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Review

Trends in antimalarial drug deployment in sub-Saharan Africa

P. B. Bloland*, S. P. Kachur and H. A. Williams

Malaria Epidemiology Branch, Division of Parasitic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30341, USA

* Author for correspondence (e-mail: Pbloland@cdc.gov)

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Summary

Antimalarial drug resistance is forcing newly developed pharmaceuticals into widespread use at an accelerating pace. To have the greatest public health impact, new pharmaceuticals will need to be deployed effectively in sub-Saharan Africa. Achieving effective antimalarial drug deployment over the short- to medium-term will require an appreciation of how drugs are currently used in Africa and the development of innovative approaches to optimize that use. Over the long-term, fundamental changes in the way that drugs are deployed will probably be required. There are many new strategies and initiatives that, to a greater or lesser degree, will influence how drugs are used. These influences may have a positive or negative effect on reducing malaria morbidity and mortality. The concept of analyzing and monitoring programmatic effectiveness allows for a more holistic understanding of these influences and allows for more unbiased, evidence-based decision making related to drug policy and deployment.

Key words: antimalarial drug resistance, Africa, malaria, drug deployment, treatment effectiveness.

Introduction

Antimalarial drug resistance is forcing newly developed pharmaceuticals into widespread use at an accelerating pace. While other regions of the world may have greater problems with multi-drug resistant malaria, the public health threat of drug resistance is greatest in Africa, which bears the bulk of the burden of malaria. While newly developed antimalarial drugs would probably be useful in any of the malarious regions of the world, to have any substantial global public health impact, new pharmaceuticals will need to be deployed effectively in sub-Saharan Africa. In addition, the particular intensity of malaria transmission in Africa, coupled with severely constrained health delivery systems that prevail in the continent, present unique challenges to effective deployment of these new treatments.

Achieving effective antimalarial drug deployment over the short- to medium-term will require an appreciation of how drugs are currently used in the real world and development of innovative approaches to optimize that use. Over the long term, however, effectively responding to antimalarial drug resistance will come to a choice between maintaining business as usual (which would include an on-going need for rapidly developing and deploying new malaria treatments in order to keep up with, if not stay ahead of, developing drug resistance) or making fundamental changes in how drugs against malaria are used in practice, in order to sustain their useful life spans as long as possible.

Despite malaria being an illness that claims as many as a million lives each year in Africa, antimalarial drugs are used within an environment that is characterized by a great degree of nonchalance. This nonchalance is largely the result of many years of surprisingly successful use of the most common antimalarial drugs, particularly chloroquine (CQ). In many situations, practices that could best be described as misuse of drugs have become routine, and in some cases, institutionalized and promoted.

Over years of deployment, there was little incentive to improve the way that antimalarial drugs are used. Both CQ and sulfadoxine/pyrimethamine (SP) were inexpensive, making it more cost-effective to treat presumptively rather than to attempt to get microscopic confirmation (especially when this is unavailable, a common situation in Africa). As both drugs were relatively safe, treating uninfected people, including infants and pregnant women, for malaria carried minimal health risk. More importantly, because of the risk of severe or fatal malaria in these groups, the potential for placing the individuals with malaria infection at even greater risk due to delays in obtaining a definitive diagnosis was felt to far outweigh that of providing malaria treatment to the many women and children who were not infected.

As is true with many different drugs in practically all cultures, it is recognized that antimalarial drugs are often taken in incorrect or incomplete doses. For years, CQ was highly

efficacious, so incomplete dosing was still likely to reduce the parasite load, if not eliminate it. CQ has an antipyretic effect and can provide some relief of symptoms even if parasites persist. Among patients with sufficiently developed acquired immunity, underdosing of CQ may still be sufficient to prevent progression to severe disease or death in many, if not most, circumstances. In fact, lack of parasite clearance post-treatment was deemed by some experts to be a desirable outcome, based on an unproven assumption that this would be necessary so as not to interfere with the acquisition and maintenance of partial immunity.

For decades, malaria therapy was also relatively easy to give. In Africa, CQ was initially given as single dose treatment (10 mg kg^{-1}) (WHO, 1973, 1986). As resistance developed, the recommended dose increased to 25 mg kg^{-1} given over 3 days (although the proportion of patients actually taking all three doses was low) (WHO, 1986). As CQ resistance further intensified and spread, some countries switched to SP, going back to an easy-to-give, single-dose regimen (Bloland and Ettling, 1999).

Until recently, therefore, first-line drugs for malaria were inexpensive, easy to give, safe and, at least initially, highly efficacious. While there was some concern over adherence, as demonstrated by a few studies looking at this phenomenon, there was little effort or incentive to devise strategies to improve the way that CQ or SP were deployed (McCombie, 1996; Deming et al., 1989; Slutsker et al., 1994; Ruebush et al., 1995). This indifference has changed only recently.

While most of the newer malaria treatments currently recommended do offer much-improved parasitologic efficacy over failing treatments like CQ and SP, that increased efficacy typically comes at a cost, both an increased economic cost and a cost of increasing complexity. Newer treatments tend to be much more expensive and are more difficult to administer. Furthermore, their safety is relatively unproven, especially among the highest risk groups for malaria in sub-Saharan Africa, young children and pregnant women. In some countries, these newer pharmaceuticals are about to be deployed on a relatively large scale long before the country's medical community has gained any practical experience with them. For the most part, few countries have considered how the introduction of newer treatment regimens might affect the delivery system. While the drug names and dosing schedules may change, the environment in which they are deployed is expected to remain unchanged.

This situation (comparatively high drug cost, complex regimens, uncertain safety, poor diagnosis, heightened concern over resistance) argues strongly in favor of a fundamental change in the way that antimalarial drugs are deployed and used. Such fundamental changes would require a new vision of malaria treatment policy and practice and substantial investments into health infrastructure within both the public and private sectors.

Paradigms of antimalarial drug deployment

Two basic and, at times, conflicting paradigms of antimalarial drug deployment are evident in discussions of antimalarial drug policies. While actual practice falls somewhere in between the two extremes, it is enlightening to understand how the two differ and the implications of these differences.

The first paradigm opts for sensitivity in case finding over specificity and maintains that the best approach to reduce malaria morbidity and mortality is to make effective treatment widely and freely available down to the most peripheral level, the household. Essentially, anyone with even a small chance of being infected receives treatment (even in situations where as few as 5% of febrile patients are actually infected) (WHO, 1997). This approach is a fundamental part of the Global Strategy for Malaria Control and Roll Back Malaria, and is a major component of related strategies, such as the Abuja Declaration goals, and the Integrated Management of Childhood Illnesses (IMCI) program. Such an emphasis on deploying efficacious malaria treatment as widely as possible is supported by observations that, under experimental conditions, it can reduce severe malaria-related morbidity and overall mortality among young children (Pagnoni et al., 1997; Kidane and Morrow, 2000).

The alternative paradigm, which favors specificity over sensitivity, maintains that a primary objective of malaria therapy should be to limit the advent and spread of drug resistance. Because drug pressure is a leading contributor to intensification of resistance, this paradigm stresses that access to treatment should be controlled sufficiently to ensure that only those with confirmed diagnosis receive treatment. This approach recognizes, even emphasizes, the existence of a very limited antimalarial armamentarium, and a slow and costly process involved in developing new antimalarial drugs.

The two paradigms are clearly at odds on a number of issues. To date, no data have been systematically collected to examine the impact that widespread, easy access to antimalarial drugs (such as described above) would have on drug resistance or other important health outcomes. Similarly, the desire to limit provision of antimalarial drugs to those who need them fails to account for the systematic realities that limit the availability of accurate diagnosis to only a small fraction of the African population.

Some of the programmatic implications of these approaches on how drugs should be deployed are outlined in Table 1. The way forward for Africa will most likely depend on a rational compromise between these two polar-opposite paradigms. Currently, compromise between these paradigms is occurring, but in an *ad hoc*, or even accidental, manner rather than through coordinated effort. Achieving durable and programmatically effective implementation of new treatment strategies will require a more purposeful and informed merging of these approaches.

Programmatic effectiveness: a public health approach to malaria treatment

Malaria treatment policy has been driven by a very narrow

Table 1. *Comparisons of paradigms for antimalarial drug deployment*

		Paradigm	
Factor	Component	Improved access	Limitation of drug resistance
Drug	Dosage	Single dose, therefore long half-life	Short half-life, therefore multiple doses likely
	Regimen	Simple – i.e. single dose treatment ideal, but the fewer doses the better	Combinations of drugs typically increase complexity
	Availability	Widely available at most peripheral level	Available at the most peripheral level offering definitive diagnosis and directly observed therapy (DOT)
	Administration	By patient or patient's guardian (in home); directly observed therapy possible if single dose given at clinic/source	DOT is the ideal administration method to ensure adherence to full dosing
	Adherence	Strategies to maximize very important	Because DOT, adherence assured
Diagnosis		Anyone with reasonable risk of needing malaria therapy, therefore clinical is acceptable	Only of confirmed cases, therefore based on lab-based diagnosis
Sources of drugs		As many as possible – private sector (including public sector; informal/itinerate drug sellers); traditional healers	Only from licensed and trained personnel/ pharmacies and with prescription by appropriately trained and supervised HCW
Regulatory requirements		Minimal – primarily assurance of quality of drugs being distributed within community	Maximal: Assurance of quality, licensing and monitoring of drug outlets, formal training and supervision of HCW
Goals of therapy	Clinical relief	Yes	Yes
	Stop progression to severe disease	Proven	Assumed
	Prevent death	Proven	Assumed
	Parasitologic cure	Ideal, but not necessary	Necessary
	Interruption of transmission	Ideal, but not necessary	Highly desirable
Cost per case treated		Relatively low	Likely to be very high
Follow-up of cases to identify failures		Desirable, but not necessary	Necessary
Use of 2nd line treatment		Ideally on identification of clinical failure – in practice, multiple attempts with 1st line	Immediately on identification of parasitologic failure
Need to coordinate with vector control	Reduction in transmission pressure	Not an essential component of drug policy, *per se*	Very important if not essential
Information, Education and Communication (IEC) Needs		Complex: improved recognition of symptoms, understanding drug choices, dosages and adherence	Simple: go to health sector for diagnosis and treatment
Health Worker Training and Supervision needs		Simpler: no specific interventions aimed at reducing overtreatment (no change from *status quo*)	Complex: maintenance of diagnostic competency, recognition of treatment failures, many drug regimens possible
Evaluation	Process/ Implementation	Indicators reflecting availability of drugs in communities; penetration of IEC materials/ messages into community; others	Indicators reflecting availability of treatment algorithms, availability of drugs and diagnostic resources at health centers
	Outcome/ Effectiveness	Difficult: requires understanding of complex community beliefs, behaviors, and practices	Simpler: indicators reflecting understanding and correct use of diagnostic and treatment algorithms by health workers
	Impact	Difficult: HIS systems; demographic surveillance systems; special studies; *in vivo* evaluations as currently used	Difficult: long term tracking of changes in molecular markers, *in vitro* and *in vivo* resistance; demographic surveillance systems, special studies

Table adapted from P. B. Bloland, CDC (unpublished) and Robb et al. (2003).
HCW, health care workers.

concept of what it means for a malaria drug to 'work'. This narrow concept appears to be a reflection of the influence of the type of training that malariologists tended to have: biology or, more specifically, parasitology. As a result, 'working' was traditionally equated with drug *efficacy* (i.e. under ideal conditions of correct dose of quality drug given under direct observation). The methods used to measure drug efficacy have evolved over the years and this evolution has changed the actual definition of drug efficacy from parasitologic clearance to clinical response to some degree of both (WHO, 1996). Contemporaneous development of laboratory-based methods, such as *in vitro* cultivation and sensitivity testing and identification of molecular markers linked to drug resistance, have both complemented and confused this evolution, due to the uncertain and variable correlations between these laboratory-based indicators and actual treatment outcomes.

More recently, broader concepts of what it means for a malaria drug to 'work' have been introduced, due in large part to the development of epidemiology and public health practice as disciplines in their own right, as well as an increased interest in malaria on the part of anthropologists, economists, and other social scientists. For example, for a drug to 'work', it must not only clear parasites, but must also be perceived to have worked on both an individual and cultural level. In some situations, the perception of treatment is more important than its biological effect.

With the input of these additional disciplines, not only have concepts of what it means for a drug to work changed, but also greater emphasis has been placed on understanding why drugs might not work. Greater emphasis on the influence of cultural beliefs, treatment-seeking behavior, household economics, actual behaviors and practices, among others, have all contributed to a more comprehensive concept of antimalarial treatment.

This more inclusive concept of malaria treatment, *programmatic effectiveness*, is the first that truly addresses the issues that are central to actually achieving reductions in malaria morbidity and mortality. Programmatic effectiveness attempts to identify and maximize the favorable outcomes at the critical junctures that occur between infection of an individual with malaria parasites and ultimate clearance of those parasites and survival of the infected individual. It is through this process of maximization that the most reasonable compromise between the two conflicting paradigms of treatment will occur and, in turn, malaria control programs can achieve the greatest impact that treatment can have on malaria and morbidity.

Two examples of the concept of programmatic effectiveness related to malaria case management have been published. In the most recent, a Piot model, previously used successfully to evaluate TB and sexually transmitted infection control programs, was developed for malaria case management (Mumba et al., 2003). According to this model there are six steps that a patient would have to achieve in order to be successfully cured of malaria: awareness of a need for treatment, motivation to seek treatment, diagnosis, initiating correct treatment, completing that treatment, and the treatment being efficacious. The second example takes a similar approach and applies it to a specific situation (Krause and Sauerborn, 2000). In this model, the authors have identified what they felt were the critical steps in correct management of malaria: (i) patient seeks care at a health facility, (ii) a complete history is taken, (iii) a complete physical examination is performed, (iv) the correct drug at the correct dose is recommended, (v) the correct drug at the correct dose is bought by patient, (vi) the complete dose is taken and (vii) the drug is efficacious. Using data collected in Burkina Faso, the authors suggest that only 3% of patients are actually managed correctly. Furthermore, both examples illustrate that optimizing a single factor while leaving the other factors alone can have minimal impact in terms of improved case management: in the Burkina Faso example, increasing the efficacy of the antimalarial drug used from 85% to 100% increased overall programmatic effectiveness by <1%. The authors correctly point out that patients could still achieve a favorable outcome even if not correctly managed (for example, receiving and taking the correct drug at the correct dose could occur even though the health care worker did not take a complete history or perform a proper physical examination), and clearly the selection of which steps are truly critical for optimal case management is open to debate. Nonetheless, it is a logical conclusion that morbidity and mortality will decline as more patients receive correct management, and that optimizing correct management will require a holistic approach rather than single-minded focus on isolated factors taken one at a time.

Programmatic effectiveness has implications for more than just patient outcomes. Many of the components of effectiveness that contribute to improved patient health will also contribute to selection for and/or intensification of drug resistance: critical components such as the quality of the drug being used and the ability and willingness of the patient to correctly take a complete treatment will also either facilitate or inhibit drug resistance.

Trends in antimalarial drug deployment

As mentioned previously, over the short- to medium-term, newly developed pharmaceuticals will need to be deployed within the epidemiological and health care environment that exists today in Africa. This environment is changing. However, a number of recent or developing trends and initiatives will have an impact on drug deployment, as well as on the programmatic effectiveness of that deployment, both in terms of patient outcome and drug resistance. This impact may be positive, negative or mixed, depending on the activity and how well it is actually implemented.

Lack of recognition of populations at risk in drug development and deployment

In tropical sub-Saharan Africa, the two groups at greatest risk of severe malaria morbidity and mortality are very young

children and pregnant women (WHO/UNICEF, 2003). Antimalarial drugs must be both safe and effective for the treatment of malaria in these high risk groups to be of greatest use. Unfortunately, drug companies often do not conduct the appropriate research to establish safety in these groups before marketing their products. For example, one potentially important addition to the antimalarial pharmacopoeia, lumefantrine-artemether (Co-artem), is not approved for use in the very groups that are likely to need it the most, children <10 kg in weight and pregnant women, making the drug either of limited value or forcing health care providers (and patients) to bear the risk of off-label use.

In addition to use for treatment of acute illness, preventive use of antimalarial drugs is being promoted for both pregnant women and infants (see below). The safety profile of drugs needs to be even more favorable to justify their use among otherwise healthy individuals, as the risk:benefit ratio is very different from that among acutely ill patients.

Combination therapy

Much has been written about combination therapy (White et al., 1999; White, 1999; Bloland et al., 2000; Nosten and Brasseur, 2002). There is also a review on combination therapy in this issue (Olliaro and Taylor, 2003). Combining antimalarial drugs, especially when one of the components is an artemisinin compound, offers increased efficacy and the potential for inhibition of development of resistance and reductions in overall transmission, at least in some environments. Use of drugs in combination (especially artemisinin-containing combinations or ACTs) is currently the World Health Organization's recommended strategy for coping with drug resistance globally (WHO, 2001).

Unfortunately, as is true for any drug (whether in combination or not, whether coformulated or coadministered), the mere existence of a new treatment does not guarantee that the treatment will have any public health impact (Bloland et al., 2000). These therapies must not only exist, but must be affordable, accessible and acceptable to the end user. Additionally, the end-user must be able to take them in correct quantities and for correct amounts of time. They must be sufficiently safe, especially among users in the highest risk groups. Finally, they must be robust enough in terms of their ability to withstand the misuse that is likely to occur and the selective pressure that this misuse will place on the parasite.

The decline of the public health system

In much of the region, public health infrastructure is inadequate to fully meet existing needs (Kager, 2002; Moerman et al., 2003). This manifests in many ways that affect the provision and use of antimalarial agents. Relatively few health facilities have or use laboratory-based diagnostic tests for identifying patients with malaria infections, therefore the majority of febrile patients receive malaria treatment, regardless of whether or not they are actually infected (see section on diagnosis below). Staff training and motivation can be poor and many facilities operate without reliable access to medicines, electricity or clean water (Gilson et al., 1994; Isra et al., 2000).

Nonetheless, the formal public health sector provides an important service to communities, especially when home-based treatments for fever fail. Strategies to address improvements in public health sector should address the specific reasons why people might choose to avoid those facilities, such as poor quality service, leakage of drugs for private resale, informal patient charges, mismanagement of patient user fees, distance to facilities, lack of drugs and other desired services, cost and lengthy waiting times (Agyepong, 1995; Baume et al., 2000; Lindblade et al., 2000; McPake et al., 1999; Mumba et al., 2003; Ndyomugyenyi et al., 1998; Nyamongo, 2002; Tarimo et al., 2000; Williams et al., 1999).

The growing importance of the private sector

In Africa, private sector sources of antimalarial drugs often refer not only to officially recognized businesses, such as private pharmacies or general merchandisers, but also to informal sources, such as small kiosks or even itinerant drug sellers. Regardless of the permanence or formality of the shop, the importance of private sector sources of antimalarial drugs is substantial in many African communities (Adome et al., 1998; Baume et al., 2000; Gilson et al., 1994; Ndyomugyenyi et al., 1998; Thera et al., 2000). In some studies, as much as 60% of patients (or more) seeking help for febrile illness receive medicines from the private sector (McCombie, 1996; WHO/UNICEF, 2003; S. P. Kachur, CDC, 2003, unpublished data).

The popularity of the private sector is, in part, a result of the poor state of the public sector, but also because private sector outlets tend to be more numerous, closer to home, offer rotating credit schemes, have drugs in stock, and involve less time to obtain the desired treatments (Armstrong-Schellenberg et al., 2001; Marsh and Mutemi, 1997; Molyneux, 2002; Ongore and Nyabola, 1996; Reynolds-Whyte and Birungi, 2000). These outlets also tend to interact with the customer in a friendlier fashion than health care workers interacting with patients. Unfortunately, it has been well established that the private sector is poor at providing appropriate advice, complete doses, or even the correct drug for the problem (Djimde et al., 1998; Mwenesi, 1994; Massele et al., 1998; Oketch-Rabah et al., 1998).

Due to the importance of private sector sources of medicines, many groups are investigating ways to improve the process by which these drug sellers provide drugs (Marsh et al., 1999; Reynolds-Whyte and Birungi, 2000). In Kenya, providing shop keepers with specific training on how best to provide malaria medicines and what advice to give patients resulted in an increase in the appropriate use of over-the-counter chloroquine by at least 62% (Marsh et al., 1999). Other efforts are aimed at social marketing of licensed or franchised drug shops where provision of quality treatment advice is available and a higher degree of quality assurance can be achieved (for example, see http://www.msh.org/features/gates/kenya-release.html). It is now being recognized that the educational system could be used

to target messages about antimalarials and the need for prompt and effective treatment, supplementing efforts at improving health care through the public system (Bundy et al., 2000; Geissler et al., 2001). Some novel programs are now being conducted that focus on training school children in the appropriate use of drugs (van der Geest and Geissler, 2003). Many countries are now facing the choice between continuing to support malaria treatment primarily through a failing public health system or divert those needed funds to improve access and use of malaria medicines through a largely uncontrollable private sector, or to try to do both and run the risk of doing neither well.

Pre-packaging medicines

To improve both the private sector's ability to provide malaria drugs correctly as well as the likelihood that patients will take the correct dose and complete the full regimen, schemes have been developed to pre-package medicines for specific age ranges. In most circumstances, such pre-packaging has not only been well received by the end-users but well-designed drug packages have increased patient compliance by, on average, 20% (Yeboah-Antwi et al., 2001; Pagnoni et al., 1997). Initial findings are encouraging for the use of pre-packaged antimalarial drugs. In a recent study in Burkino Faso, mothers could recognize and treat malaria in a prompt and correct manner, given appropriate training and adequately packaged drugs (Sirima et al., 2003).

Pre-packaging has its own limitations. For logistical reasons related to drug management and supply, a small number of packages are created, covering broad age ranges (such as for patients under 1 year, 1 to 6 years, 7 to 11 years, and 12 years and above). This situation raises the possibility of over- or under-dosing at the extremes of the age range, especially among populations where malnutrition is prevalent.

Labeling of medicines

Packaging of pharmaceuticals, malaria drugs included, is woefully inadequate given the settings in which they are used (C. Goodman, London School of Hygiene and Tropical Medicine, personal communication). When drugs are given with printed information, that information is typically written using complicated or technical language, or written in a language foreign to the end user, or of little use to a predominantly illiterate population. More often, especially for drugs provided through the private sector, no information is given at all: pills and syrups are provided to the patient wrapped in slips of paper or unmarked bottles. Due to their lower costs, medicines are often bought in bulk jars that are labeled with nothing more than 'Use as directed by physician' (if labeled at all), leaving both vendor and patient clueless as to how to properly dose the medicine.

Increasingly, these shortcomings are being recognized and addressed. Efforts to produce pre-packaged medicines are often accompanied by efforts to improve patient information, including graphic representations of proper use for illiterate patients and written information in a locally appropriate language. These innovations, however, add to the cost of the drug and, particularly within the private sector, may not be sufficient to ensure adequate patient education.

Integrated management of childhood illness (IMCI)

IMCI is an algorithm that, when used properly, assists health care workers to identify and treat the most common childhood illnesses on the basis of clinical signs and symptoms. The algorithm is intended to rationalize the diagnosis and treatment of these illnesses in settings where health care workers are minimally trained and have poor or non-existent access to laboratory or radiographic diagnosis (Perkins et al., 1997). This approach is intended to be an improvement over an unstructured clinical diagnostic approach in that it encourages health care workers to spend more time and effort conducting a more thorough assessment of children.

This approach does not change malaria diagnosis much, as any child with fever or history of fever is assumed to have malaria, even in areas where as little as 5% of febrile children actually have parasites on blood smear. The result is considerable misdiagnosis and unnecessary treatment. In a health facility survey recently conducted in Tanzania, for example, a greater proportion of children with IMCI-diagnosed 'malaria' was found to be aparasitemic than among children with 'malaria' diagnosed using traditional, non-structured clinical diagnosis (62% *vs*. 40%, respectively) (L. Causer, CDC, 2003, unpublished data).

Improved access and use of laboratory-based diagnostics

As mentioned previously, the prevailing method for diagnosing malaria in sub-Saharan Africa is by clinical impression, which, in turn, typically amounts to treating all fevers as malaria. The inaccuracies of this method are well known. In various studies of clinical diagnosis of malaria using IMCI, the sensitivity of clinical diagnosis (i.e. the proportion of clinically diagnosed malaria patients that actually have malaria infection) can range from 87% to 100%. The specificity of clinical diagnosis (the proportion of all patients that do not get a diagnosis of malaria who actually do not have malaria infection) can range from 0% to 8% (Perkins et al., 1997; Weber et al., 1996).

Laboratory-based diagnostic tests can improve this situation dramatically; however, access to laboratory diagnosis is rare. Even in facilities with laboratories capable of performing diagnostic tests, the results of these tests are often ignored (Barat et al., 1999).

The advent of simple-to-use, rapid-diagnostic tests (RDTs) for malaria holds the promise of more definitive diagnosis occurring even in settings lacking laboratory capacity (Moody, 2002). Under controlled conditions, RDTs reportedly have very high sensitivity and specificity (ranging between 81% and 100% for both), although their sensitivity drops with very low parasite densities (Moody, 2002). Although South Africa uses RDTs for primary malaria diagnosis (and requires laboratory-

based confirmation before treatment), and other countries have used RDTs during emergency situations, these tests are currently far too expensive for the majority of endemic countries in Africa to sustain (US$0.80–2.50 per test) (National Research Council, 2003). Nonetheless, in some settings, microscopic diagnosis of malaria has been shown to be cost-effective, even cost-saving (Jonkman et al., 1995).

Home-based management of malaria/'community IMCI'

There is increasing interest in pushing malaria treatment closer to home, or even to within the home (Winch et al., 2002). The argument in favor of this strategy is based on the assertions that (i) malaria infections can progress to severe or fatal illness very rapidly, (ii) many children die within the home without visiting a health facility and (iii) a majority of treatment already occurs in the home with medicines either bought from shops or left over from previous clinic trips. Although there is no single accepted definition of what exactly home-based malaria therapy actually is, the general desire is to vastly improve access to efficacious medicines at the most peripheral level (in terms of availability and price) and to increase community members' knowledge about how to properly use them.

A number of studies have shown that such approaches can be highly effective. In Ethiopia, for example, local mothers were trained to provide their neighbors within their village with information on how to identify likely malarial illness and to supply chloroquine packaged with pictorial instructions for appropriate use. This strategy led to a reduction of 41% in the under-five mortality rate over 2 years, compared to villages with the more typical community health workers who were not specifically supplied with malaria treatment (Kidane and Morrow, 2000).

Intermittent Preventive Treatment for pregnant women (IPT) and infants (IPTi)

A relatively new approach to preventing the effects of malaria in pregnancy has been developed and is being actively promoted. In this strategy, pregnant women are given full treatment doses of an antimalarial drug regularly during pregnancy regardless of malaria infection or illness status (Intermittent Preventive Treatment or IPT). Such treatment should occur, at a minimum, once in the second and once in the third trimester of pregnancy, although in most settings, more frequent treatment is advisable (WHO, 2002). This strategy has been associated with substantial reductions in maternal anemia, fetal loss and low birth weight and, because low birth weight is a primary risk factor for infant mortality, IPT may improve child survival (WHO/UNICEF, 2003). A similar approach, Intermittent Protective Treatment for Infants (IPTi), has been proposed and is currently being evaluated extensively. In this strategy, children are given periodic treatment doses of antimalarial drugs with the aim of reducing morbidity and mortality during infancy. The only published study of this strategy suggests that, when linked to a child's routine immunization schedule, IPTi resulted in a decrease in clinical malaria and severe anemia of about 50–60% (Schellenberg et al., 2001).

Global Fund for AIDS, Tuberculosis and Malaria (GFATM) and other financing schemes

The newer malaria medicines, including artemisinin-containing combination therapies (ACTs), are substantially more expensive than the single-drug treatments in common current usage (e.g. US$0.15–0.20 for an adult dose of chloroquine or SP compared with US$1.20–2.40 for ACTs). The ability of most African economies to sustain these increased malaria treatment costs is limited. The GFATM, which delivered its first grants in 2001, has provided substantial funds to a number of countries in sub-Saharan Africa to support malaria control activities (see www.globalfundatm.org). Some countries have applied these funds to changing their antimalarial drug policies, including the purchase of ACTs. The World Bank has indicated that its loans could be used to buy malaria medicines. In other situations, non-governmental organizations (NGOs) have offered to supply governments with ACTs.

While these mechanisms offer some hope for governments not otherwise able to afford the expensive, new medicines, there are lingering concerns over financial sustainability. Concerns over the longevity of the Global Fund have already been raised (Kapp, 2002). Countries are reluctant to take on additional national debt for malaria drugs. While donations *via* NGOs can be helpful in the short-term for specific situations, the long-term sustainability of those donations is doubtful.

Finally, all of these mechanisms are best suited to providing drugs *via* the public health sector. None of these funding initiatives have identified a way to provide free or heavily subsidized malaria treatment *via* the private sector, which is relied upon so extensively in sub-Saharan Africa.

Conclusions

As the above initiatives and trends illustrate, there remains a distinct division in paradigms for malaria case management. On the one side, technologic advances offer improved application of antimalarial drugs at the cost of diminished access, either intentionally (moving towards specific diagnosis-based treatment or restricting distribution of drugs to controlled and licensed outlets) or unintentionally (high-cost treatment regimens). On the other side is a willingness to accept and work within the realities of malaria treatment in sub-Saharan Africa in order to minimize obstacles to obtaining efficacious treatments (i.e. better ensure that people who might need malaria treatment, get treated with the recommended drug at an effective dose), but at the cost of control (home-based treatment; IMCI; increased utilization of private sector outlets for treatment).

While a few attempts at reconciling these divergent paradigms have occurred (pre-packaging; improved labeling and instructions; improved education of private sector drug vendors), far more needs to be done in order to ensure that new,

highly efficacious treatments are in fact, programmatically effective and, therefore, offer the best chance of contributing positively towards reducing the burden of malaria in sub-Saharan Africa. This will be likely to require investment in large-scale studies to ascertain the likely impact of these strategies, both to illustrate improvements in health outcomes associated with wider and easier access to antimalarials as well as to better understand the implications of this wider and easier access to antimalarials might have on development of drug resistance.

It is clear, however, that Africa cannot and will not wait until everything is known before moving ahead. The risk is real that the promise of these new therapies might be squandered by deploying them in a 'business as usual' fashion. But by being cognizant of the implications of the realities of the environment in which antimalarial drugs are used in sub-Saharan Africa and deploying these various new treatments in a manner that maximizes programmatic effectiveness, the positive impact of these promising new therapies can be realized.

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