ORIGINAL RESEARCH ARTICLE

Drug Safety 2008; 31 (10): 867-876
0114-5916/08/0010-0867/$48.00/0

Spontaneous Adverse Drug Reaction Reporting in Rural Districts of Mozambique

Esperança Sevene,[1] *Alda Mariano*,[1] *Ushma Mehta*,[2] *Maria Machai*,[3] *Alexander Dodoo*,[4] *David Vilardell*,[5] *Sam Patel*,[1] *Karen Barnes*[2] and *Xavier Carné*[5]

1 Eduardo Mondlane University Medical School, CIMed, Maputo, Mozambique
2 Division of Clinical Pharmacology, University of Cape Town Medical School, Cape Town, South Africa
3 Ministry of Health, Maputo, Mozambique
4 University of Ghana Medical School, Accra, Ghana
5 Clinical Pharmacology Service, Hospital Clinic and IDIBAPS, Barcelona, Spain

Abstract

Background: The roll out of various public health programmes involving mass administration of medicines calls for the deployment of responsive pharmacovigilance systems to permit identification of signals of rare or even common adverse reactions. In developing countries in Africa, these systems are mostly absent and their performance under any circumstance is difficult to predict given the known shortage of human, financial and technical resources. Nevertheless, the importance of such systems in all countries is not in doubt, and research to identify problems, with the aim of offering pragmatic solutions, is urgently needed.

Objective: To examine the impact of training and monitoring of healthcare workers, making supervisory visits and the availability of telecommunication and transport facilities on the implementation of a pharmacovigilance system in Mozambique.

Methods: This was a descriptive study enumerating the lessons learnt and challenges faced in implementing a spontaneous reporting system in two rural districts of Mozambique – Namaacha and Matutuíne – where remote location, poor telecommunication services and a low level of education of health professionals are ongoing challenges. A 'yellow card' system for spontaneous reporting of adverse drug reactions (ADRs) was instituted following training of health workers in the selected districts. Thirty-five health professionals (3 medical doctors, 2 technicians, 24 nurses, 4 basic healthcare agents and 2 pharmacy agents) in these districts were trained to diagnose, treat and report ADRs to all medicines using a standardized yellow card system. There were routine site visits to identify and clarify any problems in filling in and sending the forms. One focal person was identified in each district to facilitate communication between the health professionals and the National Pharmacovigilance Unit (NPU). The report form was assessed for quality and causality. The availability of telecommunications and transport was assessed.

Results: Fourteen months after the first training, 67 ADR reports involving 74 adverse events were received by the NPU involving 25 separate drugs, 16 of which were causally (certainly, probably or possibly) linked to the reaction. Most reported ADRs were dermatological reactions (83.1%). Antimalarial drugs (chloroquine, amodiaquine, quinine, artesunate and sulfadoxine/pyrimethamine) were mentioned in 33 (50.8%) of the reports. There were 14 reactions classified as serious and no fatal reactions were reported. There were differences in telecommunications and transport facilities between the districts that might have contributed to the different number of reports.

Conclusion: Health professionals of all levels of education (including basic training) from rural areas could contribute to ADR spontaneous reporting systems. Training, quality-assurance visits and the ongoing presence of focal persons can promote reporting and improve the quality of reports submitted.

Background

Pharmacovigilance is defined by the WHO as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

A national pharmacovigilance programme can contribute significantly towards ensuring the safe use of medicines within a country. Signals of previously unknown or poorly understood adverse drug reactions (ADRs) and drug-related problems can be detected and assessed through spontaneous reporting systems.[1,2] Unlike any other monitoring system, spontaneous reporting is able to oversee the safety of all drugs available in a certain country, covers the whole population and helps in identifying drug safety signals, which may have resulted from preventable or inherent risks associated with the use of a drug.[3,4] The effectiveness of such a system depends on all levels of health staff throughout the country supporting this activity and recognizing its importance in patient care.

Spontaneous reporting is relatively new; the first national ADR reporting schemes were set up in the 1960s in some ten developed countries.[5] Thereafter, many other countries started pharmacovigilance, but unfortunately only a small number of African countries have formal pharmacovigilance systems. These include Morocco, South Africa, Tanzania, Tunisia, Zimbabwe, Ghana, Egypt, Nigeria, Mozambique, Uganda and Togo, all of which are full members of the WHO Programme for International Drug Monitoring.[6]

Implementation of spontaneous reporting systems in resource-limited, developing countries is particularly problematic where other pressing health priorities and challenges, such as remote location, poor telecommunication services and low numbers and level of education of health professionals, are commonplace.

The introduction of new policy recommendations for drug treatment of poverty-related diseases, such as malaria, tuberculosis and HIV/AIDS, offers a number of challenges to health services in resource-poor countries. There are new drugs and new drug combinations whose efficacy, effectiveness and safety have not been adequately monitored under the conditions of large-scale use in these settings. Population differences in the pharmacokinetics and toxicity of some of these drugs have been reported elsewhere and may affect the safety and use of these drugs in local populations.[7,8]

Appropriate pharmacovigilance systems to monitor the potential occurrence of both expected and unexpected ADRs to these treatments are needed to optimize the health of the local population. Where such pharmacovigilance systems are not available, simple techniques to promote and facilitate reporting of unusual clinical events that could be considered ADRs are recommended.[9]

Currently, the WHO is promoting the introduction of pharmacovigilance into public health pro-

grammes. As public health programmes are well established, operate according to standard guidelines and are well supported and funded, there is an opportunity to form a mutually beneficial relationship with pharmacovigilance activities.[10]

With the recent introduction of a new malaria treatment policy (which includes artemisinin-based combination therapies) and an operational plan to introduce antiretroviral therapy, the Ministry of Health of Mozambique has committed itself to ensuring the safety of medicines used in the country.[11,12] To address this need, the Ministry's Pharmaceutical Department has supported the establishment of a national pharmacovigilance system housed within the Drug Information Centre (CIMed) at Eduardo Mondlane University in Maputo, Mozambique. CIMed developed this pilot study in two remote districts of Maputo province (Namaacha and Matutuíne) in order to evaluate the feasibility of the implementation of a pharmacovigilance system in Mozambique.

The aim of this study was to describe the feasibility of creating an ADR spontaneous reporting system in two rural districts in Mozambique where remote location, poor telecommunication services and the low level of education of health professionals are ongoing challenges. This included the training of health personnel in pharmacovigilance, piloting of the proposed national ADR spontaneous reporting forms and evaluation of the flow of ADR information between health staff and CIMed.

Methods

This study is a descriptive, prospective examination of the feasibility of implementing pharmacovigilance systems in two districts in southern Mozambique. Namaacha and Matutuíne districts of Maputo province were selected to pilot the implementation of pharmacovigilance activities because their infrastructure is representative of rural Mozambique. The pharmacovigilance system was introduced into these two districts to coincide with the introduction of a new antimalarial therapy. The provincial directorate, in collaboration with the Malaria Control Programme, was changing first-line antimalarial therapy from chloroquine to sulfadoxine/pyrimethamine plus artesunate. Namaacha is a district with 32 000 inhabitants[13] located 75 km west of Maputo, the national capital. The road conditions are favourable, and telephone facilities are present. Matutuíne is a district with 37 189 inhabitants[13] located 120 km southwest of Maputo. Health facilities in Matutuíne, unlike those in Namaacha, are sparsely distributed, and the road conditions within the district are poor. Telephone communications in Matutuíne are very limited.

In both districts, healthcare personnel prescribing medicines possess varying levels of educational qualifications. The healthcare facilities are serviced by medical doctors, healthcare technicians (10 years of schooling plus 3 years of specific training), healthcare and pharmacy agents (7 years of schooling plus 2–3 years of training) and nurses (7–10 years of schooling plus 2–3 years of training). The healthcare technicians and healthcare agents are trained to diagnose and treat a limited number of the more prevalent diseases, according to their educational levels. The cases that they cannot manage are referred to the medical doctor. The pharmacy agents are trained to dispense medicines. Malaria is an important public health problem in the two districts. The average infection rate in the younger age group (2–14 years) was 64% after a prevalence survey performed in December 1999 in sentinel sites of both districts.[14] Medicines in these districts are delivered through the national health system, with most essential medicines distributed in essential drug kits. The private sector in both districts is very limited.

Based on the existing healthcare infrastructure, access and health staff demographics, a reporting system was developed to allow for the distribution and collection of ADR forms (figure 1). Two workshops were carried out in order to provide health professionals from Namaacha and Matutuíne with the knowledge, skills and motivation required for the diagnosis, treatment and reporting of ADRs. The workshops introduced participants to different pharmacovigilance topics, including the importance of and need for pharmacovigilance, recognition and

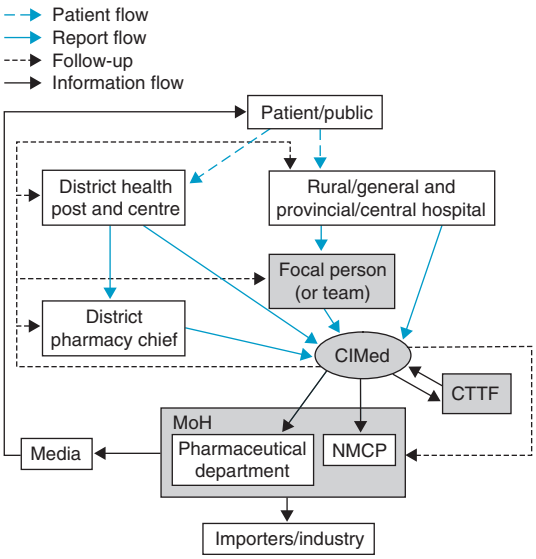

Fig. 1. Description of the flow of information in the CIMed (Drug Information Centre) pharmacovigilance system. In this system, the patients report their symptoms to health facility staff in District Health Centres (patient flow). At the district level, the health facility staff send the forms to district pharmacy chief and then to CIMed. At the provincial level, health facility staff send the forms to provincial focal person or team. The health facility staff can at any time send the report directly to CIMed (report flow). CIMed coordinate communications with the Pharmacy and Therapeutic Technical Commission (CTTF) and the Ministry of Health (MoH) of Mozambique (pharmaceutical department and National Malaria Control Programme [NMCP]). Communications with manufacturer/importers and the media are coordinated by the MoH (information flow). CIMed gives feedback to all health facility staff (follow-up).

diagnosis of ADRs, the principles of causality assessment, how to complete the ADR form, known as the 'yellow card', and an overview of the flow of information within the pharmacovigilance system. Five months later, retraining was carried out to reinforce the topics of the first workshop. Problem-based teaching methods including role play, group work and facilitated discussions were used in both training workshops.

CIMed drafted the yellow card and that was discussed and tested with health professionals during the training workshops. The input from the trainees was critical for ensuring that the final version of the form was concise, locally relevant and user-friendly. On the back page were instructions on how to fill out the form. Thereafter, it was reviewed with the participants and field-tested in the study districts.

CIMed staff conducted four on-site supervisory visits to each pilot district to assess how effective the training had been in promoting the new pharmacovigilance system, verify the availability and utilization of ADR forms at the health facilities, identify the difficulties and constraints experienced by health staff in completing the ADR forms and identify any other challenges hindering the successful implementation of the pharmacovigilance system.

One focal person was identified in each district to facilitate communication between the health staff and the pharmacovigilance unit at CIMed. After completing the form, the reporting health personnel reviewed it with the focal person in the district for completeness and correctness. The focal person then sent the forms to the pharmacovigilance unit once a week when the ambulance routinely transported other documents or patients to Maputo. After receiving any ADR form, an acknowledgement letter to the reporter with information about causality assessment was provided. The reporting flow was the same for the two districts (figure 1).

In the National Pharmacovigilance Unit (NPU), each yellow card was attributed a number, reviewed for quality and causality assessment and entered into a database. The quality parameters evaluated were as follows: completeness; a clear description of the reaction (it was recommended to the health professional to describe exactly what happened with the patient and not to write the diagnoses); and a clear description of the drugs involved. There was a check list for quality assessment before accepting or rejecting the report. The ADRs were classified by the reporters as serious according to the WHO definition. In this definition, serious adverse events are those that (i) are life threatening or fatal; (ii) cause or prolong hospital admission; (iii) cause persistent incapacity or disability; or (iv) concern misuse or dependence.[15] The serious cases were discussed with the Pharmacy and Therapeutic Technical Committee. Medication errors were also assessed according to the definition provided by the US National

Coordinating Council for Medication Error Reporting and Prevention.[16]

Results

Thirty-five health professionals were trained. These included medical doctors (3), technicians (2), nurses (24), basic healthcare agents (4) and pharmacy agents (2) from the two districts. The focal person in each district was the pharmacy agent.

Fourteen months after the first training workshops, 67 yellow cards were received by the pharmacovigilance unit; two of them were excluded because the reporters failed to mention any reaction and no further information could be obtained. From the remaining 65 reports, 74 ADRs were described. Table I describes the reported ADRs and the suspected drugs.

Of the 65 reports, 52 (80%) were from Namaacha and 13 (20%) from Matutuíne (see figure 2). Thirty-nine (60%) reports were from healthcare and pharmacy agents, 15 (23.1%) from nurses, 6 (9.2%) from technicians and 5 (7.3%) from medical doctors.

Twenty-five different medicines were mentioned in the reports, 16 of which were causally linked to the reactions after causality assessment (table I). Antimalarial drugs (chloroquine, amodiaquine, quinine, artesunate and sulfadoxine/pyrimethamine) were mentioned in 33 (50.8%) of the reports. Since malaria is endemic in these areas, antimalarials are likely to be the most widely used drugs, although

Table I. Distribution of reported adverse drug reactions (ADRs) and suspected drug, after causality assessment

ADR	n	Drug suspected
Skin and appendages disorders	**54**	
Maculo-papular rash	20	Cotrimoxazole [trimethoprim/sulfamethoxazole] (4), SP + artesunate (4), chloroquine (3), amoxicillin (3), phenoxymethylpenicillin (2), SP (1), paracetamol [acetaminophen] (1), pyrazinamide (1), procaine benzylpenicillin + aspirin [acetylsalicylic acid] (1)
Pruritus	13	Chloroquine (10), cotrimoxazole (2), paracetamol (1)
Maculo-papular rash + mucous ulcerations	7	Cotrimoxazole (3), SP (3), cotrimoxazole + benzathine benzylpenicillin (1)
Vesicular rash-like burns	5	SP + artesunate (2), cotrimoxazole (1), erythromycin (1), nalidixic acid (1)
Rash erythematous with nodules	5	Cotrimoxazole (2), SP + artesunate (1), SP (1), phenoxymethylpenicillin (1)
Urticaria	4	Cotrimoxazole (1), SP (1), amoxicillin (1), pyrazinamide (1)
CNS disorders	**14**	
Convulsions	4	Procaine benzylpenicillin (2), quinine (1), SP + artesunate (1)
Dizziness	3	Ferrous sulphate + folic acid, SP, SP + amodiaquine
Psychomotor agitation	2	Procaine benzylpenicillin
Weakness	2	SP + amodiaquine
Headache	1	SP + artesunate
Insomnia	1	Ferrous sulphate + folic acid
Tremors	1	SP + artesunate
Gastrointestinal system disorders	**2**	
Abdominal discomfort	1	SP
Nausea	1	SP + amodiaquine
Vision disorders	**1**	
Visual acuity alteration	1	SP
Treatment failure	**3**	SP + artesunate
Total number of reactions	**74**	

SP = sulfadoxine/pyrimethamine.

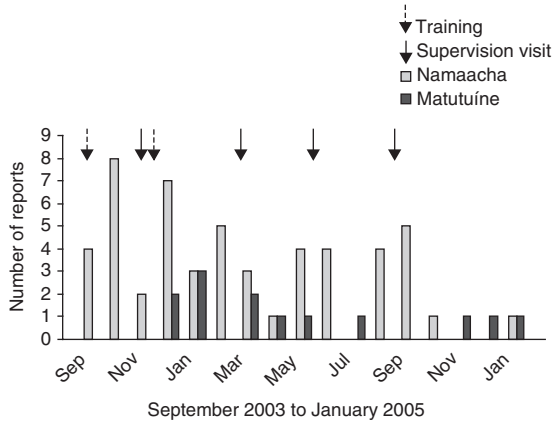

Fig. 2. Distribution of the reports from Namaacha and Matutuíne according to the date of report.

denominator data are only available for artesunate. This drug was distributed only through the malaria control programme in 50 mg tablets (about 66 700 tablets for Namaacha and 25 700 tablets for Matutuíne). Quinine, chloroquine and sulfadoxine/pyrimethamine were provided in the essential drug kits, and no records of quantities distributed were kept.

The most commonly reported ADRs were skin reactions (83.1%) [table I]. There were 14 ADR cases classified as serious. Nine resulted in hospitalizations and five resulted in prolonged hospitalizations. Only four out of the 65 reports resulted in sequelae (all of which were skin pigmentation). There were no fatal reactions. The nine serious cases that resulted in hospitalization are presented in table II.

All ADRs reported were evaluated by the CIMed clinical staff who had been trained in pharmacovigilance to assess causality according to WHO classification.[15] Of the 74 reactions, 11 were classified as 'certain', 45 as 'probable', 14 as 'possible' and 4 as 'unlikely'/'unclassified'.

Before the second training, there was incompleteness in the filling in of the yellow card; the reaction was not clearly described and the reporters did not include all drugs taken by the patient. When possible, telephone contact with the reporter was done to review the form. During each site visit, the yellow cards were reviewed personally with the reporter. During the training session, all aspects related with how to fill in the form were reviewed, leading to improvement in the quality of reports.

There were differences between the two districts in terms of availability of telecommunication and transport facilities. Matutuíne is a more rural district, where the road conditions are poor, there are some villages that are difficult to reach, and the health facilities are visited only once every 2–3 months. Telephone facilities are available in the central village and no fax was available. Namaacha is a more urban district, where the road conditions are good, the villages communicate by phone or mobile phones, and there are fax facilities available. Of the 67 reports, 7 (10.8%) suggested the contribution of a medication error. These included two administration errors, three instances of combined use of two sulphonamides or related drugs in one prescription, and two unsupervised rechallenges with drugs.

Discussion

We have shown that it is possible to implement a reasonably successful pharmacovigilance system in two resource-constrained districts in southern Mozambique. The strategy employed included training of healthcare personnel, supplemented with routine visits, monitoring and feedback and the engagement of a pharmacovigilance focal person in each district. The implementation had to be adapted to the reality of each district in relation to personnel, local conditions and communications. ADR reports were collected from the reporters by the focal person and sent once a week to the NPU when the ambulance took other documents or patients to Maputo.

The health staff in the two pilot districts included personnel of varying levels of education, ranging from medical doctors to healthcare technicians with medium level training, and nurses, healthcare and pharmacy agents with a basic degree. They were all able to fill in the ADR forms. The healthcare and pharmacy agents reported more ADRs than other health professionals. This may be because they are usually the first health professionals to receive patients in the health facility. Since nurses were the

Table II. Description of the nine serious adverse reactions that resulted in hospitalization

Case no.	Description
Psychomotor agitation and convulsions	
1	A 41-year-old male patient presented with pneumonia and was treated with procaine benzylpenicillin. Immediately after intramuscular injection, the patient developed symptoms of psychomotor agitation and convulsions. The patient was admitted and treated with adrenaline and diphenhydramine and recovered without sequelae
2	A 55-year-old female patient presented with pneumonia and was treated with procaine benzylpenicillin. Immediately after intramuscular injection, the patient developed symptoms of psychomotor agitation and convulsions. The patient was admitted and treated with adrenaline (epinephrine) and diphenhydramine and recovered without sequelae.
Skin reactions	
3	A 46-year-old female from Namaacha with a history of HIV was diagnosed with tuberculosis. She started treatment with ethambutol, isoniazid, rifampicin and pyrazinamide. Twenty-four hours after taking the tablets, the patient developed an urticarial skin reaction with pruritus. The patient was admitted, and the clinician stopped all treatment and started chlorpheniramine. After 1 week, the clinician rechallenged the patient sequentially with the anti-tuberculosis treatments. When pyrazinamide was introduced, the same symptoms were observed and were more severe
4	A 46-year-old female from Matutuíne with tuberculosis. She started treatment with ethambutol, isoniazid, rifampicin and pyrazinamide. Two days after taking the tablets, the patient developed a maculo-papular rash. The patient was admitted, and the clinician stopped all treatment and started chlorpheniramine. After 1 week, the clinician rechallenged the patient sequentially with the anti-tuberculosis treatments. When pyrazinamide was introduced, the same symptoms were observed and were more severe
5	A 60-year-old HIV-negative male was diagnosed with uncomplicated malaria and treated with artesunate and sulfadoxine/pyrimethamine. After the first day of treatment, the patient developed hyperchromic maculo-papular rash with blister-like burns and was admitted to hospital 2 days later after finishing the 3 days' treatment. The patient stayed at the hospital for 12 days and recovered with hyperpigmented scars sequelae
6	A 39-year-old female with uncomplicated malaria was treated with artesunate and sulfadoxine/pyrimethamine. After taking the first dose, the patient presented with maculo-papular rash with blister-like burns and was admitted to hospital 2 days later after finishing the 3 days' treatment. The patient recovered with hyperpigmented scars sequelae
7	A 25-year-old male, diagnosed with malaria and pneumonia was admitted and started treatment with quinine, cotrimoxazole (trimethoprim-sulfamethoxazole), paracetamol (acetaminophen) and vitamin B complex. Two days later, the patient developed a skin reaction with dark stains and blister-like burns throughout the body including the genitalia. Cotrimoxazole was stopped and the patient was successfully treated with antihistamines without sequelae
8	A 73-year-old male, diagnosed with bronchitis treated with cotrimoxazole. Two days later, the patient developed a maculo-papular rash. The patient was admitted, cotrimoxazole was stopped and the patient was successfully treated with antihistamines without sequelae
Headache and tremors	
9	An 18-year-old pregnant woman with uncomplicated malaria was treated with artesunate + sulfadoxine/pyrimethamine. After taking the first dose, the patient presented with a severe headache and tremors. The patient was admitted and started treatment with quinine and prednisolone and recovered without sequelae

only prescribers in some facilities, a higher number of reports were expected from them, but this did not happen. There were only three doctors in both districts and this probably accounts for the low number of reports (nine) by doctors, although other factors, such as high workload, could have also played a part. The active support and contributions of basic clinical health staff in the planning and implementation phases (particularly in pilot testing the ADR forms) of such a system, and the role of the focal person were critical for the successful implementation of the pharmacovigilance system in the study areas. We believe that a similar approach would be feasible in other developing countries or areas with very limited resources.

Nevertheless, there was a need for a different flow of information in areas like Matutuĭne, where communication facilities and transport were limited. In both districts, an improved quality of reports was observed after the second training session. This emphasizes the importance of frequent training and feedback on improving ADR reporting.

There were 65 reports from a population of about 67 000 (i.e. 1 in 1000). This works out to 831 reports

per million inhabitants per year. This compares with reporting in high-report countries such as New Zealand (740.7 reports per million inhabitants per year), Australia (479.7 reports per million inhabitants per year) and the US (416.1 reports per million inhabitants per year),[6] but is not generalizable across the whole of Mozambique because a large amount of resources were put into this pilot implementation.

The study focused on the feasibility of the pharmacovigilance system, and reports obtained spontaneously indicate that the system has been accepted and well received by healthcare workers in the two districts.

The quality of the reports improved after retraining. The large proportion of 'certain'/'probable', and the low proportion of 'unlikely' causalities could be related to the type of reactions described. Most of the reactions were skin reactions, including the well known pruritus reaction to chloroquine.

The implementation of a pharmacovigilance system in a resource-constrained environment has to be followed by training and supervisory site visits, to allow for clarification of doubts and to stimulate health professionals to report ADRs. This was a pilot study in only two districts. When the system is expanded nationally, the follow-up at all health facilities and districts will be expensive and probably not feasible with the limited human and financial resources available. Different approaches will thus be required, including training of trainers at provincial level and the use of mass media and behaviour change communication strategies to stimulate health workers to report ADRs.

Within this study, CIMed exploited the feedback mechanism in pharmacovigilance to address the issue of medication errors and to promote the rational use of medicines. In addition to signal generation, we believe that pharmacovigilance in Mozambique can contribute to the education of health staff to minimize medication errors and promote rational and cost-effective use of drugs, as has been described in other settings.[17]

The sustainability of the pharmacovigilance system is an important challenge for both developed and developing countries. Underreporting has being described as a major drawback of this system.[18,19] The trainers need to follow up implementation at the district level in order to sustain reporting over time (see figure 2). In addition, feedback to reporters on a case-by-case basis is crucial and must be a routine exercise performed by the focal persons at provincial and district levels. Furthermore, CIMed will include information on the reports in its regular national *Drug Information Bulletin*.

There were differences between the two districts in the number of reports. Many reasons may have contributed to this, including poor transport and telecommunication infrastructure, less access of the local communities to the health facility, fewer malaria cases in Matutuĭne and probably inter-individual variation in personnel motivation. However, the study did not set out to evaluate these systematically, and a different study design would be needed to explain the differences in reporting rates in the two districts

The large majority of reported reactions were skin reactions. This is an expected finding in rural primary healthcare settings with limited access to diagnostic equipment and clinical expertise. Skin reactions are more easily recognized ADRs and thus more frequently reported.[3] Other reactions with more subtle manifestations are more likely to be overlooked, particularly when laboratory tests and special clinical expertise are needed for correct diagnosis, as is often the case for neurological, haematological, renal and hepatic effects. When ADR reporting is introduced in secondary and tertiary care institutions in the country, reports of adverse reactions involving other organ and system classes are likely to increase.

Antimalarials, which are by far the most commonly used medicines in these facilities, were the most frequently mentioned class of drugs in the ADR reports. In addition, the recent change in first-line antimalarial therapy and its association with this pilot programme could also have contributed to this reporting trend. Another drug that was frequently mentioned in the reports was cotrimoxazole (trimethoprim-sulfamethoxazole), which is widely used for the treatment of upper respiratory tract

infections, urinary tract infections and as a prophylactic medicine in HIV-infected patients; most of the ADRs related to this drug were skin reactions. Quantification of the use of drugs is not very accurate in these settings. Information about distributed drugs has been considered as an approximation of the drug used, knowing that the number of drugs distributed does not necessarily equate to the number of drugs actually consumed by patients.[20,21] The absence of reliable data on the total number of drugs distributed, prescribed and dispensed makes it difficult to estimate incidence rates for the observed reactions.

We believe that the strength of our approach to pharmacovigilance implementation in Mozambique was the development of a reporting system and information flow that was sensitive enough to the local conditions and specific challenges faced by health staff, even in the most poorly resourced and remote health facilities in the country. Health professionals with basic and medium levels of education from rural areas could effectively contribute to the development and ongoing support of ADR spontaneous reporting systems. Training, quality assurance visits and the presence of focal persons can promote reporting and improve the quality of reports submitted.

The availability of telecommunication and transport facilities could improve the reports, as the health professionals could send reports more quickly and could in the same way receive feedback. This may explain the differences in number of reports obtained from Namaacha district compared with Matutuíne district. In Matutuíne district, the use of alternative methods of communication, such as the use of the focal person and the ambulance to send the report, were more feasible.

Conclusion

This study has shown that pharmacovigilance systems can be established in resource-limited countries in Africa. They can therefore potentially be applied elsewhere. Thirty-five health professionals of varying qualifications were trained in two rural districts of Mozambique. These health professionals submitted 67 ADR report forms covering the most commonly used medicines in the districts. The quality and quantity of the reports was high, taking into account the complex system and the level of education of the health professionals involved.

The study has confirmed that pharmacovigilance systems can be established in resource-constrained environments, as long as the challenges in these environments (e.g. the availability of telecommunication and transport facilities and personnel difficulties) are taken into consideration in the establishment of the system. The use of alternative ways of communication (like in this case, the use of a focal person and an ambulance to send the reports) could contribute to improvement in reporting. Pharmacovigilance systems in these settings could be useful in detecting medication errors and promoting the rational and cost-effective use of drugs rather than purely for signal generation, as occurs in developed countries. Regular training, monitoring and feedback are key success factors in such an enterprise.

Acknowledgements

The South East African Combination Antimalarial Therapy (SEACAT) evaluation, within which this study was nested, received core financial support from the United Nations Development Programme (UNDP)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). The authors have no conflicts of interest that are directly relevant to the contents of this study. The work of healthcare personnel from Namaacha and Matutuíne was important for the successful completion of the pilot implementation project on pharmacovigilance in Mozambique, and they are gratefully acknowledged.

Contributors and sources: this article arose from discussions within our team while preparing the implementation of a pharmacovigilance system in Mozambique. ES, KB and XC designed the study. ES, AM and MM collected the data. ES, UM, AD, DV and SP led the analysis and reviewed the causality assessment for all the ADR reports, to which the other authors contributed. ES, UM, AD, KB and XC led the writing of the paper, to which the other authors contributed. ES and KB will act as guarantors for the paper. The guarantors accept full responsibility for the conduct of the study, had access to the data and controlled the decision to publish.

References

1. Lindquist M. Seeing and observing in international pharmacovigilance. Uppsala: Uppsala Monitoring Centre, 2000

2. Meyboom RH, Egberts AD, Edwards IR, et al. Principles of signal detection in pharmacovigilance. Drug Saf 1997; 16 (6): 355-65
3. Laporte JR. Princípios basicos de investigação clinica. Madrid: Zeneca Farma, 1993
4. Edwards IR. The accelerating need for pharmacovigilance. J R Col Physicians Lond 2000; 34 (1): 48-51
5. Edwards IR, Lindquist M, Meyboom R, et al. Pharmacovigilance in focus in drug safety. Uppsala Monitoring Centre, 2000
6. Uppsala Monitoring Centre. WHO programme for international drug monitoring [online]. Available from URL: http://www.who-umc.org/DynPage.aspx?id=13140 [Accessed 2008 Aug 5]
7. Haas DW, Ribaudo JR, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an adult AIDS clinical trial group study. AIDS 2004; 18: 2391-400
8. Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Safety 2004; 27 (1): 25-61
9. Edwards IR. Safety monitoring of new anti-malarials in immediate post-marketing phase. Med Trop (Mars) 1998; 58 (3): 93-6
10. Simooya O. Introducing pharmacovigilance in public health programmes. Drug Safety 2005; 28 (4): 277-86
11. Programa Nacional de Controlo da Malaria. Normas de tratamento da malaria. Maputo: MISAU, 2001
12. Programa Nacional de Controlo de ITS/HIV/SIDA. Plano estratégico nacional de combate às ITS/HIV/SIDA do MISAU 2004-2008. Maputo: MISAU, 2004
13. Instituto Nacional de statistica. Dados demograficos [online]. Available from URL: http://www.ine.gov.mz [Accessed 2005 Sep 21]
14. Sharp BL, Kleinschmidt I, Streat E, et al. Seven years of regional malaria control collaboration: Mozambique, South Africa, and Swaziland. Am J Trop Med Hyg 2007; 76 (1): 42-7
15. World Health Organization. Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre. Uppsala: Uppsala Monitoring Centre, 2000
16. The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP): the first ten years. "Defining the problem and developing solutions". Dec 2005 [online]. Available from URL: http://www.nccmerp.org [Accessed 2008 Aug 05]
17. Moore N. The role of the clinical pharmacologist in the management of adverse drug reactions. Drug Safety 2001; 24 (1): 1-7
18. Avarez-Requejo A, Carvajal A, Begaud B, et al. Under-reporting of adverse drug reactions: estimate based on a spontaneous reporting scheme and a sentinel system. Eur J Clin Pharmacol 1998; 54 (6): 483-8
19. Bégaud B, Martin K, Haramburu F, et al. Rates of spontaneous reporting of adverse drug reactions in France. JAMA 2002; 288: 1588
20. Figueiras A, Caama F, Gestal J. Metodología de los estudios de utilización de medicamentos en atención primaria. Gac Sanit 2000; 14 Suppl. 3: 7-19
21. Alvarez Luna F. Pharmacoepidemiology. Drug utilization studies. Part I. Concept and methodology. Seguim Farmacoter 2004; 2 (3): 129-36

Correspondence: Dr *Esperança Sevene*, Department of Pharmacology, Faculty of Medicine, Eduardo Mondlane University, Av. Salvador Allende n. 702 R/c, Maputo, Mozambique.
E-mail: esevene68@gmail.com

