EDITORIAL

SENTINEL MALARIA SURVEILLANCE — MORE THAN A RESEARCH TOOL

The monotonic increase in South African malaria cases, with an over 100-fold increase in notifications during the past three decades, from 364 notified cases in 1971 to 51 433 cases in 1999, has elicited consternation throughout the public health sector.[1] Although this dramatic increase is clearly multifactorial, resulting from the effects of meteorological changes, human parasite-carrier migratory patterns, resistance of a mosquito vector (*Anopheles arabiensis*) to synthetic pyrethroid insecticides and an inconsistent notification system, the contribution of ineffective first-line malaria therapy should not be underestimated. The situation in KwaZulu-Natal (KZN) deserves particular mention, given this province's increasing proportional contribution to the national malaria burden. A recent dramatic increase in case numbers in KZN and anecdotal reports from clinic staff of patients returning with recurrence of symptoms within 2 weeks of treatment with sulfadoxine-pyrimethamine (SP) raised the alarm that the province might be in the grip of high-grade malaria parasite (*Plasmodium falciparum*) resistance to SP. Earlier results of a small 1996 hospital-based study found a 23.5% RI/RII/RIII parasitological failure rate on SP therapy (Medical Research Council — unpublished data). Although this finding was inconclusive because of the possibility of referral selection bias, it should have prompted an urgent, through evaluation of the effectiveness of SP therapy. The establishment of a sentinel surveillance site in KZN could have addressed this need.

Resistance of *P. falciparum* to antimalarial drugs is a serious impediment to controlling malaria.[2-4] *P. falciparum* resistance to chloroquine was first reported in Africa in 1979, while clinical evidence of *P. falciparum* resistance to chloroquine emerged in South Africa during the mid-1980s.[5-8] Despite resistance, chloroquine is often still used in areas of stable malaria because of the additive effect of host immune factors resulting in clinical but not parasitological cure. In South Africa, however, where the majority of the population resident in malaria areas are unlikely to enjoy any immunity, the risk of rapid progression to severe disease and even death necessitates effective first-line therapy that will rapidly eliminate *P. falciparum* and effect a parasitological cure. Thus the findings of *in vitro* tests demonstrating high levels of chloroquine resistance in KZN and Mpumalanga, and a striking increase in positive follow-up smears after chloroquine therapy in Mpumalanga, from 1.7% in 1990 to 16.7% in 1995, demanded confirmation by a carefully conducted *in vivo* evaluation.[9-13]

Following examples in other countries, Mpumalanga established sentinel site at Naas and Mangweni health centres in their most affected malaria districts for collecting *in vivo* resistance data. A standardised chloroquine *in vivo* study, based on the World Health Organisation (WHO) protocol, with 28-day follow-up, was conducted at these health centres during 1997.[14] Unacceptable levels of RII/RIII (moderate to high level) parasitological failure (17.9%) and clinical failure (24%) were documented in Mpumalanga, with the total RI/RII/RIII parasitological failure rate being 48.4% (Freese J A, Report to the Department of Health). Similar patterns were found in Northern Province (RI/RII/RIII of 40%) and KZN (RI/RII/RI I of 62.5%) during surveys of smaller numbers of patients. This catalysed a national policy change from chloroquine to SP for first-line malaria treatment, although KZN had already made this change a decade earlier in 1988.

The same sentinel sites in Mpumalanga were used to conduct an informative baseline *in vivo* SP resistance survey c n introduction of the change in first-line treatment.[15] This evaluation, with 42-day follow-up, confirmed the efficacy of S P first-line therapy and demonstrated slower resolution of clinical symptoms than parasite clearance. In addition, it raise d important questions about the adequacy of the recommended SP dosage for adults exceeding 60 kg, and the viability of gametocytes found to peak 7 - 14 days after therapy. The results of the most recent evaluation conducted 2 years after S P introduction at the same site in Mpumalanga (in this issue of the journal) confirm the continued efficacy of SP.[16] This findin , raises the possibility that SP usefulness may be extended through combination with artesunate, thus sustaining affordable therapy in Mpumalanga.[17] This is necessary, since when used as monotherapy, resistance to SP has been shown o emerge more rapidly than resistance to chloroquine. Once hig n levels of SP resistance exist, few affordable treatment options remain.

The discovery of high-level failure of SP in the treatment of uncomplicated malaria in KZN, found in the standardised *in vivo* study conducted at clinic level in KZN in this issue of the journal), confirms concerns regarding the effectiveness of SP in this province.[18] More alarmingly, this has precluded the use of the SP-artesunate combination in KZN. Although the true impact of persistent use of failed SP first-line therapy during the recent past in KZN on morbidity, mortality, economic losses, malaria transmission and resultant public health expenditure cannot be accurately determined, the resulting crisis could have been circumvented had regular clinic-level sentinel surveillance been conducted.

Public health surveillance has many uses, the most well known being detection of epidemics, evaluation of control and prevention activities, detection of changes in health practice, quantitative estimates of the magnitude of health problems, and monitoring of changes in infectious agents, particularly the

volution of drug resistance.[19] Although the term 'surveillance' as initially restricted to the collection, analysis and issemination of data and did not encompass direct esponsibility for responding to findings, more recently the uality of surveillance has been judged by its capacity to rovide 'data for action'.[20-22]

Sentinel surveillance encompasses those activities focused n monitoring key health indicators in the general population ibgroups. The term sentinel is applied to health events, cluding cholera, malaria or maternal deaths, which provide a arning signal that the quality of preventive or therapeutic ealth services merits investigation.[23,24] Sentinel surveillance so refers to specifically chosen sites, whether health facilities health providers, where data that are not routinely available e collected.[25] Careful selection of sites allows for adequate sources, including experienced and dedicated personnel, for llecting detailed information on each case and providing reful follow-up. As the collection of data is the most costly d difficult component of any surveillance system, it is sential that all elements to assure quality, reliability and iformity of data are in place.[26] These include the ease of data llection facilitated by clarity, simplicity and lack of biguity of standardised forms and flow charts; well-defined se definitions; timeliness; mechanisms for preventing loss to llow-up; and measures to motivate data collectors, including edback, participation in planning and review, recognition and her incentives.

In selecting a sentinel surveillance site, consideration must be ven to a number of issues. These include the particular rpose of surveillance, frequency of the health event curacy of sample estimate), available resources, feasibility, e need to generalise findings (external validity), duration ends) and likely quality of data (internal validity). Use of spitals or other sophisticated facilities may pose problems cause of the selection bias that usually operates.[27] However, spitals are particularly valuable sites for tracking mortality nds or for detecting severe diseases that are almost evitably admitted.[28,29]

South Africa has been tardy in recognising the potential value of sentinel sites. A number of malaria control programmes in other African and South-East Asian countries have an established tradition of assessing the efficacy of their first-line malaria therapeutic regimens at sentinel surveillance sites to guide public health policy. In recent years both Zambia and Malawi have altered their national malaria treatment policies on the basis of results from standardised *in vivo* studies conducted at sentinel clinics.[30,31]

Malaria sentinel sites may serve additional valuable functions. In particular, their usefulness as an epidemiological early warning system for malaria epidemics is being increasingly realised. The alarm is triggered when monthly morbidity thresholds set for particular clinics are exceeded.[32-34] Mpumalanga has also harnessed the capacity developed at its sentinel sites to field test the accuracy and utility of rapid malaria diagnostic tests.[35,36] The seasonal nature of malaria transmission in South African creates the opportunity for using the capacity developed at these sites to the benefit of other public health programmes.

The need for a sentinel surveillance network as a prerequisite for epidemiological research and health planning in South Africa was mooted more than 60 years ago.[37] This plea appears to have been vindicated by the high-quality drug efficacy information and data on the accuracy of diagnostic tests already collected at the malaria sentinel sites in South Africa that have facilitated major policy changes. The proposed plan to establish similar sites in KZN, Northern Province, Swaziland and Mozambique should therefore be vigorously pursued. However, the true value of these sites will not be measured by the volume of information they generate, but by the public health actions triggered.

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FAILURE OF SULPHADOXINE-PYRIMETHAMINE IN TREATING *PLASMODIUM FALCIPARUM* MALARIA IN KWAZULU-NATAL

To the Editor: Sulphadoxine-pyrimethamine (SP) has been in use as the first-line curative drug for *Plasmodium falciparum* malaria in KwaZulu-Natal, South Africa since January 1988. It replaced chloroquine, to which resistance had been demonstrated.

There is widespread concern about the rate at which resistance has developed to SP elsewhere in the world, with anecdotal evidence suggesting that substantial resistance to it had developed in the malarious areas of KwaZulu-Natal.[1] Evolution of resistance may be exacerbated by SP's long half-life, with parasites therefore exposed to subtherapeutic drug concentrations for relatively long periods of time.

An *in vivo* study was conducted on patients attending the malaria clinic at Ndumo, KwaZulu-Natal. Patients were treated with SP and followed up daily for 3 days and thereafter at 7, 14, 21, 28 and 42 days post-treatment.

Ndumo clinic, in the Ingwavuma district of KwaZulu-Natal, is a satellite clinic of the Mosvold Hospital, and serves a rural population of approximately 15 000 people. Malaria transmission in this district is predominantly seasonal and the population is not thought to have acquired significant levels of immunity.

Patients diagnosed positive with malaria by the clinic staff were referred to the study team. They were retested with a rapid immunochromatographic diagnostic system (ICT MLC, AMRAD Operations, Pty Ltd, Australia), and informed consent was obtained from patients before proceeding with enrolment. Thick and thin blood smears were prepared from finger-prick blood and stained with Giemsa's stain. The standard *in vivo* inclusion criteria and detailed methodology used have been described elsewhere.[2]

SP tablets were administered as a single oral dose (25 mg sulphadoxine plus 1.25 mg pyrimethamine per kilogram body weight) and patients were asked to return on each of days 1, 2, 3, 7, 14, 21, 28 and 42. Parasitological evaluation using quantitative microscopy of Giemsa-stained blood smears was undertaken by the clinic microscopist, and clinical evaluation, including measurement of oral temperature and assessment of symptoms, was done by the research team at each visit.

Parasitaemia occurring in patients after day 21 was investigated with polymerase chain reaction amplifications of the genetic markers MSP1, MSP2 and GLURP1 and 2 in order to differentiate between true recrudescence of the original infection and possible new infections.[3]

At least 79 of the 129 enrolled patients failed (61.2%), but this may have been as high as 79/90 (87.8%) if those patients lost to follow-up are excluded from the analysis. The results of the 90 patients followed up to day 42 or failure are reflected in Table I.