

empower patients. It was proposed in 2001,<sup>8</sup> yet the government has so far ignored the idea.

The human tissue authority should also be subject to greater parliamentary accountability, and the licensing requirements need to be more tightly defined to avoid pointless bureaucracy. The poor wording of the bill also needs to be addressed; seeking to create legislative flexibility is not an excuse for ambiguous and complex drafting. If the human tissue bill is not amended then it will ultimately fail the public; perceived improvements in the regulation of human tissue will come at the price of less medical research, education, and training.

Peter Furness *professor*

Department of Pathology, Leicester General Hospital, Leicester LE5 4PW (peter.furness@leicester.ac.uk)

Richard Sullivan *head of clinical programmes*

Research Management and Planning Directorate, Cancer Research UK, London WC2A 3PX

(Richard.Sullivan@cancer.org.uk)

Competing interests: PF is involved in training health service staff in ways that use human tissue in microscopic slides and with photomicrographs. He is also involved in research that uses tissue (from biopsies).

- 1 Royal Liverpool Children's Inquiry. *The report of the Royal Liverpool children's inquiry (the "Richards report")*, 2001. www.rlcinqury.org.uk/
- 2 Donaldson L. *Proposals for new legislation on human organs and tissue*. London: Department of Health, 2003. www.doh.gov.uk/tissue/legislationproposals.pdf (accessed 1 Mar 2004).
- 3 Winterton R. Verbal response. *House of Commons official report (Hansard)*. 2004 Feb 3, col 188.
- 4 Medical Research Council. *Public perceptions of the collection of human biological samples*. London: MRC, 2001. www.wellcome.ac.uk/en/images/biolcoll\_3182.pdf (accessed 25 Feb 2004).
- 5 Agarwal M, Sugden J, Quirke P. Introduction of consent for surgically removed tissue—report of two audits. *J Pathol* 2003;201(suppl):49A.
- 6 Department of Health. *Good practice in consent implementation guide: consent to examination or treatment*. London: DoH, 2001. www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Tissue/TissueGeneralInformation/TissueGeneralArticle/fs/en?CONTENT\_ID=4002298&chk=s2N3bw (accessed 25 Feb 2004).
- 7 Medical Research Council. *Human tissue and biological samples for use in research*. London: MRC, 2001. (Medical Research Council Ethics Series.)
- 8 Royal College of Pathologists. *Transitional guidelines to facilitate changes in procedures for handling "surplus" and archival material from human biological samples*. London: Royal College of Pathologists, 2001. www.rcpath.org/index.php?PageID=208 (accessed 25 Feb 2004).

## Treating malaria in Africa

### *Sulfadoxine-pyrimethamine may still have a future despite reports of resistance*

For many years the treatment of malaria in Africa has relied on chloroquine, sulfadoxine combined with pyrimethamine, and quinine, with the latter being used mainly to treat severe cases. Quinine remains efficacious, but chloroquine and sulfadoxine-pyrimethamine are failing, and this is leading to an increase in mortality from malaria especially in East Africa.<sup>1 2</sup>

Although resistance to chloroquine was first detected on the east coast of Africa in 1977, the drug has provided effective treatment for malaria for much of Africa for over 20 years.<sup>3 4</sup> Unfortunately this is unlikely to be the case for sulfadoxine-pyrimethamine, the combination adopted by several African countries as the first line treatment for malaria when chloroquine has failed. Systematic surveillance for resistance to malaria drugs and the results of trials of new drugs or drug combinations that could be used to replace chloroquine or sulfadoxine-pyrimethamine are showing a worryingly high level of resistance to sulfadoxine-pyrimethamine across eastern and southern parts of Africa.<sup>5 6</sup> Resistance to sulfadoxine-pyrimethamine is particularly severe in north east Tanzania, where clinical failure rates of up to 50% have been described,<sup>7</sup> but high levels of resistance have been recorded also in parts of Burundi, Kenya, Rwanda, and Uganda.<sup>8</sup> Levels of resistance to sulfadoxine-pyrimethamine are generally lower in West Africa, but clinical failures are not infrequent, and parasites carrying mutations associated with resistance to sulfadoxine-pyrimethamine are distributed widely across West Africa. Genetic studies show that resistance to sulfadoxine-pyrimethamine may have arisen in southern and eastern Africa on only a few occasions, so these resistant strains have spread extensively and rapidly.<sup>9</sup> Sulfadoxine-pyrimethamine seems to have little future as a first line antimalarial in Africa. However, the results of a recent study by Plowe

et al (p 545) in Malawi raise the possibility that this conclusion may be too pessimistic.<sup>10</sup>

Malawi changed from chloroquine to sulfadoxine-pyrimethamine as first line treatment for malaria in 1993, the first country in Africa to do so. Plowe et al report clinical and parasitological responses of children with uncomplicated clinical episodes of malaria to treatment with sulfadoxine-pyrimethamine five to nine years later (in 1998 and 2002). In 1998, 86% of children showed an adequate clinical response 14 days after treatment; four years later the response rate was still 83%. Twenty eight days after treatment clinical response rates were 73% and 61%, respectively, a modest but statistically significant fall over time. Parasitological cure rates 14 days after treatment were 73% in 1998 and 60% in 2002 but were much worse 28 days after treatment—38% and 27%, respectively. Some of the apparent 28 day failures may have been reinfections, but even if this was the case it indicates a high level of resistance to sulfadoxine-pyrimethamine, as a single dose of sulfadoxine-pyrimethamine gives up to four weeks of prophylaxis against parasites that are sensitive to the combination.

How robust are these unexpected findings of a relatively stable level of resistance to sulfadoxine-pyrimethamine? The strengths of this study are that it was carried out by the same investigators at the same site using the same methods of analysis over the four year study period and that the numbers of children studied each year (82-425) were large enough to have detected a decline in efficacy. Dropout rates were quite high but were similar in each survey. A progressive fall in the clinical efficacy of sulfadoxine-pyrimethamine would have been detected had it occurred.

The results of this study from Malawi indicate that, in contrast to the situation in other countries such as Thailand and South Africa, a moderate level of resistance to

sulfadoxine-pyrimethamine can be sustained over several years and that once resistance has emerged a rapid decline in sensitivity is not inevitable. Why this has happened in Malawi but not elsewhere is uncertain. The investigators think that this may be due to the high level of transmission of malaria in Malawi, which results in early acquisition of immunity and many asymptomatic infections. Because most asymptomatic infections are not treated, only a relatively small proportion of the parasites circulating in Malawi are exposed to an antimalarial at any one time. This contrasts with the situation in areas where transmission is low, such as Thailand, where nearly all infections cause symptoms and are treated, thus providing any resistant parasites with a strong survival advantage. Although considerations of this kind could explain why resistance seems to have developed more slowly in Malawi than in South East Asia, it does not account for the rapid spread of resistance to sulfadoxine-pyrimethamine in parts of East Africa where the level of transmission is as high as, or higher than, in Malawi.

Although the findings from this study are better than might have been expected, they should not induce complacency about the use of sulfadoxine-pyrimethamine for the treatment of malaria in Africa. Clinical and parasitological failure rates 28 days after treatment of 20% and 70% are not satisfactory, and many of the children with parasitaemia on day 28 will subsequently develop a clinical attack. If these findings are representative of the situation in other parts of Malawi a further change in treatment policy is needed. The results of this study should not be used to justify a switch to monotherapy with sulfadoxine-pyrimethamine by countries in Africa contemplating a change from chloroquine. Strong evidence now exists

to support a change to combination therapy with two or more drugs, each of which is highly effective locally.<sup>11</sup> Malawi has been fortunate to obtain 10 years of effective use from sulfadoxine-pyrimethamine; other countries in Africa are unlikely to be as fortunate.

Brian Greenwood *professor of clinical tropical medicine*

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT  
(brian.greenwood@lshtm.ac.uk)

Competing interests: None declared.

- 1 Trape J-F, Pison G, Preziosi M-P, Enel C, Desgrées du Loû A, Delaunay V, et al. Impact of chloroquine resistance on malaria mortality. *C R Acad Sci Paris* 1998;321:689-97.
- 2 Korenromp EL, Williams BG, Gouws E, Dye C, Snow RW. Measurement of trends in childhood malaria mortality in Africa: an assessment of progress towards targets based on verbal autopsy. *Lancet Infect Dis* 2003;3:349-58.
- 3 Fogh S, Jepsen S, Efferson P. Chloroquine-resistant *Plasmodium falciparum* in Kenya. *Trans R Soc Trop Med Hyg* 1979;73:228-9.
- 4 Kean BH. Chloroquine-resistant *falciparum* malaria from Africa. *JAMA* 1979;241:395.
- 5 East Africa Network for Monitoring Antimalarial Treatment (EANMAT). Monitoring antimalarial drug resistance within national malaria control programmes: the EANMAT experience. *Trop Med Int Health* 2001;6:891-8.
- 6 Wongsrichanalai C, Pickard AL, Wernsdorfer WH, Meshnick SR. Epidemiology of drug-resistant malaria. *Lancet Infect Dis* 2002;2:209-18.
- 7 Mutabingwa T, Nzila A, Mberu E, Nduati E, Winstanley P, Hills E, et al. Chlorproguanil-dapsone for treatment of drug-resistant *falciparum* malaria in Tanzania. *Lancet* 2001;358:1218-23.
- 8 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;8:860-7.
- 9 Roper C, Pearce R, Bredenkamp B, Gumede J, Drakeley C, Mosha F, et al. Antifolate antimalarial resistance in southeast Africa: a population-based analysis. *Lancet* 2003;361:1174-81.
- 10 Plowe CV, Kublin JG, Dzinjalalama FK, Kamwendo DS, Mukadam RAG, Chimpeni P, et al. Sustained efficacy sulfadoxine-pyrimethamine for uncomplicated *falciparum* malaria in Malawi after 10 years as first line treatment: five year prospective study. *BMJ* 2004;328:545-8.
- 11 Nosten F, Brasseur P. Combination therapy for malaria. The way forward. *Drugs* 2002;62:1315-29.

## What's the E for EBM?

*Theme issue will question the evidence for evidence based medicine*

Interest in evidence based medicine has grown exponentially from one Medline citation in 1992 to more than 13 000 in 2004. Professional organisations and training programmes for healthcare professionals have moved from whether to teach evidence based medicine to how to teach it, resulting in an explosion in the number of courses, workshops, and seminars offered in this practice. Reports describing evidence based rejuvenations of traditional educational events are burgeoning, and case reports and a survey of residency programmes have concluded that some of the determinants of continuing high attendance at postgraduate journal clubs include the teaching of critical appraisal skills and emphasising the primary literature (and not surprisingly, providing free food).<sup>1 2</sup> Familiarity with its terminology has extended into the popular press, as evidenced by a recent article in the *Times* describing the number needed to treat.<sup>3</sup> But all this leads to the question, "What's the E for EBM?"

Discussion about the practice of evidence based medicine naturally engenders negative and positive reactions from clinicians. Some of the criticisms focus on

misunderstandings and misperceptions of evidence based medicine such as the concerns that it ignores patients' values and preferences and promotes a cookbook approach.<sup>4</sup> But this debate has highlighted limitations unique to the practice of evidence based medicine that must be considered. For example, the difficulty of developing new skills in seeking and appraising evidence cannot be underestimated. Moreover, the need to develop and apply these skills within the time constraints of our clinical practice must be addressed.

The body of evidence relating to the impact of evidence based medicine on healthcare professionals ranges from systematic reviews of training in the skills of evidence based medicine to qualitative research describing the experience of evidence based medicine practitioners.<sup>5 6</sup> However, studies of the effect of teaching and practising evidence based medicine are challenging to conduct. In many studies, the intervention has been difficult to define. What the appropriate "dose" or "formulation" should be is unclear. Some studies use an approach to clinical practice while others use training in one of the discrete microskills of evidence based medicine such as searching Medline or