, White NJ. The evolution of drug-resistant malaria: the role of drug elimination half-life. Philos Trans R Soc Lond B Biol Sci. 2002; 357:505–19. [PubMed: 12028788]
44. Kublin JG, Cortese JF, Njunju EM, et al. Re-emergence of chloroquine-sensitive *Plasmodium falciparum* malaria after cessation of chloroquine use in Malawi. J Infect Dis. 2003; 187:1870–75. [PubMed: 12792863]
45. Nzila AM, Mberu EK, Sulo J, et al. Towards an understanding of the mechanism of pyrimethamine–sulfadoxine resistance in *Plasmodium falciparum*: genotyping of dihydrofolate reductase and dihydropteroate synthase of Kenyan parasites. Antimicrob Agents Chemother. 2000; 44:991–96. [PubMed: 10722502]
46. Mharakurwa S. *Plasmodium falciparum* transmission rate and selection for drug resistance: a vexed association or a key to successful control? Int J Parasitol. 2004; 34:1483–87. [PubMed: 15582525]
47. Talisuna AO, Okello PE, Erhart A, Coosemans M, D'Alessandro U. Intensity of malaria transmission and the spread of *Plasmodium falciparum* resistant malaria: a review of epidemiologic field evidence. Am J Trop Med Hyg. 2007; 77:170–80. [PubMed: 18165490]
48. Laufer MK, Takala-Harrison S, Dzinjalamala FK, Stine OC, Taylor TE, Plowe CVJ. Return of chloroquine-susceptible falciparum malaria in Malawi was a re-expansion of diverse susceptible parasites. J Infect Dis. 2010; 202:801–08. [PubMed: 20662717]
49. Lynch C, Roper C. The transit phase of migration: circulation of malaria and its multidrug-resistant forms in Africa. PLoS Med. 2011; 8:e1001040. [PubMed: 21655316]
50. Clyde DF. Drug resistance of malaria parasites in Tanzania. East Afr Med J. 1966; 43:405–08. [PubMed: 5341684]
51. Payne D. Did medicated salt hasten the spread of chloroquine resistance in *Plasmodium falciparum*. Parasitol Today. 1988; 4:112–15. [PubMed: 15463062]
52. Dondorp AM, Newton PN, Mayxay M, et al. Fake antimalarials in southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. Trop Med Int Health. 2004; 12:1241–46. [PubMed: 15598255]

53. Newton PN, McGready R, Fernandez F, et al. Manslaughter by fake artesunate in Asia—will Africa be next? PLoS Med. 2006; 3:e197. [PubMed: 16752952]
54. Gardella F, Assi S, Simon F, Bogreau H, et al. Antimalarial drug use in general populations of tropical Africa. Malar J. 2008; 7:124. [PubMed: 18611279]
55. Hodel EM, Genton B, Zanolari B, et al. Residual antimalarial concentrations before treatment in patients with malaria from Cambodia: indication of drug pressure. J Infect Dis. 2010; 202:1088–94. [PubMed: 20726764]
56. Wootton JC, Feng X, Ferdig MT, et al. Genetic diversity and chloroquine selective sweeps in *Plasmodium falciparum*. Nature. 2002; 418:320–23. [PubMed: 12124623]
57. Roper C, Pearce R, Nair S, Sharp B, Nosten F, Anderson T. Intercontinental spread of pyrimethamine-resistant malaria. Science. 2004; 305:1124. [PubMed: 15326348]
58. WHO Regional Office for Africa. Integrated disease surveillance strategy—a Regional strategy for communicable diseases 1999–2003. World Health Organization Regional Office for Africa; Harare: 1999.
59. Nsubuga P, Brown WG, Groseclose SL, et al. Implementing integrated disease surveillance and response: four African countries' experience, 1998–2005. Glob Public Health. 2009; 13:1–17.
60. Nájera JA. Prevention and control of malaria epidemics. Parassitologia. 1999; 41:339–47. [PubMed: 10697881]
61. Teklehaimanot HD, Schwartz J, Teklehaimanot A, Lipsitch M. Weather-based prediction of *Plasmodium falciparum* malaria in epidemic-prone regions of Ethiopia II. Weather-based prediction systems perform comparably to early detection systems in identifying times for interventions. Malar J. 2004; 3:44. [PubMed: 15555061]
62. Thomson MC, Doblas-Reyes FJ, Mason SJ, et al. Malaria early warnings based on seasonal climate forecasts from multi-model ensembles. Nature. 2006; 439:576–79. [PubMed: 16452977]
63. Cox J, Abeku T, Beard J, et al. Detecting epidemic malaria, Uganda. Emerg Infect Dis. 2007; 13:779–80. [PubMed: 18044039]
64. Frosch AE, Venkatesan M, Laufer MK. Patterns of chloroquine use and resistance in sub-Saharan Africa: a systematic review of household survey and molecular data. Malar J. 2011; 10:116. [PubMed: 21554692]
65. Pearce RJ, Pota H, Evehe MS, Bâ el-H, et al. Multiple origins and regional dispersal of resistant dhps in African *Plasmodium falciparum* malaria. PLoS Med. 2009; 6:e1000055. [PubMed: 19365539]
66. Naidoo I, Roper C. Following the path of most resistance: dhps K540E dispersal in African *Plasmodium falciparum*. Trends Parasitol. 2010; 26:447–56. [PubMed: 20728060]
67. Van Geertruyden J-P, Menten J, Colebunders R, Korenromp E, D'Alessandro U. The impact of HIV-1 on the malaria parasite biomass in adults in sub-Saharan Africa contributes to the emergence of antimalarial drug resistance. Malar J. 2008; 7:134. [PubMed: 18647387]
68. Watkins WM, Mberu EK, Winstanley PA, Plowe CV. The efficacy of antifolate antimalarial combinations in Africa: a predictive model based on pharmacodynamic and pharmacokinetic analyses. Parasitol Today. 1997; 13:459–64. [PubMed: 15275132]
69. Stepniewska K, Ashley E, Lee SJ, et al. In vivo parasitological measures of artemisinin susceptibility. J Infect Dis. 2010; 201:570–79. [PubMed: 20085495]
70. Zurovac D, Sudoi RK, Akhwale WS, et al. The effect of mobile phone text-message reminders on Kenyan health workers' adherence to malaria treatment guidelines: a cluster randomised trial. Lancet. 2011; 378:795–803. [PubMed: 21820166]
71. Zurovac D, Talisuna AO, Snow RW. Mobile phone text messaging: tool for malaria control in Africa. PLoS Med. 2012; 9:e1001176. [PubMed: 22363212]
72. Flegg JA, Guerin PJ, White NJ, Stepniewska K. Standardizing the measurement of parasite clearance in falciparum malaria: the parasite clearance estimator. Malar J. 2011; 10:339. [PubMed: 22074219]
73. East African Network for Monitoring Antimalarial Treatment (EANMAT). Monitoring antimalarial drug resistance within National Malaria Control Programmes: the EANMAT experience. Trop Med Int Health. 2001; 6:891–98. [PubMed: 11703843]

74. Tatem AJ, Smith DL. International population movements and regional *Plasmodium falciparum* malaria elimination strategies. Proc Natl Acad Sci USA. 2010; 107:12222–27. [PubMed: 20566870]

75. Eastern African scientists pledge immediate action to confront the threat of malaria drug resistance; Antimalarial Resistance Stakeholders Meeting; May 25, 2012; press statementhttps://www.wwarn.org/sites/default/files/AntimalarialStakeholders-MeetingPressStatement250512.pdf

76. Chan M, Kazatchkine M, Lob-Levyt J, et al. Meeting the demand for results and accountability: a call for action on health data from eight global health agencies. PLoS Med. 2010; 7:e1000223. [PubMed: 20126260]

77. Harinasuta T, Suntharasamai P, Viravan C. Chloroquine-resistant falciparum malaria in Thailand. Lancet. 1965; 286:657–60. [PubMed: 4158213]

78. Campbell CC, Chin W, Collins WE, Teutsch SM, Moss DM. Chloroquine-resistant *Plasmodium falciparum* from east Africa: cultivation and drug sensitivity of the Tanzanian I/CDC strain from an American tourist. Lancet. 1979; 314:1151–54. [PubMed: 91887]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

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

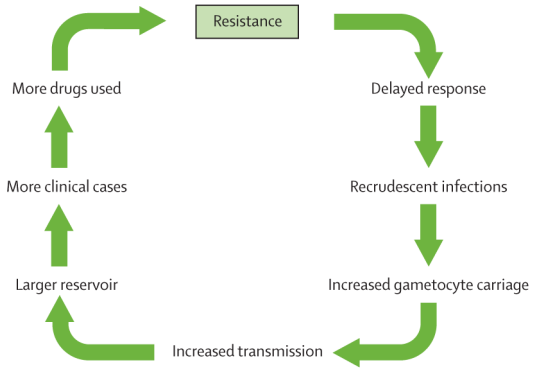

Figure 1. Evolution of antimalarial drug resistance

Drug resistance first appears as delayed parasite clearance, which progresses to recrudescent 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.

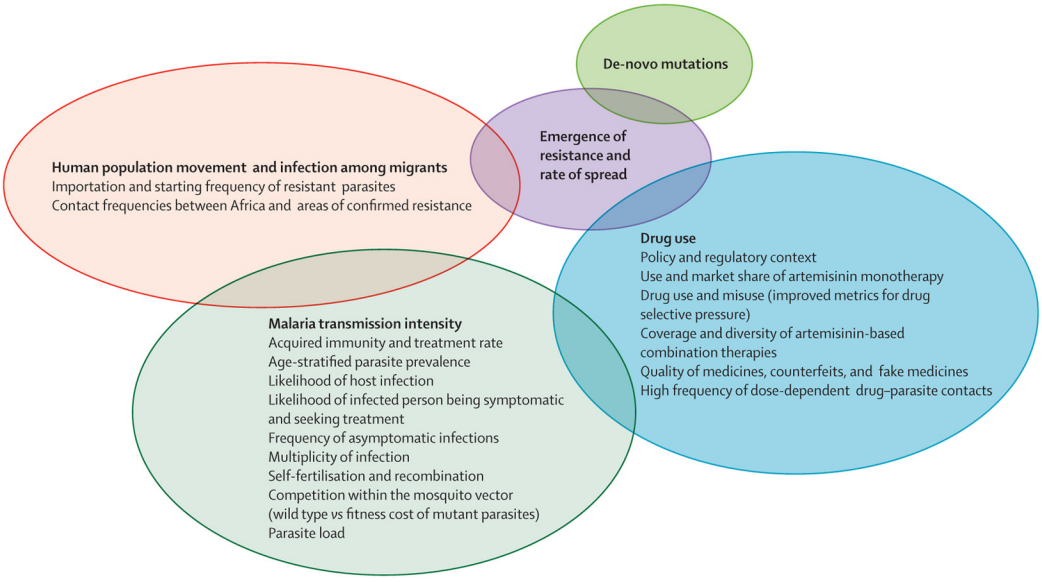

Figure 2. Risk-factor analysis for emergence of drug-resistant malaria

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),[24] clear policies for travellers from areas of confirmed artemisinin resistance (tier 1 areas as defined by the WHO global plan for artemisinin resistance containment)[25] 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.

Europe PMC Funders Author Manuscripts

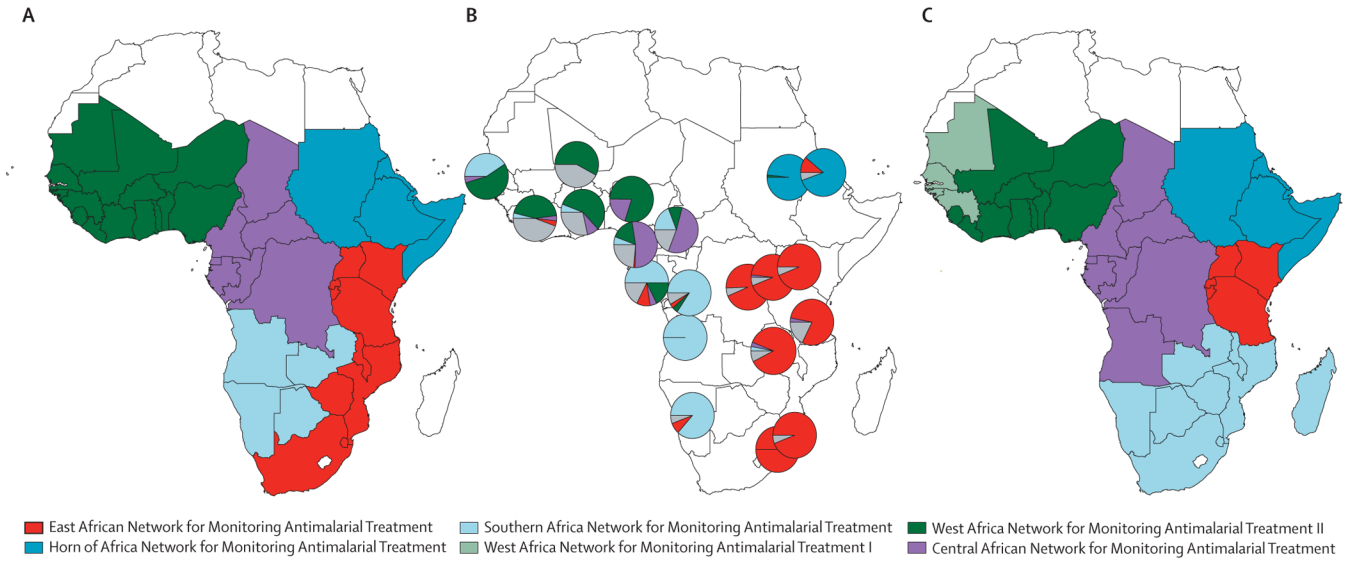

Figure 3. Malaria migration, drug resistance, and surveillance networks in Africa

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*.

Europe PMC Funders Author Manuscripts