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C.J.M. Whitty

*London School of Hygiene and Tropical Medicine*

R. Allan

*World Health Organisation*

V. Wiseman

*London School of Hygiene and Tropical Medicine*

S. Ochola

*Ministry of Health*

M.V. Nakyanzi-Mugisha

*Ministry of Health*

*See next page for additional authors*

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**Authors**

C.J.M. Whitty, R. Allan, V. Wiseman, S. Ochola, M.V. Nakyanzi-Mugisha, B. Vonhm, M. Mwita, C. Miaka, A. Oloo, Zul Premji, C. Burgess, and T.K. Mutabingwa

# Averting a malaria disaster in Africa — where does the buck stop?

Christopher J.M. Whitty,<sup>1</sup> Richard Allan,<sup>2</sup> Virginia Wiseman,<sup>1</sup> Sam Ochola,<sup>3</sup> Maria Veronicah Nakyenzi-Mugisha,<sup>4</sup> Benjamin Vonhm,<sup>5</sup> Mahemba Mwita,<sup>6</sup> Constantin Miaka,<sup>7</sup> Aggrey Oloo,<sup>8</sup> Zul Premji,<sup>9</sup> Craig Burgess,<sup>10</sup> & Theonest K. Mutabingwa<sup>11, 1</sup>

**Abstract** The serious threat posed by the spread of drug-resistant malaria in Africa has been widely acknowledged. Chloroquine resistance is now almost universal, and resistance to the successor drug, sulfadoxine-pyrimethamine (SP), is growing rapidly. Combination therapy has been suggested as being an available and potentially lasting solution to this impending crisis. However, the current cost of combination therapy, and especially that of artemisinin combination therapy (ACT), is potentially a serious drawback, even if a significant part of its cost is passed on to the end-user. If the question of cost is not successfully addressed this could lead to adverse results from the deployment of combination therapy as first-line treatment. These adverse effects range from an increase in potentially fatal delays in infected individuals presenting to medical services, to exclusion of the poorest malaria sufferers from receiving treatment altogether. Urgent steps are needed to reduce the cost of combination therapy to the end-user in a sustainable way if it is to be usable, and some possible approaches are discussed.

**Keywords** Malaria, Falciparum/drug therapy; Antimalarials/economics; Drug therapy, Combination; Artemisinins/economics; Drug costs; Patient acceptance of health care; Financing, Organized; Africa (source: MeSH, NLM).

**Mots clés** Paludisme plasmodium falciparum/chimiothérapie; Antipaludique/économie; Polychimiothérapie; Artemisinines/économie; Coût médicament; Acceptation des soins; Organisation financement; Afrique (source: MeSH, INSERM).

**Palabras clave** Paludismo falciparum/quimioterapia; Antimaláricos/economía; Quimioterapia combinada; Artemisininas/economía; Costos en drogas; Aceptación de la atención de salud; Organización (fuente: DeCS, BIREME).

الكلمات المفتاحية: الملاريا، الملاريا المنجلية، المعالجة الدوائية للملاريا الدوائية، مضادات الملاريا، اقتصاديات مضادات الملاريا، المعالجة الدوائية، توليفة، ارتيميسينين، اقتصاديات الأرتيميسينين، تكاليف الأدوية، قبول المرضى للرعاية الصحية، التمويل، التمويل المنظم، أفريقيا. (المصدر: رؤوس الموضوعات الطبية - إقليم شرق المتوسط)

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Voir page 383 le résumé en français. En la página 384 figura un resumen en español.

يمكن الاطلاع على الملخص بالعربية في صفحة 384.

## Drug-resistant malaria — the gathering storm

The serious threat posed by drug-resistant malaria in Africa is widely acknowledged (1). Chloroquine resistance is now universal, and the days of treating malaria with a single cheap drug are generally believed to be numbered. Resistance to sulfadoxine-pyrimethamine (SP) the natural successor to chloroquine was increasing by the end of the 1990s. It was argued then that the only way to protect this or any other single drug is to give it in

combination with another unrelated antimalarial as combination drug therapy (CDT) as in the case of tuberculosis (TB) treatment (1). Since the 1990s, the accelerating emergence and spread of resistance to SP has been documented in many areas, with parasitological failure rates of around 20% being widely reported, and up to 40–80% in certain areas (2, 3). Two relatively cheap drugs could potentially replace SP as monotherapy; amodiaquine (an older drug with similarities to chloroquine) and chlorproguanil-dapsone (Lapdap, an anti-folate). Both are

<sup>1</sup> Gates Malaria Partnership, London School of Hygiene and Tropical Medicine, 50 Bedford Square, London WC1B 3DP, England. Correspondence should be sent to Christopher J.M. Whitty (email c.whitty@lshtm.ac.uk).

<sup>2</sup> World Health Organization, 1211, Geneva 27, Switzerland.

<sup>3</sup> National Malaria Control Programme, Ministry of Health, Nairobi, Kenya.

<sup>4</sup> Department of Epidemiology, Ministry of Health, Kigali, Rwanda.

<sup>5</sup> National Malaria Control Programme, Ben Vonhm, Liberia.

<sup>6</sup> National Malaria Control Programme, Ministry of Health, Dar es Salaam, United Republic of Tanzania.

<sup>7</sup> Ministry of Health, Kinshasa, Democratic Republic of Congo.

<sup>8</sup> Department of Epidemiology and Preventive Medicine, Moi University, Eldoret, Kenya.

<sup>9</sup> Department of Parasitology, Muhimbili University College of Health Sciences, Dar es Salaam, United Republic of Tanzania.

<sup>10</sup> Medical Emergency Relief International (MERLIN), London, England.

<sup>11</sup> East African Antimalarial Network (EANMAT), Muheza, United Republic of Tanzania.

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currently effective in many areas where SP resistance already occurs, but this situation may well not last for much longer (2, 4). Resistance to amodiaquine already exists at an appreciable level in some areas (up to 26% in Kenya) (5). Because of its similarity to SP, there is a concern that resistance to chlorproguanil-dapsone may follow rapidly if it is deployed widely in areas of widespread SP resistance. We therefore face a crisis in treating malaria which is one of the most important causes of morbidity and mortality in Africa. The proposed CDT has received widespread scientific support and has the potential for returning Africa to sustainable, highly effective antimalarial treatment. The solution has, however, one serious drawback.

It has been suggested for some years that combinations of drugs, and especially combinations that include artemisinin drugs, will be highly effective in treating malaria. There is indirect evidence from south-east Asia (but not from Africa) that these combinations could also delay or halt the emergence of drug resistance. An informal expert consultation held by WHO in 2001 supported the conclusion that combinations of drugs are the best, and possibly the only, long-term solution (6). Setting aside the question of cost, the consultation proposed a list of three artemisinin-containing combinations (lumefantrine–artemether, amodiaquine–artesunate and SP–artesunate) that they considered to have the greatest potential, and one non-artemisinin combination (SP–amodiaquine) was suggested as a fall-back option. Subsequent studies have confirmed that these combinations are highly effective and safe (4, 5). A number of technical questions (for example on local effectiveness and safety in pregnancy) have yet to be answered and operational studies are required. One potential advantage of artemisinins, namely that they reduce transmission by reducing gametocyte carriage (7), has not been confirmed in Africa and may not be relevant in areas with high transmission of malaria.

The principle that combination therapy could provide a rapid solution to a serious crisis and do so in a sustainable manner has, however, gained widespread support.

## Cost — the major flaw

There remains a serious problem with combination therapy, and that is its cost (1, 8, 9). Chloroquine and SP cost approximately US\$ 0.15 for a course of treatment. Negotiation between the WHO and some drug companies has already successfully reduced the cost of combination treatment to between US\$ 0.90 and US\$ 1.4 for a course of treatment for children up to seven years old and to approximately US\$ 2 per adult dose. There are theoretical reasons for assuming that the cost might fall over time (10), but it seems unlikely to fall substantially below that negotiated by WHO in the immediate future, and making policy based on the assumption that cost may fall significantly is rash. It is well established that combination therapies are more expensive than current monotherapy and that the true opportunity cost of switching to combination therapy will significantly exceed current drug price estimates. Therefore, issues of affordability can no longer be disregarded. The potential cost of combination therapy was viewed as “disastrous” in 1998 (11), a “major obstacle” in 2000 (8), a “serious challenge” in 2001 (12), a “critical factor” in 2002 (9), and we still face a crisis in 2004.

In many parts of Africa a family member may have malaria several times per year, and febrile episodes treated as malaria more often still. A household may therefore have to pay for malaria treatment many times a year. If household income is only a few dollars a month, increasing the cost of malaria treatment with combination therapy even by US\$ 0.5 will have grave consequences, both direct and indirect.

At this cost, the poorest members of society will not be able to afford malaria treatment at all. Increasing user fees has been shown to have the potential to discriminate against the group in society whose health needs are greatest and who can therefore least afford to be deterred from seeking health care (13, 14). Malaria is particularly a disease of the poor and of populations affected by long-term conflict. One-third of the annual deaths from malaria worldwide occur in African countries affected by conflict (15). In one such area, up to 75% of the population were reported as being unable to afford even a full course of chloroquine from official health facilities or private markets (16). Consequently poorer parents already buy incomplete treatment or divide a full course of drugs between several family members. This results in treatment failure, increased selection pressure for drug resistance and increased prevalence of severe anaemia.

The problems of significantly increased costs are not restricted to people who cannot pay at all. Parents faced with high treatment costs commonly delay bringing their children or themselves for treatment until they are sure of the diagnosis. By this time the patient is often too sick to be treated successfully. It is the delay in receiving adequate treatment that kills many people with malaria. With prompt diagnosis and treatment with an efficacious drug, most cases of malaria are entirely curable.

Other malaria sufferers will be put off going to formal medical services if the costs of drugs are too high and will seek their treatment from the informal sector where much antimalarial treatment is already provided, often inappropriately (17). The effects of cost are not always predictable; in some instances financial cost has had little effect on access to treatment or on adherence, but elsewhere it has played an important role in deterring people from attendance at antenatal clinics and hospitals (18).

Increased cost also has wider public health implications. The incentive to produce counterfeit drugs increases with the price at which they can be sold. Counterfeit antimalarials are only beginning to be a problem in Africa where low-cost drugs are used for first-line treatment (19), but the problem is reaching serious proportions in south-east Asia where artemisinin-containing combinations are in use (20).

## Two conflicting, but correct positions

On the one hand there are drugs universally accepted to be close to ideal for the treatment of malaria. On the other hand, deploying these drugs as first-line treatment if more than a fraction of the current cost is passed on to households, may prevent, delay or divert effective treatment-seeking behaviour. The public health impact of using these excellent drugs may even be worse than that of using a less effective but cheaper drug. Trying to pretend that there is no conflict is pointless — both positions are correct: combination therapy probably is the best solution, but deploying combination drugs at their current or foreseeable cost could be at best inequitable and at worst actively harmful.

The only way to reconcile these two positions is to provide combination therapy at a cost to households that is no greater than that of current malaria treatment, or better still, to provide treatment free of charge. This would render irrelevant all the current concerns about deploying combination therapy once the remaining technical issues have been addressed.

As there are only a few relatively well-defined ways that this could be achieved, the technical questions to be answered are also relatively well defined.

## Cost — some solutions will not work

We have already discussed the reasons why transferring the increased cost burden to individuals will fail, regardless of whether the drugs were bought on the market or through a revolving drug fund or user fee. Published evaluations of user and drug-fee schemes suggest that they have been easier to impose than to enforce or sustain. The regressive nature of these fees continues to undermine the success of this type of health financing policy (21, 22). Social insurance schemes would also be likely to fail, as those people most often affected by malaria are least often covered by insurance. In their review on rural risk-sharing schemes, Creese & Bennet (23) reported that schemes in low-income countries generally have only limited coverage, low cost-recovery rates and little ability to protect the most needy.

Individual governments in the affected countries, many of which are also coping with the twin epidemics of AIDS and TB, would rightly say that improvements in the medical and diagnostic infrastructure must take priority when allocating their limited resources. Malaria remains a severe economic burden on most of these countries, reducing GDP by up to 18% (24), and, therefore, dealing with it effectively should be an economic as well as a humanitarian priority. Diagnostic facilities for malaria do already exist, although as with TB and HIV services, the diagnostic services for malaria in many areas need to be strengthened significantly as a matter of priority, especially if more expensive drugs are to be used. In areas with low endemicity of malaria such improvements may include considering the use of new malaria dipsticks, although these have severe technical limitations in areas of high endemicity. Improving diagnostic infrastructure is necessary irrespective of which drugs are used, although with more expensive drugs, improved rational use of drugs increases their cost-effectiveness.

However, the burden of subsidizing the drug costs is almost certainly unrealistically high for the governments of countries with a high endemicity of malaria to bear. Put in perspective, the entire health care budget of a country such as Rwanda is around US\$ 10 million. According to recent estimates, this might just cover the cost of changing malaria treatment (10). Malaria is a problem that is not going to disappear with investment, so loans are not appropriate. In the many countries of Africa affected by long-term conflicts, bank loans and bilateral grants are not even an option. This limits the available choices. Although some of the countries in which malaria is endemic may be able to contribute significantly towards the solution to the growing malaria treatment crisis with both material and management resources, most cannot meet the costs of more expensive drugs without assistance.

## Subsidy — the only realistic option

Support from pharmaceutical companies and donors has an important role to play, but if combination therapy for malaria is to be deployed, the international donor community would have to make a major and indefinite commitment to buying or subsidizing the drugs so that the cost to the end-user is low or non-existent. This could mean subsidizing indigenous production, subsidizing the drugs before they arrive in countries in which malaria is endemic, or supporting low-cost production. Subsidy up to the point that the costs of combination therapy are equivalent to the costs of the currently used drugs is one option, but the provision of free drugs has many additional advantages. Ironically drug treatment for malaria is free in almost all middle-income and high-income countries — but not in the poorest. Strong political support will also be essential at country level to ensure that low-cost or free malaria treatment provided at the centre remains so to health providers and malaria patients.

The provision of free drugs would be a bold step, but not without precedent. Several excellent TB and leprosy control programmes have worked on the basis of free (donated) drug programmes. Such a programme would be achievable over a short period of time as the basic infrastructure already exists and the drugs are licensed. Few of the operational problems that have been highlighted for antiretroviral treatment for HIV/AIDS in Africa (25) would occur with malaria because treatment courses are relatively short, and there is no need for follow-up and monitoring. The Global Fund to Fight AIDS, Tuberculosis and Malaria potentially provides a mechanism that could be used to fund malaria drugs sustainably, without relying on a single donor (26).

## Conclusion

Combination drug therapy offers a safe and effective potential solution to the spread of drug-resistant malaria which is one of the great public health crises looming over Africa. Unless the real cost considerations of combination drug therapy are met, this urgently needed new therapeutic approach can never achieve its full potential. Attempting to deploy combination therapy as first-line treatment without addressing this problem could paradoxically make things worse for the poorest and most vulnerable malaria sufferers. The solution is, ultimately, a political rather than a scientific one. This is not an issue that can be ignored, and the speed of onset of the crisis means that finding a solution cannot be delayed. ■

**Conflicts of interest:** none declared.

## Résumé

### Eviter une catastrophe liée au paludisme en Afrique : quel compromis ?

La grave menace que constitue la propagation du paludisme pharmacorésistant en Afrique est largement reconnue. La résistance à la chloroquine est maintenant presque générale et la résistance à la sulfadoxine-pyriméthamine, le successeur de la chloroquine, gagne rapidement du terrain. On a émis l'idée que la polychimiothérapie pouvait représenter une solution accessible et peut-être durable à cette crise imminente. Cependant, le coût actuel d'un tel traitement, en particulier lorsqu'il comporte une artémisinine, risque d'être un inconvénient majeur, même s'il est supporté pour une grande partie par le patient lui-même. Si l'on

ne résout pas la question du coût du traitement, l'adoption de la polychimiothérapie comme traitement de première intention risque d'avoir des conséquences fâcheuses, allant du décès de malades qui auront attendu trop longtemps avant de faire appel aux services médicaux, à l'exclusion des malades les plus pauvres de tout traitement. Il est urgent de prendre des mesures pour réduire durablement le coût de la polychimiothérapie pour le patient si l'on veut qu'elle soit applicable ; certaines orientations sont proposées.

## Resumen

### Malaria en África: delimitar las responsabilidades para evitar una catástrofe

La grave amenaza planteada por la propagación de la malaria farmacorresistente en África es un problema ampliamente reconocido. La resistencia a la cloroquina es ya casi universal, y la resistencia al medicamento sucesor, la sulfadoxina-pirimetamina (SP), está extendiéndose rápidamente. Se ha sugerido el recurso a la politerapia como solución disponible y potencialmente duradera para esta crisis inminente. Sin embargo, el actual costo de la politerapia, especialmente el de las combinaciones basadas en la artemisinina (PA), constituye un posible inconveniente grave, aun cuando una parte significativa de ese costo se traslade al usuario.

Si no se aborda satisfactoriamente ese problema, el despliegue de la politerapia como tratamiento de primera línea podría conducir a resultados adversos, desde un aumento de los retrasos potencialmente mortales en la búsqueda de atención médica por los individuos infectados, hasta la exclusión total del tratamiento de los enfermos de malaria más pobres. Se requieren medidas urgentes a fin de reducir el costo de la politerapia para el usuario de manera sostenible y hacer así viable esa opción, y se examinan aquí algunas de las posibles estrategias en esa línea.

## ملخص

### التغلب على كارثة الملاريا في أفريقيا، أين يتوقف النجاح؟

المستخدم النهائي. وإذا لم تتم معالجة مسألة التكاليف بنجاح فإن نتائج ضائرة قد تنتج من استخدام المعالجة المشتركة كخط معالجة أولي. وتتراوح هذه النتائج الضائرة من ازدياد محتمل في التأخير المميت لمراجعة المرضى للخدمات الطبية إلى إقصاء أشد الناس فقراً من الحصول على المعالجة. ولا بد من اتخاذ خطوات لإنقاذ تكاليف المعالجة المشتركة على المستخدم النهائي بطريقة مضمونة الاستمرار إذا كان من المقرر استخدامها مع مناقشة بعض الأساليب لتحقيق ذلك.

الملخص: أصبح من المعروف بشكل واسع مدى خطورة التهديد الذي يمثله انتشار الملاريا المقاومة لأدوية متعددة في أفريقيا. وتكاد المقاومة للكولوروكين تعم العالم بأسره، فيما يتسارع انتشار المقاومة لسلفه السلفادوكسين برميثامين، وقد اقترح أن توفير معالجة مشتركة سيكون حلاً دائماً لهذه الأزمة الوشيكة الحدوث، إلا أن التكاليف الحالية للمعالجة المشتركة ولاسيما ما يتضمن منها الأرتيميسينين يعد من المعوقات التي يحتمل أن تكون هامة جداً رغم أن جزءاً كبيراً من هذه التكاليف سيتحمله

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