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The WHO 'Roll Back Malaria Project'

Planning for Adverse Event Monitoring in Africa

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Abstract

Artemisinin combination therapies (ACTs) have been recommended for the treatment of malaria in countries where there is widespread resistance to commonly used antimalarial drugs. Several sub-Saharan African countries are, therefore, in the process of introducing ACTs in their malaria drug policies. However, there is limited information about the safety of ACTs outside South East Asia, where their use has been well documented. As with all other new medicinal compounds, the monitoring of a drug's safety or 'pharmacovigilance' is important, especially in areas where co-morbid conditions, such as HIV/AIDS, malnutrition and tuberculosis, are common. Because in most malaria endemic countries, particularly Africa, there are no pharmacovigilance programmes in place, it has been suggested that the introduction of ACTs offers an opportunity for these countries to put drug safety monitoring systems in place. Backed by the WHO Roll Back Malaria department and other international cooperating partners, five African countries, which are in the process of introducing ACTs (Burundi, Democratic Republic of the Congo, Mozambique, Zambia and Zanzibar), have drawn up action plans to introduce pharmacovigilance in their health sector. It is planned that once the safety monitoring of antimalarials has been established, these activities can then be extended to cover medicinal compounds used in other public health programmes, such as HIV/AIDS, tuberculosis and the immunisation programmes. This article looks at the rationale for pharmacovigilance, the process of setting up monitoring centres and the challenges of implementing the project in the region.

Malaria continues to be one of the most important parasitic diseases of man. Worldwide, it is estimated that there are between 300 to 500 million cases of malaria each year, while the number of deaths attributed to malaria, annually, ranges from 1.5 to 2 million, of which most are young children.[1] From time immemorial, sub-Saharan Africa has borne the brunt of malaria because of its hot and humid climate, which is favourable for the life cycle of the human malaria parasite.

There have been several attempts to tackle malaria in the past. In the period following the Second World War, the concept of malaria eradication was adopted and endorsed by the WHO.[2-4] The basis of this policy was the use of insecticides to eliminate the mosquito vector. For some time this strategy

appeared to succeed, but was soon to be hampered by the emergence of vector resistance to insecticides and concerns about the viability of this approach in countries with poor economies and weak health systems. There were also, increasingly, reports of parasite resistance to the available drugs.[5,6]

Subsequently, the momentum against malaria appeared to have been lost until the 1990s, when there was widespread recognition by the international community that the burden of malaria was not only affecting the health of populations in afflicted regions of the world, but was also an impediment to sustainable economic and social development. Responding to this concern, in 1998 the United Nations Development Programme (UNDP), the United Nations Children's Fund (UNICEF), the World Bank and the WHO, in partnership with governments from malaria endemic nations, launched Roll Back Malaria (RBM), an ambitious initiative to stem the tide of malaria.[7]

The vision of RBM is to halve the burden of malaria by the year 2010. To achieve this goal, the strategy proposed is the aggressive promotion of the use of insecticide-treated bed nets, prompt access to effective treatments for malaria and the prevention of malaria in pregnancy. The goals of RBM were later endorsed by African heads of state who met in Abuja, the Nigerian capital, in 2000.[8]

In many sub-Saharan African countries, chloroquine has for many years been the drug of choice for the treatment of malaria. However, now, in many parts of the region, chloroquine is no longer effective for the treatment of *Plasmodium falciparum* malaria, the most lethal form of human malaria. This development, together with the growing problem of parasite resistance to pyrimethamine/sulfadoxine combinations,[9,10] the first-line treatment for chloroquine resistant malaria, poses a major challenge to the vision of RBM.

In view of this situation, there is an urgent desire by health authorities in the region to change to more effective therapeutic regimes.[11,12] Artemisinin derivatives have been shown to be highly effective in the treatment of uncomplicated and severe malaria[13-15] and have been recommended, in combination with other antimalarials, for use in malaria endemic countries. Several countries in the region are, therefore, in the process of changing to artemisinin combination therapies (ACTs) for the treatment of malaria. However, experience with ACTs is limited and has mainly come from South East Asia, where their safety and efficacy has been well documented.[16,17] Similarly, and like for all other newly introduced drugs or drug combinations, the safety and efficacy of the compound must be monitored as it gets used in a bigger and more diverse patient population.

Pharmacovigilance is the science of monitoring the safety of a medicinal compound after it has been released into the market.[18] Although well established in many developed countries, there are few countries in sub-Saharan Africa with drug safety monitoring systems in place. Therefore, the introduction of ACTs in the region offers some of these countries an opportunity to introduce drug safety monitoring systems. The WHO and many other international partners support this process.[19]

This paper looks at the preparations for pharmacovigilance in five sub-Saharan African countries (Burundi, Democratic Republic of the Congo, Mozambique, Zambia and Zanzibar).

1. Project Description

1.1 Goals and Objectives

The main goal of the project is to improve drug safety and promote the rational use of drugs in the participating countries of Burundi, Democratic Republic of the Congo, Mozambique, Zambia and Zanzibar. The establishment of pharmacovigilance centres in these countries will be used to achieve this goal.

It is proposed that these centres will initially focus on ACTs and other anti-malarial therapies, but will later be used to collect information on all other medicinal products.

1.2 Specific Objectives

The specific objectives of the project are:

- to introduce the concept of adverse drug reaction (ADR) monitoring in the health systems of the five countries;
- to develop methods for reporting ADRs that may occur in health institutions in these countries;
- to stimulate health professionals in the participating countries to report ADRs;
- to act as a resource base for drug safety information for governments, health professionals and the general public;
- to facilitate the membership of the five countries in the international drug monitoring network.

1.3 Definitions

1.3.1 Adverse Drug Reaction (ADR)

An ADR is any noxious and unintended reaction that follows the administration of a medicinal product and that occurs at doses normally used in patients for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.[20]

This definition emphasises the normal use of medications and excludes therapeutic failures, prescription errors, overdosage or non-adherence to prescribed regimens.

1.3.2 Adverse Event

An adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product, but that may not necessarily have a causal relationship with the treatment.

The use of the term 'adverse event' reduces the potential for reporting bias as all events are recorded and not only those that are known or are familiar to the reporter, which is an important consideration for newly emerging centres.

The project will encourage health workers at all levels to record all adverse events associated with the drugs of interest and this information will then be assessed to determine causality of events by the national centres.

1.4 Country Profiles

All five participating countries are in sub-Saharan Africa and are located in a malaria endemic region. In addition to high malaria transmission, these countries have also been severely affected by the HIV/AIDS pandemic and the associated upsurge in tuberculosis. Burundi and Zanzibar have adopted artesunate and amodiaquine as first-line treatments for malaria, Democratic Republic of the Congo is considering a change to artemisinin-based combinations, whereas Mozambique has adopted artesunate and pyrimethamine/sulfadoxine as first-line treatments and artemether/lumefantrine as second-line treatment. Zambia will use artemether/lumefantrine as first-line treatment for malaria.[7]

1.5 Work Plan for Adverse Event Monitoring

In order to achieve the objectives of the project, each of the five countries in the programme has developed their own action plans for the introduction of pharmacovigilance. These proposals follow the principles of the WHO International Drug Monitoring programme.[21] The key steps in the process are:

- training in pharmacovigilance for key resource persons from the malaria programmes and national drug regulatory institutions;
- introduction of the concept of pharmacovigilance to health authorities in individual countries and submission of detailed proposals for drug safety monitoring;
- creation of national centres for pharmacovigilance and identification of supporting staff;

- preparation of protocols and case report forms for ADR monitoring and the development of a database for the storage and retrieval of data;
- training of health professionals in the concept of pharmacovigilance and reporting of ADRs;
- launch of pharmacovigilance by public or health authorities;
- stimulation of reporting by meeting with the general public, the media, health workers and academic and professional societies;
- establishment of links with international pharmacovigilance systems.

1.5.1 Pharmacovigilance Training Workshop

A pharmacovigilance training workshop was held in Lusaka, Zambia, from 23 March 2003 to 2 April 2003. Eighteen health experts drawn from the five participating countries attended the workshop. Participants included national malaria programme managers and officials from drug regulatory authorities. The WHO RBM department and the WHO Department of Essential Drugs and Medicines Policy organised the workshop. The WHO Collaborating Centre on International Drug Monitoring (Uppsala Monitoring Centre [UMC]) of Uppsala, Sweden, led the course. Other resource persons came from the National Adverse Drug Event Monitoring Centre of the Medicines Control Council of South Africa, the Ghana National Pharmacovigilance Centre and the New Zealand Intensive Medicines Monitoring Programme.

The curriculum for the course was based on the International Course on Pharmacovigilance developed and regularly run by the UMC.[22] During the course, delegates were exposed to the basic methods and skills of ADR monitoring with the aim of introducing a common system of pharmacovigilance linked to the WHO network. The training methods were highly interactive and consisted of lecture presentations, case studies, demonstrations, problem solving sessions and practical sections in which role plays were used.

1.5.2 Introduction of the Concept of Pharmacovigilance and Submission of Proposals for Drug Safety Monitoring

Because dedicated drug safety monitoring was a relatively new concept for the health sector in the region, it was recommended that the strategy for introducing pharmacovigilance would include approaching governments to highlight the importance of monitoring the safety of drugs in their countries. All delegates agreed to prepare detailed briefings on pharmacovigilance for their health ministries.

Additionally, and before the end of the course, each team was requested to develop a draft of a work plan for pharmacovigilance in their country. These proposals were presented and discussed in the plenary and suggestions were made. It was decided that all proposals would be presented to other health programme managers in each country before they were adopted.

1.5.3 Identification of National Centres for Pharmacovigilance

A successful pharmacovigilance programme requires a designated location. It was evident from the Lusaka workshop that the most favoured site for the location of the drug safety centres appeared to be the national malaria programmes, drug regulatory offices and drug information centres.

The minimum requirements to run a pharmacovigilance centre include: an office with a telephone/fax line/Internet connection; a desktop computer and printer; a photocopier; and a filing cabinet. All five countries have these facilities in place but may need to buy new equipment to improve the efficiency of their units.

In terms of staff, a fully functional centre requires a person with a background in pharmacy, pharmacology or medicine to serve as the project manager or head of operations. A full-time secretary should assist the manager with the day-to-day office routine. All the country teams indicated that they would

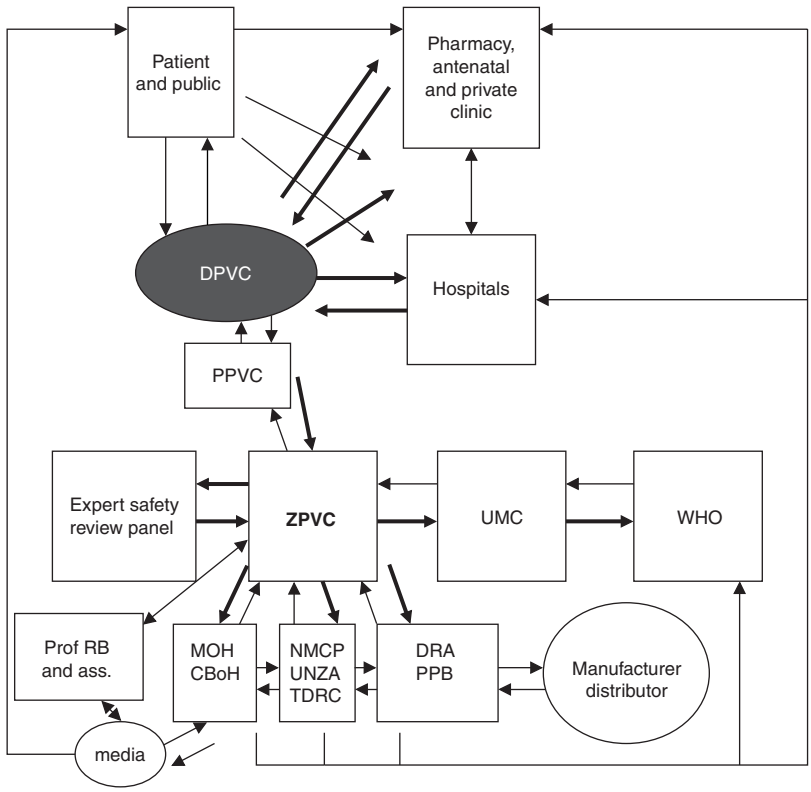

Fig. 1. Organisational and functional structure of the Zambian pharmacovigilance system. **CBoH** = Central Board of Health; **DPVC** = District Pharmacovigilance Centre; **DRA** = Drug Regulatory Authority; **MOH** = Ministry of Health; **NMCP** = National Malaria Control Programme; **PPB** = Pharmacy and Poisons Board; **PPVC** = Provincial Pharmacovigilance Centre; **Prof RB & ass.** = Professional Regulatory Bodies and associations; **TDRC** = Tropical Diseases Research Centre; **UMC** = Uppsala Monitoring Centre; **UNZA** = University of Zambia; **ZPVC** = Zambia Pharmacovigilance Centre.

include provision for staff emoluments in their final budgets.

1.5.4 Preparation of Protocols, Case Report Forms and Database Programmes

During the workshop, each country team was asked to propose a flow chart that showed how ADRs would be reported in their systems. Each team considered the nature and organisation of their national health system in drawing up their proposed ADR reporting system. The reporting cascades that were developed were meant to be robust, but flexible. For most countries, the majority of ADR reports will first be made at the peripheral health facility before they are sent to a facility at a higher level and then to the national centre. The proposed reporting system in Zambia is shown in figure 1.

In addition to the reporting cascades, all five countries have prepared case reporting forms. Participants were given a chance to look at samples of ADR report forms used in the UK (the' yellow card' system),[23] New Zealand, Ghana, South Africa and Sweden, before they developed their own country-specific forms. The form proposed for Zanzibar is illustrated in figure 2.

When fully functional, all countries will report their ADRs online on Vigibase, an Internet-based programme that was recently developed by the UMC.[24] Vigibase has a record of over 3 million adverse drug reports and each report includes the

ZANZIBAR REVOLUTIONARY GOVERNMENT

MINISTRY OF HEALTH AND SOCIAL WELFARE

ZANZIBAR ADVERSE EVENTS REPORT FORM

Patient Particulars

Name: Address

Ref No.: Age: Sex:

Date of birth:

Weight (kg):

If (female) is the patient pregnant Yes No Not sure

If yes Date of Last Menstrual Period

Date of Report Date of Reaction Duration

Reaction Details

Suspected Reaction : Brief description of reaction/side effects/drug interaction and laboratory results

Suspected Drugs

Name	Date Started	Date Stopped	Daily dose	Route	Disease/Condition

Other drugs used

Describe how the reaction was treated

Outcome of reaction Recovered completely Not yet recovered Recovered with long term consequences

Date of recovery ../../....

Remarks: eg include relevant medical history, drug allergy, previous exposure to similar drugs and other laboratory investigation

Reporter Details:

Name	Qualifications	Date:
Address:	Tel no. if available	Signature

Fig. 2. The adverse drug reaction reporting form proposed for use in Zanzibar.

details of the country from which the report was made, the patient's demographics, the suspected drug and a description of the adverse event. Vigibase is accessible to all countries participating in the WHO drug monitoring programme.

1.5.5 Training of Health Professionals in Adverse Drug Event Monitoring

It has been recognised that the success of drug safety monitoring in all countries will to a very large extent depend on the collaboration between the national centres and health professionals at the frontline of health delivery. The reporting cascades that are suggested for all countries begin with the documentation of adverse events at the health centre, clinic or hospital before they are forwarded to the pharmacovigilance centres.

Therefore, all the participating countries agree that it will be essential for health workers to be trained about the importance of drug safety monitoring and the methods for reporting adverse drug events. A provision for the training of health workers has been included in all of the budgets.

1.5.6 Launch of Pharmacovigilance by Health Authorities

Once the national centres have been established and are functional, a senior public official will launch the activity. It has been argued that in view of the importance of the issue of drug safety and because of its relatively low profile in many countries, a well-publicised inauguration of the project will assist in generating interest and support for the activities of the national centres from members of the public and health professionals in each country.

1.5.7 Stimulation of Reporting of Adverse Drug Events

Several methods of encouraging the reporting of adverse drug events were proposed at the workshop and these included holding meetings on pharmacovigilance with members of the public, health workers and academic and professional societies. In addition, the media was identified as an important partner in the implementation of pharmacovigilance.

The role of the press in communicating issues of drug safety has become increasingly important[24] and the support of this institution will, therefore, be crucial to the success of the project in the region. The press in many countries has a wide coverage and can reach larger audiences than professional journals. The press may also be better placed to communicate important health messages for the general public. This could be particularly decisive in situations where, for example, a new drug has aroused public concern.

All five countries in the project recognise the role of the press in their overall strategy for implementing pharmacovigilance.

1.5.8 Establishment of Links with International Pharmacovigilance Systems

For the national pharmacovigilance centres to play their expected roles as resource centres for information on drug safety, they will need to collaborate with other international drug monitoring groups. The WHO Programme on International Drug Monitoring has been coordinated by the UMC since 1978. All centres in the project will be linked to this programme. This link will enable the new centres to share information and ideas, which will enhance their portfolios in the long term.

By November 2003, three of the five countries in the project (Democratic Republic of the Congo, Mozambique and Zambia) had joined the WHO network as Associate members, with a hope to achieving full membership once their centres are fully functional.

2. Challenges of Implementing Pharmacovigilance in Africa

2.1 Incidence of ADRs is Unquantified in Africa

From studies conducted mainly in developed countries, it is estimated that 5% of all admissions to hospitals can be attributed in whole or in part to ADRs.[25-28] Furthermore, 10–20% of all hospital inpatients experience a serious ADR whilst in hospital.[29] A recent study reported that ADRs were the fourth to sixth leading cause of death in the US,[30] whereas other health workers report that ADRs may be responsible for 5–10% of hospital costs.[31]

There are few reports of ADRs from Africa and most reports of a drug's safety are based on those obtained from observations made in developed countries. In Zambia, for instance, a report prepared by the country's Ministry of Health on the drug and pharmaceutical situation in 1996, reports that although no detailed study of drug use had ever been done in the country, widespread irrational use of drugs was occurring at all levels of the healthcare system.[32] In this situation and with the high prevalence of illnesses such as HIV/AIDS, tuberculosis and malnutrition, it could be considered that the risk of ADRs and associated morbidity and healthcare costs may be higher in Africa and in other developing nations than in developed countries. Mechanisms to continuously monitor drug safety throughout the world are, therefore, needed and needed urgently.

Of the 72 countries who were members of the WHO Programme on International Drug Monitoring by November 2003, only 7 were from Africa, which is a very low membership for a continent with more than 50 countries (table I).[33] Given the high disease burden in many parts of the continent, it is imperative that healthcare in these settings be backed by systems to not only monitor drug safety, but drug use as well.

2.2 New Treatments and New Concepts

For both health professionals and the general public, the introduction of ACTs for the treatment of malaria will bring with it new challenges. Chloroquine, the drug being phased out, has a very good operational record in Africa. It is affordable, safe and well tolerated. Concerted efforts will, therefore, be needed to educate health workers and the public about the changes in policy and the rationale for the use of ACTs.

In countries where ACTs are being introduced, drug safety monitoring is a relatively new concept and its importance will need to be explained to the general public in order to avoid the new treatments being viewed as experiments and patients being labelled as 'guinea pigs'. It has been proposed that the media be used to promote both the new treatments and drug safety monitoring.

Table I. Membership of the WHO International Drug Monitoring Programme as at November 2003[a]

Full members	Mexico (1999)
Argentina (1994)	Moldova (2003)
Armenia (2001)	Morocco[b] (1992)
Australia (1968)	Netherlands (1968)
Austria (1991)	New Zealand (1968)
Belgium (1977)	Norway (1971)
Brazil (2001)	Oman (1995)
Bulgaria (1975)	Peru (2002)
Canada (1968)	Philippines (1995)
Chile (1996)	Poland (1972)
China (1998)	Portugal (1993)
Costa Rica (1991)	Romania (1976)
Croatia (1992)	Russia (1998)
Cuba (1994)	Serbia & Montenegro (2000)
Cyprus (2000)	Slovakia (1993)
Czech Republic (1992)	South Africa[b] (1992)
Denmark (1968)	Spain (1984)
Egypt[b] (2001)	Sri Lanka (2000)
Estonia (1998)	Sweden (1968)
Fiji (1999)	Switzerland (1991)
Finland (1974)	Tanzania[b] (1993)
France (1986)	Thailand (1984)
Germany (1968)	Tunisia[b] (1993)
Ghana[b] (2001)	Turkey (1987)
Greece (1990)	Ukraine (2002)
Guatemala (2002)	UK (1968)
Hungary (1990)	Uruguay (2001)
Iceland (1990)	US (1968)
India (1998)	Venezuela (1995)
Indonesia (1990)	Vietnam (1999)
Iran (1998)	Zimbabwe[b] (1998)
Ireland (1968)	**Associate member countries**[c]
Israel (1973)	Bahrain
Italy (1975)	Belarus
Japan (1972)	Democratic Republic of Congo[b]
Jordan (2002)	Ethiopia[b]
Korea, Republic of (1992)	Malta
Kyrgyzstan (2003)	Mozambique[b]
Latvia (2002)	Netherlands Antilles
Macedonia (2000)	Pakistan
Malaysia (1990)	Zambia[b]

a Figures given in parentheses indicate the year of joining.

b African countries.

c Associate members are new entrants to the network who are yet to establish fully functional reporting systems.

2.3 Insufficient Material and Human Resources

It is the reality that in many developing countries, the priority for most health ministries is the prevention and control of communicable diseases. Diarrhoeal diseases, respiratory illnesses and other infectious diseases cause great morbidity and mortality. In this situation, the need for setting up a dedicated system to monitor the safety of drugs may not be readily appreciated. Indeed, it may be mistaken for a new project and more responsibilities.

Added to the problem of interesting health managers in the importance of pharmacovigilance is the problem of poor funding to the health sector in many African countries. The WHO Africa Malaria Report for 2003[7] indicated the following per capita expenditure on health by governments in the network: Burundi 2%; Democratic Republic of the Congo 6%; Mozambique 6%; Zambia 11%; and Tanzania (Zanzibar) 6%. It is, therefore, evident that the few resources available may not be allocated to services that appear to offer little immediate benefits to the sick.

The poor staffing of most health institutions on the continent compound the issue of inadequate funding to the health sector. In Zambia, the Ministry of Health paper on the drug situation in the country lamented the fact that there were <700 physicians and <100 pharmacists for a country with >10 million people.[32] The development of systems to monitor and promote rational drug use may, therefore, be difficult to initiate without this necessary manpower. Even where trained practitioners are available, they are often too busy and are often poorly motivated, which is a situation that may not be conducive to their participation in drug safety monitoring.

2.4 Inadequate Drug Use and Legislation Standards

The subject of drug safety itself is not well covered in most medical schools and in many countries opportunities for further education are limited. Treatment guidelines and National Formularies, where they are published, are not readily available. Therefore, because of these limitations, for many health practitioners, information on drugs and drug safety issues may only come from their peers or representatives of pharmaceutical companies. In this situation, poor prescribing and dispensing practices are not uncommon and include reports of the widespread use of injections and antibacterials.

Additionally, although there are relatively low numbers of qualified health practitioners working on the continent, in many countries it is common to find a large number of untrained people who prescribe and dispense medicines. These illegal practitioners operate outside the formal health sector, but are patronised heavily, and contribute to an environment in which drug safety monitoring may be difficult to implement or may be seen as an attempt to interfere with what is often a very lucrative business.

2.5 Options and Strategies for Implementing Pharmacovigilance

Despite what appears to be an environment that is unsuitable for pharmacovigilance, the solution could lie in integrating drug safety monitoring into existing public health programmes. In many countries, and in response to specific diseases, several public health programmes have been developed and often with the support of international cooperating partners. These programmes have different strategies for achieving their objectives, but in most of them drug administration is a major component of their activities. It follows, therefore, that the surveillance of the safety of medications could be initiated within these programmes. A good example of this approach is the concept proposed in this project where the malaria programme will be the pathfinder for pharmacovigilance.

Working in harmony, the pharmacovigilance centres and public health programmes could complement each other. The drug safety unit could offer its expertise in the training of health workers in ADR monitoring, educate the public about the drugs they are taking and in general could act as a drug information resource for the public health unit. On the other hand, the public health programmes could share their databases and other resources with pharmacovigilance centres for mutual benefit.

3. Conclusion

There is no doubt that the issue of drug safety has aroused great public interest in many African countries. The continent has been badly devastated by the resurgence of malaria and the twin epidemic of HIV/AIDS and tuberculosis. In response to these serious health problems, there has been an influx of several new therapeutic compounds. Concern has been raised about the long-term effects of these new medicinal compounds. The development of mechanisms to monitor the safety of these novel and indeed other older compounds has, therefore, become an urgent issue for health authorities on the continent.

Five sub-Saharan African countries (Burundi, Democratic Republic of the Congo, Mozambique, Zambia and Zanzibar) have taken the opportunity presented by the change in their malaria treatment policies to introduce pharmacovigilance in their health sector. A group of health professionals with sufficient knowledge and enthusiasm to start drug safety surveillance is now available in the five countries and ready to begin monitoring the safety of drugs used in their health systems. Their success will help to extend drug safety activities to all other countries on the continent.

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References

1. Kachur SP, Bloland PB. Malaria. In: Wallace RB, editor. Maxcy-Rosenau textbook of public health and preventive medicine. 14th ed. Stamford (CT): Appleton and Lange, 1978: 313-48
2. Kevin Baird J. Resurgent malaria at the millennium: control strategies in crisis. Drugs 2000; 59 (4): 719-43
3. Bruce-Chwatt LJ. Essential malariology. London: Heinemann Medical Books, 1980
4. MacDonald G. The epidemiology and control of malaria. London: Oxford University Press, 1957
5. Campbell CC, Chin W, Collins WE, et al. Chloroquine resistant Plasmodium falciparum from East Africa: cultivation and drug sensitivity of the Tanzanian I/CDC strain from an American tourist. Lancet 1979; II: 1151-4
6. Bruce-Chwatt LJ, editor. World Health Organization Monograph Series, No. 27. Geneva: World Health Organization, 1981
7. World Health Organization. The Africa malaria report, 2003 (WHO/CDS/MAL/2003.1093). Geneva: World Health Organization and UNICEF, 2003
8. World Health Organization. The African summit on Roll Back Malaria, Abuja, Nigeria, 25th April 2000 (document WHO/CDS/RBM/2000.17). Geneva: World Health Organization, 2000
9. Stahel E, Degremont A, Lagler U. Pyrimethamine/sulfadoxine resistant falciparum malaria acquired at Dar Es Salaam, Tanzania. Lancet 1982; I: 1118-9
10. Timmermans PM, Hess V, Jones ME. Pyrimethamine resistant falciparum malaria in East Africa. Lancet 1982; I: 1181
11. World Health Organization. Framework for implementing and updating antimalarial treatment policy in Africa: a guide for malaria control programmes. Harare: World Health Organization Regional Office for Africa, 2000
12. World Health Organization. The use of essential drugs. Geneva: World Health Organization, 2000. WHO technical report series no. 895
13. Hien TT. An overview of the clinical use of artemisinin and its derivatives in the treatment of falciparum malaria in Vietnam. Trans R Soc Trop Med Hyg 1994; 88 Suppl. 1: S5-6
14. Hien TT, Day NP, Nguyen HP, et al. A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. N Engl J Med 1996; 335: 76-83
15. van Hensbrook MB, Onyiorah E, Jaffar S. A trial of artemether or quinine in children with cerebral malaria. N Engl J Med 1996; 335 (2): 69-75
16. Price R, van Vogt M, Phaipum L, et al. Adverse effects in patients treated with artemisinin derivatives. Am J Trop Med Hyg 1999; 60 (4): 547-55
17. Ribeiro IR, Olliaro P. Safety of artemisinin and its derivatives: a systematic review of published and unpublished clinical trials. Med Trop (Mars) 1998; 58: 50-3
18. Stephens M, Talbot JCC, Routledge PA. Detection of new adverse drug reactions. 3rd ed. London: Macmillan Reference Ltd, 1998
19. World Health Organization. The importance of pharmacovigilance: safety monitoring of medicinal products. Geneva: World Health Organization, 2002
20. World Health Organization. International drug monitoring: the role of the hospital. Geneva: World Health Organization, 1966. WHO technical report series no. 425
21. Uppsala Monitoring Centre. Safety Monitoring of Medicinal Products: guidelines for setting up and running a Pharmacovigilance Centre. Uppsala: The Uppsala Monitoring Centre, 2000
22. Olsson S. The role of the WHO Programme on International Drug Monitoring in coordinating world wide drug safety efforts. Drug Saf 1998; 19 (1): 1-10
23. British Medical Association. Royal Pharmaceutical Society of Great Britain. British National Formulary (No. 45). London: BMA, RPS, 2003
24. Uppsala Monitoring Centre. Dialogue in pharmacovigilance: more effective communication. Uppsala: The Uppsala Monitoring Centre, 2000
25. Einarson TR. Drug related hospital admissions. Ann Pharmacother 1993; 27: 832-40
26. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events, implications for prevention. JAMA 1995; 274: 29-34
27. Bates DW, Spell N, Cullen DJ, et al. The cost of adverse events in hospitalised patients. JAMA 1997; 277: 307-11
28. Classen DC, Pestonik SL, Evans RS, et al. Adverse events in hospitalized patients: excess length of stay, extra costs and attributable mortality. JAMA 1997; 277: 301-6
29. Pirmohamed M, Breckenridge AM, Kitteringham NR, et al. Adverse drug reactions BMJ 1999; 316: 1295-8
30. Lazarou J, Pomeraz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients, a meta analysis of prospective studies. JAMA 1998; 279: 1200-5
31. Moore N, Lecointre D, Noblet, et al. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol 1998; 45: 301-8
32. Government of Zambia. National Drug Policy. Lusaka, Zambia: Ministry of Health, 1999
33. Uppsala Monitoring Centre. Uppsala Reports. Uppsala: Uppsala Monitoring Centre, 2004 Jan

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