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Malaria Pharmacovigilance in Africa

Lessons from a Pilot Project in Mpumalanga Province, South Africa

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Abstract

Background and objectives: Prior to the introduction of artemisinin-based combination antimalarial therapy in Mpumalanga province, South Africa, a pharmacovigilance strategy was developed to pilot locally relevant surveillance methods for detecting serious adverse drug reactions (ADRs) and signals related to artesunate plus sulfadoxine/pyrimethamine.

Study design: From 1 March 2002 to 30 June 2004, five methods for detecting ADRs in patients receiving antimalarials were piloted in the rural communities of Mpumalanga province in South Africa: (i) home follow-up of patients by malaria control staff; (ii) enhanced spontaneous reporting of suspected ADRs by health professionals at clinics and hospitals; (iii) active hospital surveillance for malaria-related admissions and patients recently treated for malaria; (iv) a confidential enquiry into malaria-related deaths; and (v) adverse events monitoring during two therapeutic efficacy studies conducted in 2002 and 2004.

Results: During the study period, the malaria control programme was notified of 4778 cases of malaria while sulfadoxine/pyrimethamine monotherapy was the recommended treatment and 7692 cases after the introduction of artesunate plus sulfadoxine/pyrimethamine in January 2003. Of 2393 home follow-up visits of reported cases of malaria, three fatal adverse events were identified where recent use of artesunate plus sulfadoxine/pyrimethamine treatment was reported. Two cases were attributed to poor response to treatment, while one case was considered possibly related to artesunate plus sulfadoxine/pyrimethamine treatment. Clinic and hospital surveillance reported six ADRs in association with sulfadoxine/pyrimethamine treatment, five being treatment failures and one being a non-serious rash. During active hospital surveillance, 38 inpatients exposed to sulfadoxine/pyrimethamine were identified, including one child who experienced pancytopenia following treatment with sulfadoxine/pyrimethamine 11 days before admission; this adverse effect was considered to be possibly due to sulfadoxine/pyrimethamine treatment. The confidential enquiry into malaria-

related deaths identified three adverse events, including a death where the contribution of treatment could not be excluded. A therapeutic efficacy study of 95 patients followed over 42 days identified one case of repeated vomiting possibly associated with artesunate plus sulfadoxine/pyrimethamine.

Conclusion: Multifaceted monitoring throughout the malaria patient journey is necessary in developing countries implementing new treatments to safeguard against missing serious complications associated with malaria treatment.

Background

The evolution of malaria into a multi-drug resistant disease with concurrent increases in malaria-related morbidity and mortality is a global public health crisis.[1] Combination antimalarial treatments, preferably including an artemisinin derivative, are currently regarded as the best available treatments for uncomplicated malaria.[2,3] Since most of the safety data on these combinations are derived from relatively small, time-limited controlled clinical trials predominantly in Southeast Asia, there is a need for ongoing pharmacovigilance. Malaria control programmes in developing countries face particular surveillance challenges, including high patient loads, limited diagnostic capacity, limited capacity for postmarketing surveillance and drug regulation, counterfeit medicines, confusion regarding reporting procedures and the widespread use of traditional and over-the counter medications.[4-6]

Based on animal studies and limited clinical safety data, concerns about the artemisinin derivatives at the time of this study included their safety in pregnancy,[7-9] potential for neurological complications[10,11] and the risk of hypersensitivity reactions.[12]

The rural communities of Mpumalanga province, the setting of this study, are unlikely to have acquired immunity to malaria, because of the seasonal, low-intensity malaria transmission pattern in this area.[13] *Plasmodium falciparum* infection accounts for approximately 90% of the cases of malaria diagnosed in Mpumalanga. A population of around 1 million is resident in the malaria-risk area in the North Eastern district of Ehlanzeni.[14] This district is serviced by 82 public sector clinics, 24 mobile clinics and 6 district hospitals. Approximately 45% of patients with reported malaria in Mpumalanga acquire their infections in Mozambique, as there are substantial population flows between these neighbouring countries.[15]

In January 2003, the Mpumalanga Department of Health changed their policy on first-line treatment for uncomplicated malaria from recommending sulfadoxine/pyrimethamine to recommending artesunate plus sulfadoxine/pyrimethamine. This change was prompted by an increasing annual number of malaria cases, increasing patient fatality rate (figure 1),[16] markedly increasing gametocyte carriage detected during *in vivo* sulfadoxine/pyrimethamine therapeutic efficacy studies[17] and the increasing consensus internationally on the benefits of employing artemisinin-based combinations.[18] It was hoped that by making this change at a time when sulfadoxine/pyrimethamine monotherapy achieved a 90% cure rate,[17] it would increase the useful therapeutic life of the artesunate

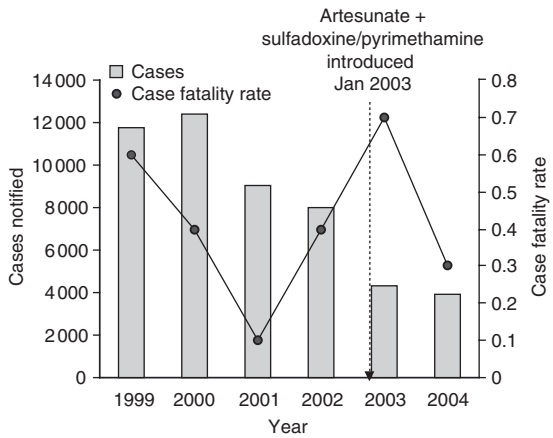

Fig. 1. Malaria cases notified and the case fatality rate per annum in Mpumalanga Province, South Africa (1999–2004).

plus sulfadoxine/pyrimethamine combination. This artemisinin-based combination therapy was preferred over artemether-lumefantrine given the programmatic advantages of administering a daily dose of artesunate for 3 days, with a single dose of sulfadoxine/pyrimethamine, compared with the six artemether-lumefantrine doses; its adequate absorption not being dependent on co-administration with fat; and its lower cost (A. Mabuza, unpublished observations).[19] The introduction of artesunate plus sulfadoxine/pyrimethamine together with strengthened vector control was associated with a 45.6% decrease in the notification of cases of malaria (figure 1). This is consistent with the decreased gametocyte carriage achieved by adding artesunate to sulfadoxine/pyrimethamine therapy.[20,21]

In the year prior to the introduction of artesunate plus sulfadoxine/pyrimethamine in Mpumalanga, a pharmacovigilance strategy was developed to meet the requirements of the national drug regulatory authority in South Africa, the Medicines Control Council. As artesunate plus sulfadoxine/pyrimethamine was not licensed in South Africa, special permission was granted by the Medicines Control Council for the use of this combination in the province of Mpumalanga, on the condition that a locally appropriate comprehensive surveillance system was established to address possible concerns regarding efficacy and safety. This paper describes the surveillance methods employed to detect signals of serious adverse drug reactions associated with first-line antimalarial therapy when used within a malaria control programme.

Methods

The monitoring system was initiated 10 months before the introduction of artesunate plus sulfadoxine/pyrimethamine, on 1 March 2002, while sulfadoxine/pyrimethamine monotherapy was the recommended treatment for uncomplicated malaria. Five methods were piloted to determine their value for continued use after the implementation of artesunate plus sulfadoxine/pyrimethamine on 1 January 2003 (figure 2), namely:

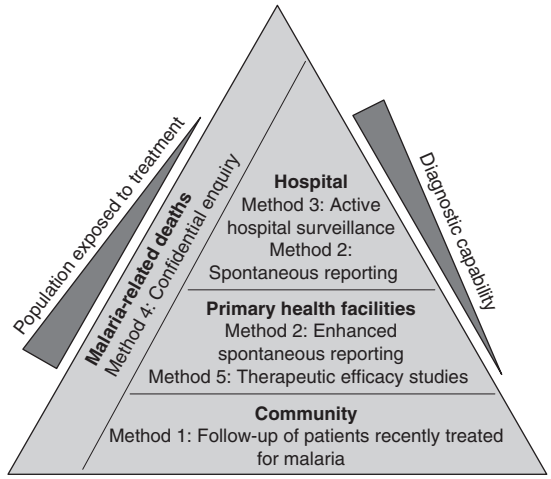

Fig. 2. Surveillance methods employed to assess safety of antimalarials. The five surveillance methods developed to monitor the safety of artesunate plus sulfadoxine/pyrimethamine considered the points of contact between the formal health sector and patients with malaria; the numbers of patients with malaria that accessed the various levels of healthcare (lower numbers of patients at higher level health institutions) and the diagnostic capacity available at each of the points of contact (increased diagnostic capacity at higher level health institutions).

1. Home follow-up of patients with notified cases of malaria by malaria control programme staff.

2. Enhanced spontaneous reporting of suspected adverse drug reactions (ADRs) by health professionals at clinics and hospitals.

3. Active hospital surveillance to detect patients recently treated with antimalarials.

4. A confidential enquiry into malaria-related deaths.

5. Adverse events monitoring during sulfadoxine/pyrimethamine and artesunate plus sulfadoxine/pyrimethamine therapeutic efficacy studies conducted in 2002 and 2004, respectively.

As this project was not a finite study but a commitment to ongoing surveillance, sample-size calculations were not performed. Instead, an opportunistic sample of all patients known to have had malaria during the study period was included for assessment. Since November 2002, adverse event reports collected using all the methods except the therapeutic efficacy studies were reviewed annually by an

international expert review panel comprising specialists in malaria, microbiology, epidemiology, pharmacology and public health. Adverse events were assessed to determine their causal association with the suspected drug(s) according to the WHO criteria for causality assessment.[22]

Because of diagnostic challenges faced by health staff regarding the differentiation between non-resolving malaria symptoms and possible ADRs, reports of poor response to treatment as ADRs were not discouraged. For review purposes, a poor response to treatment was considered if records indicated that the patient did not improve clinically or parasitologically despite a history of completing an antimalarial treatment regimen. Co-morbid disease was considered when assigning causality as this may have masked response to treatment.

Method 1: Home Follow-Up of Patients with Notified Malaria (1 August 2002 to 30 June 2004)

Malaria control programme staff routinely visited the homes of patients with notified malaria who were residing in areas of high malaria risk within the first month after they had been treated. During this visit, close contacts of the patient were tested for malaria using rapid diagnostic tests and it was determined when the last indoor residual insecticide spraying occurred in their home. Prior to the study, control programme staff were trained to complete a simple data collection form that recorded whether the patients with notified malaria had recovered, were still sick, had been hospitalised or had died since the last episode of malaria. During these visits, patients were also asked whether they had any remaining antimalarial tablets at home.

If the patient was still ill at the time of the visit, the programme officer advised the patient to report directly to the nearest clinic or hospital, depending on the severity of their illness. In case of deaths reported by family members or neighbours, additional information was sought as described under the confidential enquiry.

Method 2: Enhanced Spontaneous Reporting of Suspected Adverse Drug Reactions (ADRs) (1 March 2002 to 30 June 2004)

The official national ADR and product quality problem-reporting forms were made available in all public and private sector health facilities in the study area by the malaria control programme. At the start of the study in March 2002 and in November 2002, June 2003 and February 2004, nursing and medical staff were trained on the value of ADR reporting using this form. Reporting of ADRs to any essential medicine was encouraged. District malaria control programme and communicable disease control staff were trained to remind clinic and hospital staff to report and collect completed ADR and disease notification forms on a weekly basis.

Approximately 3 months after the clinic nurses were initially trained, they were contacted by telephone to determine whether there had been any problems associated with artesunate plus sulfadoxine/pyrimethamine treatment. These messages were reinforced at regular follow-up training sessions.

Method 3: Active Hospital Surveillance (1 April to 30 June 2002)

A retired hospital nurse was employed for 3 months to collect data on every patient admitted to Shongwe district hospital with either a presumptive diagnosis of malaria or a history of receiving malaria treatment in the previous month, regardless of the cause of admission. A detailed drug history and relevant clinical details were collected using a semi-structured questionnaire after written informed consent was obtained from the patient or caregiver. The patient's medical records and interview forms were reviewed by the author and suspected drug-related causes for admission were reviewed by the international expert panel. As this method was not considered cost effective by the international expert review panel in November 2002, intensive hospital surveillance was terminated prior to the introduction of artesunate plus sulfadoxine/pyrimethamine.

Method 4: Confidential Enquiry into Malaria-Related Deaths (1 March 2002 to 30 June 2004)

As has previously been described in a report on the confidential enquiry into malaria-related deaths in the three malaria provinces in South Africa,[23] all deaths identified during the study period were investigated. These deaths were identified through the notification system, spontaneous reporting and routine home follow-up visits of patients with malaria by the malaria control programme. As previously described, a semi-structured interview with the patient's close contacts (i.e. family members, work colleagues or neighbours) was conducted by the malaria control programme. Relevant medical records and results of the home-visit interview were reviewed by the international expert review panel.

Method 5: Adverse Events Monitoring during Therapeutic Efficacy Studies

Therapeutic efficacy studies were conducted for sulfadoxine/pyrimethamine treatment in 2002 and artesunate plus sulfadoxine/pyrimethamine treatment in 2004 in a subset of patients with notified malaria. Sample size calculations and eligibility criteria were based on the standard methodology for monitoring antimalarial drug resistance and are described elsewhere.[17] Study participants were followed up on days 1, 2, 3, 7, 14, 21, 28 and 42 after initial enrolment on day 0 for assessment of efficacy endpoints and adverse events. Patients were asked about their between-visit use of concomitant medications at each visit. Serious adverse events were investigated by specifically trained nurses and malaria control programme staff.

Data Management and Ethical Issues

Data entry and analysis were performed using Microsoft® Excel (Microsoft Corporation, USA, 2003) and Statistical Program for Social Sciences for Windows version 12.0 (SPSS Inc., Chicago, IL, USA, 2003). Ethical approval of the studies was granted by the Mpumalanga Provincial Department of Health and the University of Cape Town's Research Ethics Committee. The confidentiality of all patient records, healthcare professionals and healthcare facilities was maintained.

Results

From 1 March to 31 December 2002, when sulfadoxine/pyrimethamine monotherapy was the recommended treatment, the malaria control programme was notified of 4778 cases of malaria. Following the introduction of artesunate plus sulfadoxine/pyrimethamine in 1 January 2003 until 30 June 2004, the programme was notified of 7692 cases of malaria, and 6934 courses of artesunate plus sulfadoxine/pyrimethamine were dispensed. The cases that were not treated with artesunate plus sulfadoxine/pyrimethamine were predominantly high risk patients (young children and pregnant women) and those with severe malaria who were treated with quinine in hospital.

Home Follow-Up of Patients

Of the 8924 cases of malaria that had been reported to the malaria control programme in the period from 1 August 2002 to 30 June 2004, 2393 (26.8%) patients were followed up at home by programme staff. Of these 2393 patients, within the month following treatment, 7 (0.3%) were untraceable; 45 (1.9%) had died, of whom 41 were included in the confidential enquiry; and 4 (0.2%) were still ill after having recently been treated for malaria with artesunate plus sulfadoxine/pyrimethamine (n = 3) or quinine (n = 1). The four fatal cases excluded from the confidential enquiry included two cases with no evidence of a confirmed malaria diagnosis by rapid diagnostic test or malaria smear, one case that was found to be cryptococcal meningitis that was initially misdiagnosed as malaria and one case where the patient's records were not available. In three of the four patients who reported ongoing illness, a history of not completing the course of treatment was obtained. Three fatal adverse events that occurred after treatment with artesunate plus sulfadoxine/pyrimethamine were investigated as part of the confidential enquiry and are described in table I.

Table I. Details of the suspected adverse drug reactions (ADRs) that were reported

Patient (by method)[a]	Date of ADR	Age (y)	Sex	Suspect drug	Type of ADR	Healthcare professional who reported the ADR	Serious ADR[b]
Method 1: Home follow-up by malaria control programme							
Three fatal adverse events suspected to be drug related investigated as part of confidential enquiry							
Four patients still ill, of which three reported non-adherence to treatment							
Method 2: Enhanced spontaneous reporting at clinics							
1	19/03/2002	25	F	Sulfadoxine/pyrimethamine	Lack of effect	Nurse	Yes
2	19/04/2002	16	F	Sulfadoxine/pyrimethamine	Rash	Nurse	No
3	30/04/2002	9	M	Sulfadoxine/pyrimethamine	Lack of effect	Nurse	Yes
4	01/05/2002	33	M	Sulfadoxine/pyrimethamine	Lack of effect	Nurse	Yes
5	09/05/2002	60	F	Sulfadoxine/pyrimethamine	Lack of effect	Nurse	Yes
6	22/05/2002	45	M	Sulfadoxine/pyrimethamine	Lack of effect	Nurse	Yes
Method 3: Active hospital surveillance							
1	10/4/2002	7	M	Sulfadoxine/pyrimethamine	Pancytopenia	NR	Yes
Method 4: Confidential enquiry							
1	17/04/2003	31	M	Artesunate + sulfadoxine/ pyrimethamine	Respiratory distress and hypotension	NR	Yes
2	9/11/2003	24	F	Artesunate + sulfadoxine/ pyrimethamine	Haematuria	NR	Yes
3	28/05/2003	42	M	Artesunate + sulfadoxine/ pyrimethamine	Confusion, dizziness headache, difficulty breathing, death	NR	Yes
Method 5: Therapeutic efficacy study							
1	17/3/2004	11	M	Artesunate + sulfadoxine/ pyrimethamine	Repeated vomiting	Study nurse	Yes

a Each method of detection produced its own independent set of patients.

b Fatal, life-threatening events or events resulting in hospitalisation or prolonged hospitalisation. Congenital anomalies and clinically significant events were also considered serious.

F = female; **M** = male; **NR** = not reported.

Enhanced Spontaneous Reporting of Suspected ADRs

A total of 21 spontaneous ADR reports were received from Mpumalanga clinics and hospitals, of which 12 (57%) were from clinics and hospitals in the malaria risk area. Six reports were associated with sulfadoxine/pyrimethamine monotherapy (table I), of which five were reports of treatment failure and one was a report of a non-serious rash. The 15 remaining reports involved hypersensitivity reactions associated with other medicines, predominantly β-lactam antibacterials (n = 6) and cotrimoxazole (trimethoprim/sulfamethoxazole) [n = 5]. There were no spontaneous reports of adverse effects or suspected lack of efficacy associated with artesunate plus sulfadoxine/pyrimethamine use.

Active Hospital Surveillance

At Shongwe hospital, 120 malaria-related admissions (80 adults and 40 children and adolescents aged <16 years) were followed up by the research nurse, all of whom were admitted with an initial diagnosis of malaria. The median age of adult patients recruited into this study was 29 years (interquartile range 23–42 years). Forty-three patients reported that they had received sulfadoxine/pyrimethamine treatment for malaria either during or prior to their hospital stay, of whom five (12%) were excluded as the clinic or referring hospital's referral letter made no mention of treating the patient with sulfadoxine/pyrimethamine. In four patients, sulfadoxine/pyrimethamine was administered while in hospital with no complications. Sulfadoxine/pyrimethamine was inappropriately administered at the clinic to two patients; one was a pregnant woman and one was an 8-month-old infant with cerebral malaria. Of the remaining 32 patients, 11 patients were admitted to hospital on the same day as sulfadoxine/pyrimethamine was administered after having either vomited following sulfadoxine/pyrimethamine treatment at the clinic (n = 4) or having further deteriorated after receiving sulfadoxine/pyrimethamine (n = 7). Poor response to sulfadoxine/pyrimethamine treatment was the reason for admission in 20 cases (17% of all malaria-related admissions). In 11 of these cases, poor response was reported within 2 days of treatment. Adverse events identified after sulfadoxine/pyrimethamine treatment included vomiting, nausea, rigors, anaemia and diarrhoea, all of which were considered more likely to be due to the underlying condition than drug treatment. One case of pancytopenia (white blood count $2.7 \times 10^3/\mu L$ with 48% neutrophils, haemoglobin 7.4 g/dL, a platelet count of $38 \times 10^3/\mu L$) was diagnosed in a 7-year-old boy treated with sulfadoxine/pyrimethamine approximately 11 days prior to admission; this was considered to be possibly due to sulfadoxine/pyrimethamine treatment given the temporal association and the previously reported safety profile of sulfonamides.[24]

The cost of active follow-up per patient previously exposed to sulfadoxine/pyrimethamine through the hospital surveillance method was $US48 (2002 value) and detected only one possible serious ADR. The international expert review panel considered this component to be the least cost effective and unsustainable; thus, it was terminated after the initial 3-month pilot period. Instead, during the following season, the clinical staff at both district hospitals serving the malaria area were trained to report ADRs through the spontaneous reporting system. There were only two spontaneous reports of ADRs received from these hospitals during the 2003 malaria season, one involving an antibacterial and the other involving an antihypertensive.

Confidential Enquiry into Malaria-Related Deaths

Seventy deaths were identified during the study period (1 March 2002 to 30 July 2004), of which 65 met the study inclusion criteria as previously reported.[23] The median age of malaria-related deaths was 36 years (range 1–81 years), and two adults were of unknown age. Among the 29 (44.6%) female patients who died, 59.3% were of child-bearing age (15–45 years).

Three patients deteriorated clinically after administration of artesunate plus sulfadoxine/pyrimethamine. Two of these episodes were considered unlikely to be ADRs, as defined by the WHO;

poor response to treatment was considered the probable cause (table I).[22] They included respiratory distress and hypotension in a 31-year-old man who experienced repeated vomiting and was inappropriately treated with artesunate plus sulfadoxine/pyrimethamine for severe malaria as an outpatient, and severe haematuria in a 24-year-old woman who had been treated 13 days previously with artesunate plus sulfadoxine/pyrimethamine for apparently uncomplicated malaria. The third case, identified during a home follow-up visit, was a 42-year-old male with baseline hypotension (blood pressure = 90/60mm Hg) and a history of chronic weakness, who developed dizziness and experienced a fall 4 days after initiating treatment with artesunate plus sulfadoxine/pyrimethamine. He was discharged from hospital with another course of artesunate plus sulfadoxine/pyrimethamine, amoxicillin and paracetamol (acetaminophen). Two days later he became confused, developed a headache and had difficulty talking and breathing. He collapsed that night and died at home. A causal link with artesunate plus sulfadoxine/pyrimethamine treatment was possible in the light of the temporal association, although the information on his underlying chronic weakness was inadequate to exclude alternative diagnoses. In addition to system failures, which are not described in this paper, key drug-related problems were identified by the international expert review panel.[23]

Adverse Event Monitoring during Therapeutic Efficacy Studies

During the sulfadoxine/pyrimethamine therapeutic efficacy study conducted in 2002, serious adverse events were reported in 8 (5.3%) of 152 patients recruited, of which 7 did not respond to treatment (these patients had polymerase chain reaction [PCR]-confirmed malaria). In one case, a 16-year-old woman with a baseline haemoglobin level of 10 mg/dL presented to the clinic with a 2-day history of poor appetite, body pains and malaise on day 11 of the study. She was re-hydrated at the clinic and referred to hospital where a clinical diagnosis of anaemia and tonsillitis was made. It is unclear from the hospital notes how the diagnosis of anaemia was made; however, she was discharged after 2 days with ferrous sulphate, folic acid, amoxicillin and paracetamol. The patient completed the study, with a haemoglobin level of 11 mg/dL on day 42.

During the artesunate plus sulfadoxine/pyrimethamine therapeutic efficacy study conducted in 2004, serious adverse events were reported in five (5.3%) of 95 patients. Four were cases of parasitological treatment failure, of which three were found by PCR to be re-infections; one possible ADR involved a patient who vomited twice immediately after receiving treatment and was therefore transferred immediately to hospital for further malaria management.

Discussion

Intensive monitoring using five different methodologies confirms that artesunate plus sulfadoxine/pyrimethamine is a relatively safe treatment for uncomplicated malaria in Mpumlanga province, South Africa. Every point of contact with patients during their malaria journey was considered an opportunity to assess whether this drug combination was safe. This triangulated approach also allowed the detection of correctable system failures and other therapeutic management problems that could have contributed to morbidity and mortality in patients with malaria. The hospital-based monitoring system was the only method that required the employment of additional staff. In all other methods used, the main direct costs were training and follow-up of health staff.

While it is acknowledged that each of the methods employed would not on their own be sufficient for treatment safety monitoring, the introduction of a monitoring method at multiple levels of healthcare provided a safeguard against missing serious complications associated with artesunate plus sulfadoxine/pyrimethamine treatment. Based on the detection of one fatal case for which the contribution of artesunate plus sulfadoxine/pyrimethamine could not be ruled out in approximately 6934 treatment exposures, it was concluded that the risk of serious ADRs is likely to be well below one per thousand exposures. Compared with the malaria case fatality

rate of approximately five per thousand cases (58 reported deaths from in 12 245 notifications) during the study period, it is reasonable to conclude that artesunate plus sulfadoxine/pyrimethamine demonstrated an acceptable risk-benefit profile in this community. A heightened awareness of safety was established among health staff prior to and sustained during the introduction of artemisinin-based combination therapy. The multiple methods used allowed validation of findings across individual methods. Poor response to sulfadoxine/pyrimethamine monotherapy was reported more frequently than poor response to artesunate plus sulfadoxine/pyrimethamine for the three methods employed, and this was confirmed by therapeutic efficacy studies (10% vs 1%).[17] Only two reports of poor response to artesunate plus sulfadoxine/pyrimethamine treatment were detected during the confidential enquiry; none were detected through spontaneous reporting or home follow-up visits.

Malaria is a disease that is associated with significant morbidity and mortality if inadequately treated. It manifests with pan-systemic clinical features that present a challenge for the detection of drug-related events and the assessment of causal relationships. In areas without adequate drug regulation, counterfeit antimalarials are a particular concern and systems need to be developed to limit their distribution.[25] The contribution of undiagnosed concurrent diseases such as HIV/AIDS and tuberculosis, as well as the undisclosed use of over-the-counter, traditional and complementary medicines, is difficult to assess when an incomplete medical and drug history is available. Therefore, any harm associated with the use of antimalarials must be carefully assessed against the potential severity of the disease and the context of use. Effective treatment options are limited and may not be affordable in many malaria-affected countries. Public confidence in the risk-benefit profile of such treatments is, therefore, of paramount importance. Rare, serious adverse effects are unlikely to be detected without active and extensive pharmacovigilance surveillance both in hospitals and in the community. However, improper or inadequate detection systems are likely to create a false sense of security should a rare but serious ADR be missed. These detection systems need to be sensitive to the possibility that an overemphasis on safety monitoring could give rise to disproportionate public concern for unanticipated, rare risks, thereby undermining prompt seeking of treatment for malaria symptoms and adherence to the new combination treatment.

Each of the methods employed had limitations. None of the methods would have detected adverse effects in patients with malaria that had not been reported to the malaria control programme and who sought care only at a traditional healer or private practitioner. However, previous local community studies found that when malaria was suspected, local community members preferentially sought care at public sector health facilities.[26] In settings where malaria is managed or treated in the informal health sector, alternative methods of detecting ADRs will need to be explored.[4,6] The methods we used were only able to detect ADRs in patients seeking care at public sector health facilities. This was appropriate in the Mpumalanga setting because access to artesunate plus sulfadoxine/pyrimethamine is exclusively controlled by the malaria control programme. No similar products are available in South Africa or neighbouring countries.

Although the follow-up visit of patients by malaria control staff facilitated the detection of deaths that had occurred at home or ill patients that had not sought further care, only one-quarter of all reports of malaria were followed up by malaria control staff. This was due to almost half of these cases being in patients from neighbouring countries who are usually untraceable. Where patients or their families were not present at the time of the visit, homes were not revisited by malaria control programme staff because of resource constraints. Adherence was self-reported by patients and could underestimate the extent to which non-adherence existed among these patients. Malaria control programme field officers have no clinical qualifications and, as case investigators, may under-report subsequent illness, particularly milder conditions, and are likely to have a bias towards reporting only malaria-related illness.

The spontaneous reports of ADRs that were received by the malaria control programme were primarily of treatment failures and hypersensitivity reactions with dermatological manifestations. This may reflect the concerns raised by nursing staff during training sessions regarding difficulties in diagnosing adverse events and the vague criteria for reporting. Similar concerns have been raised by others in African settings.[5,6] ADRs can manifest as a wide variety of conditions, many of which are difficult to differentiate from underlying disease states. Limited diagnostic capabilities and access to drug information could have contributed to underreporting of adverse effects, with selective reporting of clearly visible and easily diagnosed adverse events at clinics. Regular telephone or in-person follow-up probably would have increased the yield from this method.

The terminated active surveillance hospital study primarily identified patients who required hospitalisation for severe malaria, special risk groups (particularly pregnant women and young children) or patients who had poor responses to treatment. Thus, most of these patients were not likely to receive first-line treatment. Despite the increased diagnostic capabilities in hospitals, there were very few spontaneous reports received from medical doctors in district hospitals compared with clinic nurses, even though they were given the same training and support from hospital infection control nurses. The limitations of spontaneous reporting in hospitals with overextended health staff has been reported by other groups in Africa.[27]

The inadequacy of medical records and recall bias among the next of kin of deceased individuals were probably the most important limitations of the confidential enquiry. Although some malaria deaths may have been missed because patients had been misdiagnosed or the deaths occurred outside the formal healthcare sector, it is likely that the majority of deaths from malaria in Mpumalanga during the study period were investigated, since burial in South Africa requires the presentation of a death certificate signed by a medical doctor.

The therapeutic efficacy studies allowed intensive monitoring for common adverse events. However, these events can be difficult to differentiate from those caused by malaria itself. In such a small cohort of exposed patients, less frequent events are unlikely to be detected.

Safety monitoring of artesunate plus sulfadoxine/pyrimethamine in pregnant women could not be evaluated as the South African national treatment guidelines recommend that all pregnant women and children aged <2 years with malaria be referred to hospital for treatment.[28] Only oral or intravenous quinine is recommended for the treatment of malaria in pregnant women in South Africa. Given that special permission was granted for the use of sulfadoxine/pyrimethamine treatment in Mpumalanga prior to its registration, with intensive training and detailed monitoring required by the regulatory authority, inadvertent use in pregnancy was even less likely to occur. Exposure to artemisinin-based combination therapy is most likely to occur in a relatively small subset of women during the first trimester; no such cases were detected during this study.

Poor treatment response was the most consistently reported adverse event across all study components. Poor response to antimalarial treatment could be due to antimalarial resistance, vomiting, undisclosed poor adherence to administration instructions, inappropriate oral treatment or the presence of significant co-morbidity. While poor or inadequate treatment response is not conventionally described as a pharmacovigilance parameter, in developing countries where diagnostic capabilities are limited concerns about counterfeit medicines are widespread and adherence may be an important determinant of programme effectiveness; suspicions of failed treatments are worth monitoring as part of a broader pharmacovigilance surveillance system.[25] These findings also argue for a more integrated approach to disease surveillance that could incorporate elements of pharmacovigilance, resistance monitoring and rumour surveillance that may be particularly useful in identifying the availability of counterfeit medicines.

The findings in this study are consistent with the favourable safety profile of artesunate plus sulfadoxine/pyrimethamine reported in the literature. Sulfadoxine/pyrimethamine-associated serious skin reactions are reported to occur at a frequency of 1.7 per 100 000 sulfadoxine/pyrimethamine exposures (increasing to 4.9 cases per 100 000 exposures in HIV-infected adults) and are thus unlikely to be detected in such a small exposed population, despite the high prevalence of HIV in South Africa.[29] To date, animal studies suggesting a risk of neurotoxicity have only been supported by three published human case reports of frank signs of neurotoxicity (ataxia and encephalopathy associated with artemisinin derivatives).[11,30,31] In all three cases reported, alternate causes, including the patient's underlying condition or concomitant medication, could have explained the event. Subtle neurological effects on hearing or learning and behavioural development are unlikely to be detected without carefully controlled, prospective trials in populations with more frequent exposure to malaria, and by employing sensitive and specific testing procedures.[32,33] A marked decrease in the occurrence of cases of malaria in 2003 following the implementation of the artesunate plus sulfadoxine/pyrimethamine policy confirmed the benefit of artemisinin-based combination therapy in reducing gametocyte carriage. However, this reduced malaria transmission resulted in a reduction in the number of individuals exposed to treatment, precluding detection of rare serious adverse events. Similar approaches need to be tested in other African settings, where there is greater malaria transmission, to determine their power for detecting rare, serious events.

Conclusions

Pharmacovigilance should be seen as part of the routine activities of a disease control programme, particularly when new medicines are being introduced. This is particularly important in malaria control programmes in sub-Saharan Africa where new artemisinin-based combinations are being deployed. Every point of contact with patients should be seen as an opportunity for collecting information on the safety of these medicines and adherence to optimal conditions for their use. Challenges in diagnosis and the detection of adverse effects in resource-poor settings need to be acknowledged and addressed through triangulated pharmacovigilance methodologies.

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