Is sulphadoxine-pyrimethamine (SP) still useful as the first-line antimalarial drug in Malawi or it must be quickly withdrawn from the antimalarial repertoire?

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In recent years our efforts to control malaria successfully have been severely hampered by widespread and high-level resistance to front-line antimalarial drugs. In 1993, Malawi had to replace chloroquine (CQ) with sulphadoxine-pyrimethamine (SP) as the first-line antimalarial owing to unacceptably high rates of CQ failure. Thirteen years after this change in treatment policy, Malawi is faced with a scenario that calls for yet another switch to a different first-line antimalarial. In vivo SP resistance has already exceeded critical levels recommended by the World Health Organization for a treatment policy change. A decision to change has been made by the national Malaria Control Programme: delay in implementing this decision could have serious consequences for Malawi.

There was no documented case of SP failure prior to the deployment of the drug in 1993.[1] A clinical trial in 1986 reported a 14-day adequate clinical response rate of 100% with SP.[2] However, following the introduction of SP in 1993, cases of SP resistance started to emerge[3-10] (Table 1), with 14-day failure rates (RI, RII and RIII) reaching as high as 36% in the town of Karonga in the year 1995 and 1996.[1] Plowe and his colleagues have prospectively monitored the clinical efficacy of SP in children since 1998. Their longitudinal study, reported in 2005, showed sustained SP clinical efficacy with 14-day adequate clinical response rates of 80-86% sustained over a 5 year period.[9] At first glance, these results might appear to suggest that SP is still working well enough and should be retained for some time as the first-line antimalarial drug in Malawi. However, we must remember these data were derived using the old WHO protocol for evaluating the clinical efficacy of antimalarial drugs in areas of intense malaria transmission.[11] This protocol has several practical limitations including the overestimation of early treatment failures[12] and short duration of follow-up (i.e. 14 days) for patients treated with long-acting drugs such as SP. Because of these limitations, the old protocol has since been modified.[13,14] The complete data presented by Plowe et al[9] show that in the same studies, 14-day parasite clearance rates were only 61-73%, and 28-day adequate clinical response rates ranged from 60% to73% with even poorer parasite clearance rates. Thus in vivo SP resistance had reached clinical failure rates ³ 15% and total clinical plus parasitological failure rates ³ 25%, levels that have since been recommended by WHO as indicative of the need for a treatment policy change.[14] This view is reinforced by results from a recent clinical trial, in which children were randomised to receive either CQ or SP as a treatment for uncomplicated P. falciparum malaria.[10] In that study, the 28-day adequate clinical and parasitological response rate of SP was only 21% (95% confidence intervals: 13 to 30%)[10]. This finding indicates that SP is not working well enough and should be withdrawn as the first-line antimalarial drug in Malawi.

Table 1: Therapeutic Efficacy of SP in Malawi from 1985 to 2005

Reference	Efficacy Measure	Year measured	Efficacy (%)
Heyman et al [2]	D7 and D21 PSR	1985	100
Nwanyanwu et al [3]	D7 and D14 PSR	1994	98
Verhoeff et al [4]	D7 PSR	1997	98
	D14 PSR		90.5
Nwanyanwu et al [5]	D7 and D14 PSR	1997--1998	81-93
MacArthur et al [6]	D14 ACR	1998	81
	D14 PSR		65
Takechi et al[7]	D14 PSR	1998	83
International Artemisinin Group8	D14 PSR	1999--2000	53
	D28 PSR		23
Plowe et al [9]	D14 PSR	1998-2003	61-73
	D28 PSR		27-39
	D14 ACR		80-86
	D28 ACR		60-73
Laufer et al [10]	D28 ACPR	2005	21

PSR = Parasitological Success Rate; ACR = Adequate Clinical Response; ACPR = Adequate Clinical and Parasitological Response

High and stable 14-day clinical efficacy rates of SP should not cause laxity and delay in adopting the new first-line treatment policy for malaria in Malawi. Continued use of the failing SP could potentially contribute to increases in malaria-associated morbidity and mortality.[15,16] Continued use of SP may also increase the economic cost of treating and preventing malaria. This cost can arise in a variety of ways. For example, treatment failures may be retreated with newer treatment agents, which are often more expensive than SP. Patients may incur extra transport costs on subsequent visits to the hospital or health centre if the first treatment has failed. Treatment failure may result in severe disease requiring hospitalisation.

In light of the foregoing discussion, SP has very little future as the first-line antimalarial drug in Malawi. Although semi-immune adults with some degree of acquired immunity may still be able to clear SP-resistant infections,[17,18] this may not be the case with young children and other high-risk groups. The most prudent thing to do would be to quickly replace SP with a combination-based therapy, and hope that SP resistance will wane in the absence of drug pressure as has been observed with CQ resistance[7,10,19,20]. The latter can only happen if some parasites remain genotypically susceptible

to SP.

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