

Sulfadoxine-pyrimethamine for uncomplicated falciparum malaria

Sulfadoxine-pyrimethamine is not working in Malawi

EDITOR—The paper by Plowe et al entitled “Sustained clinical efficacy of sulfadoxine-pyrimethamine for uncomplicated falciparum malaria” might be better titled “Sustained lack of efficacy of sulfadoxine-pyrimethamine...”¹ By the start of the study period five years ago, molecular genotyping showed that *Plasmodium falciparum* in Malawi had already acquired significant resistance to the combination.^{1,2} This explains the sustained lack of efficacy; 28 day cure rates in children with acute falciparum malaria remained steadily less than 40% over the five year study period. This is confirmed by the Malawi component of recent WHO-Special Programme for Research and Training in Tropical Diseases (TDR) multicentre trials; the 28 day cure rate with sulfadoxine-pyrimethamine in children with acute falciparum malaria was only 23%,³ and this for a major killing disease of childhood. A 77% failure rate is among the worst responses ever documented. Only 7% (5/71) of reported trials on sulfadoxine-pyrimethamine have had worse failure rates.⁴

Before sulfadoxine-pyrimethamine was introduced widely it was very effective in Malawi, but, since then, efficacy has fallen dramatically (table). The front page of the *BMJ* was wrong: sulfadoxine-pyrimethamine is not “still working.” A drug giving a cure rate of consistently less than 40% for a potentially life threatening infection cannot be described as having “good efficacy,” particularly when highly effective alternatives exist.

Can you imagine endorsing an antibiotic with a more than 60% failure rate for use in European or American children with

those words? Demographic surveillance system data from eastern and southern Africa show that mortality attributable to malaria in children almost doubled between 1990 and 1998, whereas by contrast non-malaria related mortality fell. The use of ineffective drugs, such as sulfadoxine-pyrimethamine in Malawi, may well be to blame.⁵

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Competing interests: None declared.

- 1 Plowe CV, Kublin JG, Dzinjalimala FK, Kamwendo DS, Mukadam RA, Chimpeni P, et al. Sustained clinical efficacy of sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Malawi after 10 years as first line treatment: five year prospective study. *BMJ* 2004;328:545-8. (6 March.)
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Extra references in table are available on bmj.com

Treatment failure and resistance in Malawi remain subject for debate

EDITOR—The methods applied to enhance the interpretation of the data by Plowe et al deserve comment.¹

The World Health Organization has developed several standardised protocols to assess the efficacy of antimalarial drugs,

which are intended to determine treatment failures and not resistance patterns of the parasite. Recently, WHO published a revised protocol, giving clear indications of outcome classifications and the target groups (children under 5 years in intense transmission areas) to be monitored.² The new classification is appropriate for patients with symptoms and includes not only clinical but also parasitological criteria. It becomes redundant now to report the response based on the 1973 classification. Moreover, examination of WHO's database on antimalarial drug efficacy has shown that early treatment failure corresponds closely to parasitological resistance grade RIII + RII, contradicting the authors' claim that early treatment failure is systematically overestimating the true early failure rate.

A technical meeting convened by WHO's regional office for Africa in Harare in August last year agreed that, in intense transmission areas, asymptomatic parasitological failure (quoted as LPF in the new protocol) should be an additional indicator for the interpretation of the test. It was also agreed that an unacceptable failure rate is reached when clinical failure at day 14 is $\geq 15\%$ and total failure $\geq 25\%$.² The authors' data in table 2 show that these thresholds have been reached in Ndirande since 1999.

There is clear evidence that the resistance of *Plasmodium falciparum* to sulfadoxine-pyrimethamine has increased in Malawi over the past 10 years. According to Plowe et al, resistance to sulfadoxine-pyrimethamine was absent in Malawi in 1990.³ The level of cumulative RI-RII-RIII parasitological failure probably reached a peak in Ndirande in 1999. Similar failure rates with chloroquine in six sites in Malawi led to a policy change in 1993.⁴

Data on the efficacy of sulfadoxine-pyrimethamine in Malawi are a subject of scientific debate. Behind this debate, there is a real public health issue of delivering fully effective drugs to the population.

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- 1 Plowe CV, Kublin JG, Dzinjalimala FK, Kamwendo DS, Mukadam RA, Chimpeni P, et al. Sustained clinical efficacy of sulfadoxine-pyrimethamine for uncomplicated falciparum malaria in Malawi after 10 years as first line treatment: five year prospective study. *BMJ* 2004;328:545-8. (6 March.)
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Therapeutic responses (percentages) to sulfadoxine-pyrimethamine in Malawian children with acute falciparum malaria, 1987-2003

Reference*	Day 7	Day 14	Day 21 or 28
Heymann et al 1987 ⁶	100		100 (day 21)
Nwanyanwu et al 1996 ⁷	98	98	
Verhoeff et al 1997 ⁸	98	90.5	
Nwanyanwu et al 2000 ⁹	89	81-93	
MacArthur et al 2000 ¹⁰	80		
WHO-TDR study 2000-2 ²		53	23† (day 28)
Plowe et al 2004 ¹	78-88	61-73	27-39 (day 28)

*Full details of references 6-10 are available on bmj.com

†True success rate, excluding reinfections, 32% (36/113) confirmed by polymerase chain reaction genotyping.

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Authors' reply

EDITOR—How to reconcile our article's report of a sustained 80% efficacy with White's assertion that we found cure rates of less than 40%? We used the World Health Organization's standard definition of antimalarial therapeutic efficacy in high transmission areas, which is based on follow up through 14 days after treatment.¹ We also reported parasitaemia prevalences at 28 days after treatment, but these data do not provide cure rates in any accepted or standard sense. In high transmission settings, the "cure rate" declines as follow-up is extended from 14 days to 28 days or longer.

A longitudinal study compared the efficacy of sulfadoxine-pyrimethamine and chlorproguanil-dapsone in Malawi from 1997 to 1999.² Chlorproguanil-dapsone, a short-acting antifolate combination, had 95% efficacy compared with 80% for sulfadoxine-pyrimethamine. Children treated with sulfadoxine-pyrimethamine for all episodes of malaria over a year had no more episodes of uncomplicated malaria, anaemia, or severe malaria than those treated with chlorproguanil-dapsone. Radical cure, which can be achieved with short-acting, highly efficacious combinations, should be the goal where the risk of reinfection is low, but this study demonstrates that over time, children in areas of high transmission may do as well or better with a longer acting drug with mediocre efficacy than with a highly curative short acting regimen. Assumptions that the best approach to malaria therapy in one setting can be extrapolated to all other settings are unwise.

Malawi introduced sulfadoxine-pyrimethamine as the first line antimalarial in 1993. This was accompanied by a 20% reduction in infant mortality and a 22% reduction in child mortality from 1990 through 2000,³ despite increasing rates of HIV mortality during this period, and in contrast to increasing infant and child mortality in the rest of the region, where other countries continued to use chloroquine. The continued use of chloroquine in the face of truly dismal efficacy rates was likely to be responsible for higher mortality among children in other countries of this region.

Subsequent to our study, both the protocol for monitoring antimalarial efficacy and the threshold for recommending switching malaria drugs were changed, as noted by Ringwald. Nevertheless, we agree with White and Ringwald that the observed degree of efficacy (however it is defined) reported in our study is less than satisfactory. Hence the statement in our paper that the efficacy levels we reported for sulfadoxine-pyrimethamine do not warrant complacency about seeking alternative treatments for its replacement. The situation is chang-

ing, and all countries must now seek to introduce optimal first line treatments and to monitor their effectiveness against malaria-attributable mortality in children.

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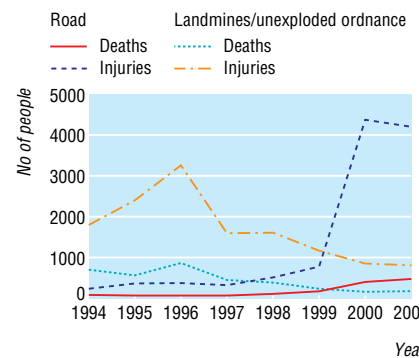
Competing interests: None declared.

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Aid may make roads more dangerous than landmines

EDITOR—Roberts and Abbasi highlight disproportionately low spending on preventing road injuries compared with more popular investment areas.¹ Perel et al address gaps in road safety in developing countries where risks are high since protective clothing, road rules, driver training, and speed limits are often absent.²

Annual injuries and deaths from road traffic crashes overtook those related to unexploded ordnance and landmines in Cambodia after 1998 (figure). Crashes continued to rise in number and severity—a disturbing trend when Cambodia ranks high for the number of landmines per head.



Numbers of deaths and injuries on roads and from landmines and unexploded ordnance in Cambodia. Sources: Ministry of Public Works and Transport (roads) and Cambodian Red Cross (CRC) and Handicap International (mines)

One aid donor, Japan, has funded bridges and road rebuilding from the 1992 ceasefire until the present, repairing damage from fighting and torrential rain.³ Japan holds a virtual monopoly in automobile sales in Cambodia, so the integration of aid and investment is convenient. Recently, roads have become more efficient and faster whereas public transport systems (trains) have decayed. Roads are also more efficient at killing.⁴

Handicap International Belgium and the Cambodian Red Cross have worked to incorporate road safety into Cambodian culture. However, donor countries that inadvertently contribute to deaths on such a massive scale should also be made to contribute: enforcing road rules, financing safety equipment and training, and designing roads to protect slower road users. This would involve a tiny fraction of countries' profits. Unexploded ordnance, landmines, and infectious diseases are a more attractive option to donors, especially when the cost of their investments is so seldom understood.

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Competing interests: None declared.

- 1 Roberts I, Abbasi K. War on the roads: two years on. *BMJ* 2004;328:845. (10 April)
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Death on the roads could be the chance of life for some

EDITOR—Tragic and wasteful as dying in a road traffic crash is, it is an opportunity for solid organ donation and procurement (liver, kidneys, heart, and lungs).¹

Although it is incumbent on governments and institutions such as the Medical Research Council to demand and develop strategies for reducing deaths from road traffic crashes, it is not unreasonable to believe that the same groups should promote every effort to support and sustain organ donation from people dying in such circumstances. Thus, some good might arise from an otherwise hopeless and seemingly futile situation.

Neither the European Liver Transplant Registry website (www.eltr.org) nor the recent paper on behalf of the same group states what proportion of patients undergoing orthotopic liver transplantation did so with an allograft from a dead donor who died as the result of a road traffic crash.² Of 5183 patients undergoing such transplantation in the United States between 1 July 2002 and 30 June 2003, 22.9% gained their allograft as the consequence of a motor vehicle crash.³

However, these data give no indication of the numbers of patients whose death as the result of a road traffic crash led to successful organ procurement for transplantation. Furthermore, so long as disparity in the laws on the status of dead people with respect to consent for organ donation exists between countries, then the opportunity for organ procurement and the gift of life for otherwise dying people will remain unfulfilled.

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Acquiring accurate crash data is important

EDITOR—Breen highlights the barriers that exist between establishing a risk for serious or fatal road injuries and the willingness of those in authority to assist the investigation or ultimately implement change.¹ Furthermore, acquiring good data on which to establish risk is hampered by a system that is biased in favour of the survivors of crashes, a police force that has little commitment to establishing the facts or releasing the results of their investigations to the relatives of the deceased, and a coroners' court that lacks the determination or authority to question the validity of the police accident report.

Many readers of the *BMJ* may be unaware of the haphazard way in which data are collected and the poor application of scientific principles to this area of investigation. Undue credibility is given to the statements of survivors, who know that silent (dead) witnesses cannot testify. In the case of fatal road crashes, we do not want to say that survivors are guilty until proved innocent, rather that survivors should establish their lack of culpability. This sounds like a semantic quibble, but until we use technology to acquire crash data from the vehicles involved, rather than from their drivers, we will continue to accept circumstantial and heavily biased statements that exonerate those who may have perpetuated these violent acts.

Given that cheap mobile phones can take and transmit instant images, surely it is not beyond technological expertise to introduce a black box to monitor a vehicle's performance and ultimately provide the evidence to support or refute culpability in the event of a crash?

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- 1 Breen J. Road safety advocacy. *BMJ* 2004;328:888-90 (10 April.)

More on treating homosexuality as a sickness

Publication of bigoted letter is worrying

EDITOR—The publication of Igbokwe's letter equating paedophilia with homosexuality in the debate on treating homosexuality as a sickness is worrying.¹ Although a debate on sexuality is positive (even if we do have to read misinformed and outdated views), it can serve to show both practitioners and the public that many general practitioners are still woefully ignorant about sexuality—and other issues too. However, to permit the publication of Igbokwe's letter is distasteful.

Such views not only show ignorance but also contribute to homophobic abuse. I am saddened, but not surprised, to see the extent of homophobia and ignorance in Igbokwe's letter and elsewhere in this debate. But I am disgusted that a medical journal should publish and by doing so endorse, a letter linking homosexuality and paedophilia.

The job of health professionals is to provide care for the public. That public will include people with different sexual orientations, views, and beliefs. General practitioners should offer all patients equal care. You may not like what your patient represents, but you should be able to care for them and understand them all equally. There is no room for bigotry in health care, although this correspondence has shown that it is thriving in the NHS.

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- 1 Igbokwe U. Treating homosexuality as sickness. *BMJ* 2004;328:955. (17 April.)

Homosexuality is punishable in India

EDITOR—Twisselmann summarised the debate on bmj.com about treating homosexuality as a sickness.¹ The differing views of doctors and society about homosexuality are well known; in India both society and doctors seem to share the same perceptions, which is worrying because of their strength and the repercussions on the homosexual community.² In India homosexuality is punishable even between two consenting adults: the laws of colonial times are yet to change. Thus homosexuals have no special rights. Mostly, they meet in public toilets and clandestine clubs.

It would be interesting to learn to what extent the prevailing opinions about homosexuality affect the way in which psychiatrists and doctors in general deal with homosexual patients. Indian psychiatrists often have negative perceptions, as do the people at large. Use of aversive options such as electroconvulsive therapy for "treating gays" is not unusual here.

Most people are bewildered and taken aback after discovering a person's homosexual preference. Highly derogatory local terms, such as *chakka* (eunuch) and *gaandu* (one who has anal sex), are used for them. Homosexuality in women (lesbianism) is comparatively well received and not resented in the same way.

The following offers a possible solution. Doctors need to have firm opinions of their own, uninfluenced by society, and they should practise rational medicine. Transparent dialogue can be helpful, especially with parents who often force doctors to "treat" homosexuals.³ This might help prevent denigration of the over 50 million strong community of homosexuals in India.

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Diabetes may be undetected in many children in the UK

EDITOR—Cases of children showing type 2 diabetes have been linked to the rising prevalence of paediatric obesity. We are concerned that the true number of children with this form of diabetes may be far larger than paediatricians realise.

A recent representative survey in England found 18% of schoolchildren to be overweight and a further 6% to be obese.¹ On this basis, some 1.8m children in the United Kingdom are overweight and a further 700 000 children are obese.

The prevalence of type 2 diabetes has been recorded in 0.14% to over 4% of obese children, with impaired glucose tolerance found in 4.5% to 14.9%.²⁻⁵ Using a conservative estimate of 0.2% prevalence for type 2 diabetes and 3% for glucose intolerance, and ignoring overweight non-obese children, we would expect some 1400 children to be currently diagnosed with type 2 diabetes in the United Kingdom, and over 20 000 children with impaired glucose tolerance.

That we are not recording these high numbers indicates that the problem may be hidden. Most of the cases detected in surveys were undiagnosed before screening. In early diabetes patients may be asymptomatic or present with symptoms such as vaginal monilial infection. The children may not be aware of relevant symptoms, or not realise that they should report them.

We must be sure that, when children do express discomfort in some form, we listen to them. There are high costs associated with missing a case of diabetes

through lack of attention, ignorance, or unconscious discrimination against overweight children.

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- 1 Stationery Office. The health survey for England 2002: the health of children and young people. Available at: www.official-documents.co.uk/documents/deps/doh/survey02/hcyp/tables/ch9t6.htm (accessed 24 Mar 2004).
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Implementing guidelines on sudden infant death

EDITOR—Fleming et al described a multi-agency approach to investigating unexpected infant deaths.¹ Such a multiagency protocol—adopted by the police, health, social services, and coroners—has existed in Sussex since 1999. This precedent was acknowledged in the Avon protocol described by Fleming et al.¹

With support from the Foundation for the Study of Infant Deaths, we recently evaluated the Sussex protocol over its first three years. We looked at the processes and outcomes of multiagency investigations into unexpected infant deaths and obtained feedback from parents and professionals.

A key finding was that implementation of the protocol was incomplete and variable throughout the county. There was no agreed implementation strategy, and how the protocol was applied in practice was left to individual professionals on duty at the time. Some aims were achieved—for example, early interagency discussions took place, and most postmortem examinations were carried out by paediatric pathologists.

There were, however, gaps and inconsistencies in postmortem investigations. For example, over one third of babies were not examined for three or more days; this meant that evidence might have been lost, particularly as early investigations in accident and emergency departments were not recorded for two thirds of babies. The system whereby coroners or their officers have control over medical investigations was not always helpful.

Professionals' response to unexpected infant deaths requires a sensitive balance between evidence based medical and forensic investigation and family support. Multi-agency guidelines and protocols must, however, have an implementation strategy

that takes account of local expertise and resources, with clear accountabilities and a review process.

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- 1 Fleming PJ, Blair BS, Sidebotham P, Hayler T. Investigating sudden unexpected infant deaths in infancy and childhood and caring for bereaved families: an integrated multi-agency approach *BMJ* 2004;328:331-4. (7 February).

Advice on ganglions is flawed

EDITOR—The POEM headline “Half of all ganglions resolve spontaneously” is likely to lead to dangerous conclusions about a common hand condition among casual readers.¹ The text discusses a form of ganglion that constitutes only 18-20% of all such lesions, which is not made clear in the bottom line.

This POEM draws on the evidence of a flawed paper and then suggests its findings apply to all ganglia. Patients do not like these lesions, and the commonest dorsal form (60-70% of cases) causes discomfort. In my experience, symptoms are closely related to the degree of inflation of the lesion, waxing and waning in unison, which suggests they are probably caused by local compressive effects.

Patients come to hand specialists seeking removal, and the quoted article by Dias and Buch makes it quite clear that the selection of patients to be managed by masterly neglect was not impartial or objective: “the surgeon's preference dictated” whether surgery or observation was chosen.²

The case made for non-operative management is further weakened by the manner of arrival at figures for post-surgical recurrence, said by Dias and Buch to have been 42%.² Volar wrist ganglion surgery is challenging and yet was carried out by a mixed bag of “senior and junior surgeons.” In properly experienced hands, however, the recurrence rate after surgery for ganglia is “very low.”³

The bottom line of this POEM is that patients with ganglia will be misled by being told not to worry as their painful lump is likely to do just as well by leaving it alone. And cash strapped local management will be only too happy to reinforce this unfortunate advice.

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CSM warning on atypical psychotics and stroke may be detrimental for dementia

EDITOR—On 9 March the Committee on Safety of Medicines (CSM) advised avoiding olanzapine and risperidone for patients with dementia, reflecting concern over the excess risk of stroke.¹

Antipsychotic drugs have long been used (off licence) in dementia to treat neuropsychiatric disturbance and are highly effective.² Atypical antipsychotic drugs have recently been favoured over older preparations to avoid anticholinergic and Parkinsonian side effects, but a recent study of elderly people receiving typical and atypical antipsychotic drugs found no significant difference in risk of stroke between pharmacological groups.³ Stroke, while potentially catastrophic, is a quantifiably rare “excess risk” event in a group already at risk, demanding balanced thinking against real reductions in agitation and aggression.⁴

We are concerned that antipsychotic treatment will be unnecessarily withheld, and also that general practitioners will now adopt widespread use of conventional antipsychotic drugs. The Adults with Incapacity (Scotland) Act 2000 specifies that informed proxy decisions should be made on the basis of sound generalist and specialist advice, and in conjunction with relatives or carers. We regularly meet such carers in clinical practice who feel well served by drug treatment, are willing to engage in life's realities of assessing and accepting risk, and make those choices in conjunction with informed medical opinion. We believe that the blanket injunction issued by the Committee on Safety of Medicines is oversimplified and may prove detrimental to patient care.

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Competing interests: TM has received support from Janssen Cilag to attend an international meeting; the authors' department has received limited educational support from various pharmaceutical companies.

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