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levels of research funding are increased. The recommendation by the Commission on Health Research for Development that at least 2% of national health budgets and at least 5% of development aid should be invested in health research and on building research capacity must be heeded without further delay.¹⁴

Research with, rather than in or about, Africa is the goal. This will demand joint working to set agendas for research and mutual respect for countries' priorities, values, and choices. Partnerships should be transparent, clearly showing what each side brings and what each stands to gain. Furthermore, there must be clear mechanisms to ensure that some funds for research are directed to strengthening the capacity to conduct research, manage research (by establishing processes to handle grant funding and to review the ethics of proposed research), and develop skills in scientific writing. Finally, Africa's researchers, policy makers, and partners will have to give special attention to ensuring that knowledge generated from research is acted on to improve health for all.

Jimmy Volmink *professor and chair of primary health care*

Faculty of Health Sciences, University of Cape Town, Groote Schuur Hospital, Observatory 7925, Cape Town, South Africa (jvolmink@cornack.uct.ac.za)

Lola Dare *chief executive officer*

Center for Health Sciences Training, Research, and Development International, Ibadan, Nigeria

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- 1 Wagner CS, Brahmakulam I, Jackson B, Wong A, Yoda T. *Science and technology collaboration: building capacity in developing countries?* 2001. www.rand.org/publications/MR/MR1357.0/ (accessed 23 Sep 2005).
- 2 Folb P. New drugs for developing countries: obstacles and opportunities. (Paper commissioned by the Working Group on Access to Medicines, UN Millennium Project Task Force on HIV/AIDS, Malaria, TB and Access to Essential Medicines. UN Millennium Project, New York, 2004.)
- 3 World Health Organization. *World report on knowledge for better health: strengthening health systems.* Geneva: WHO, 2004. www.who.int/rpc/meetings/en/world_report_on_knowledge_for_better_health2.pdf (accessed 23 Sep 2005).
- 4 Volmink J, Siegfried N, Robertson K, Gulmezoglu AM. Research synthesis and dissemination as a bridge to knowledge management: the Cochrane Collaboration. *Bull World Health Organ* 2004;82:778-83.
- 5 Nkuhlu WL. The new partnership for Africa's development: the journey so far. June 2005 <http://www.nepad.org/2005/files/documents/journey.pdf>
- 6 Swiss commission for Research Partnership with Developing Countries. *Guidelines for research in partnership with developing countries: 12 principles.* Berne: Swiss Academy of Sciences, 2000.
- 7 Costello A, Zumla A. Moving to research partnerships in developing countries. *BMJ* 2000;321:827-9.
- 8 Edejer T. North-South research partnerships: the ethics of carrying out research in developing countries. *BMJ* 1999;319:438-41.
- 9 Binka F. North-South research collaborations: a move towards true partnership? *Trop Med Int Health* 2005;10:207-9.
- 10 United Nations Development Program. *Human development report 2005.* <http://hdr.undp.org/reports/global/2005/> (accessed 23 Sep 2005).
- 11 Severe E, Lewin S, Mariano A, Woelk G, Oxman AD, Mantinhure S, et al. System and market failures: the unavailability of magnesium sulphate for the treatment of eclampsia and pre-eclampsia in Mozambique and Zimbabwe. *BMJ* 2005;331:765-9.
- 12 Chandramohan D, Owusu-agyei S, Carneiro I, Awine T, Amponsa-Achiano K, Mensah N, et al. Cluster randomised trial of intermittent preventive treatment for malaria in infants in area of high, seasonal transmission in Ghana. *BMJ* 2005;331:727-33.
- 13 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;331:734-7.
- 14 Commission on Health Research for Development. *Health research: essential link to equity in development.* New York: Oxford University Press, 1990.

Antimalarial treatment with artemisinin combination therapy in Africa

Desirable, achievable, but not easy

The steady increase of drug resistant malaria across Africa is a crisis for which there are achievable solutions, but no easy ones. The scale of the problem is not in doubt. In Africa malaria remains one of the commonest causes of death and serious morbidity, especially for children and pregnant women.¹ Despite a decision in principle by many countries in Africa to use artemisinin based combination therapies (ACTs), most cases of malaria are still treated with monotherapy and in many areas most of these treatments will fail.^{2,3}

Drug combinations, rather than monotherapy, are now seen to be the best solution for treating malaria, and artemisinin based drug combinations are highly effective, with cure rates similar to that of chloroquine 30 years ago. They seem to be a good long term choice for most African countries, being safe and well tolerated (with the caveat that their safety in early pregnancy is not yet clear). Compared with other antimalarials, ACTs can reduce gametocyte carriage and thereby lower the risk of infectiousness in those who take treatment. In areas of relatively low malaria transmission in South East Asia and South Africa, widespread use of ACTs has reduced significantly the burden of malaria.⁴ This benefit is likely to be less marked

in areas of very high transmission in Africa, where much of the reservoir of malaria infection is in asymptomatic people who never seek treatment.

The primary problem with using ACTs in Africa is cost. The least expensive treatment courses currently cost more than \$1, roughly 10 times that of current monotherapy. In much of the continent people have malaria several times a year, and this cost could be prohibitive both for governments and households. In response to this problem policy makers have made strenuous efforts—led by the Global Fund for HIV/AIDS, Tuberculosis and Malaria—both to increase the supply of artemisinins (alleviating a current global shortage) and to provide drugs to governments at well below their market price.

This has prompted two parallel debates which have not yet been fully resolved. One is among donor agencies on how to achieve a sustainable subsidy. Nobody who understands this issue believes that subsidy can be avoided if ACTs are to reach those who need them most.⁵ What form that subsidy should take is, however, a complex technical matter on which there is no current consensus. Using these drugs will depend on a sustainable stream of funding; ministries of health in Africa are understandably wary of the

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fickleness of the donor community and are reluctant to commit to a policy which depends on a subsidy which could dry up.

In Africa there is an equally difficult technical debate about how to deploy ACTs to maximise their effectiveness and cost effectiveness. In this issue (p 734) a paper from Zambia, one of the earliest adopters of ACTs, illustrates some of the many formidable barriers to effective deployment.⁶ Even where the drugs were freely available and clinic staff knew they were being observed, only 22% of patients eligible for ACTs actually received them. This is only one of several issues which need to be addressed, and the scale of the change in approach to malaria treatment that will be needed if ACTs are to achieve their potential to reduce the burden of malaria is often underestimated. Three things in particular require careful thought.

For 40 years we have been treating malaria with monotherapies, essentially in limitless supply, which are cheap enough for individual households to buy. Healthcare workers have treated almost all febrile illness as malaria on the rational grounds that it is better to treat several viral illness with an antimalarial than to miss one potentially fatal infection which could be treated with chloroquine or sulfadoxine-pyrimethamine. Most people treated for malaria, even in the formal healthcare sector, do not actually have the disease.^{7,8} To continue this approach will lead to substantial unnecessary use of ACTs and will undoubtedly threaten the affordability and sustainability of any subsidised programme. The magnitude of the shift in mindset and practice which will be required for ACTs to be used only in proved cases of malaria will not be easy to achieve, however, and attempting it increases the risk that some true cases will be missed.

Another concern is how to involve the private sector. In many countries, most treatment for malaria is provided outside the formal healthcare sector, often by shopkeepers.⁹ Providing subsidised drugs to the formal public sector but not to the private or informal sectors may make affordable ACT treatment unavailable to people who rely on the informal sector, suddenly and substantially increase the workload for the formal sector, increase the potential for fake drugs entering the market, and encourage some patients to sell on unfinished courses of subsidised drugs in the marketplace when they start to feel better.

There is also a clear tension between the need to restrict the use of more expensive drugs to reduce costs and slow the development of malarial resistance, and the need to expand access into the community so that treatment is near home and therefore accessed early. Ministries are wary of complex tiered policies for malaria treatment that differ between rural and peri-urban areas, or that target drugs at certain vulnerable groups, but they may have to consider these options.

These technical problems can be solved, but at present few data are available to inform evidence based policy decisions regarding the most effective and cost effective deployment strategies, and ministries and researchers urgently need to work in partnership to fill this evidence void. It is unhelpful to ignore these major practical questions or to assume that, when ministries express caution about deploying ACT immediately, they are doing so out of negligence or ignorance. In

some countries in Africa the high level of drug resistance means ACTs are now the only effective option, and existing resources should be concentrated on these countries. For countries with good evidence of low levels of resistance to at least two monotherapies, an interim policy using cheaper non-artemisinin combinations, at least for some, may be sensible while evidence of the best deployment strategies for ACTs is being built up.¹⁰ ACT has the potential to be one of the greatest public health interventions for Africa this decade. We must get it right.

Grace Malenga *director*

Malaria Alert Centre, Bantyre, Malawi

Ayo Palmer *director*

Centre for Innovation Against Malaria, Banjul, The Gambia

Sarah Staedke *adjunct assistant professor*

Makerere University-UCSF Malaria Research Collaboration, PO Box 7475, Kampala, Uganda

Walter Kazadi *policy adviser, West African Network for Monitoring Antimalarial Treatment II*

Malaria Consortium, Accra, Ghana

Theonest Mutabingwa *chairman, East African Network for Monitoring Antimalarial Treatment*

Muheza Designated District Hospital, Muheza, Tanga Region, Tanzania

Evelyn Ansah *district director of health services*

Dangme West District Health Directorate/Research Centre, PO Box 1, Dodowa, Ghana

Karen I Barnes *associate professor*

Division of Clinical Pharmacology, University of Cape Town, South Africa

Christopher JM Whitty *senior lecturer*

Gates Malaria Partnership, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1B 3DP
(c.whitty@lshtm.ac.uk)

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- 1 Snow RW, Guerra CA, Noor AM, Myint HY, Hay SI. The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature* 2005;434:214-7.
- 2 Adjuik M, Babiker A, Garner P, Olliaro P, Taylor W, White N. Artesunate combinations for treatment of malaria: meta-analysis. International Artemisinin Study Group. *Lancet* 2004;363:9-17.
- 3 Mutabingwa TK, Anthony D, Heller A, Hallett R, Ahmed J, Drakeley C, et al. Amodiaquine alone, amodiaquine+sulfadoxine-pyrimethamine, amodiaquine+artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian children: a four-arm randomised effectiveness trial. *Lancet* 2005;365:1474-80.
- 4 Muheki C, McIntyre D, Barnes KI. Artemisinin-based combination therapy reduces expenditure on malaria treatment in KwaZulu Natal, South Africa. *Trop Med Int Health* 2004;9:959-66.
- 5 Arrow KJ, Panosian C, Gelband H, Eds. *Saving lives, buying time: economics of malaria drugs in an age of resistance*. Washington, DC: Institute of Medicine, 2004.
- 6 Zurovac D, Ndhlovu M, Rowe AK, Maner 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;331:734-7.
- 7 Amexo M, Tolhurst R, Barnish G, Bates I. Malaria misdiagnosis: effects on the poor and vulnerable. *Lancet* 2004;364:1896-8.
- 8 Reyburn H, Mbatia R, Drakeley C, Carneiro I, Mwakasungula E, Mwerinde O, et al. Overdiagnosis of malaria in patients with severe febrile illness in Tanzania: prospective study. *BMJ* 2004;329:1212-5.
- 9 Marsh VM, Mutemi WM, Willetts A, Bayah K, Were S, Ross A, et al. Improving malaria home treatment by training drug retailers in rural Kenya. *Trop Med Int Health* 2004;9:451-60.
- 10 Staedke SG, Mpimbaza A, Kanya MR, Nzarubara BK, Dorsey G, Rosenthal PJ. Combination treatments for uncomplicated falciparum malaria in Kampala, Uganda: randomised clinical trial. *Lancet* 2004;364:1950-7.