Disponibilidad y seguridad de medicamentos en población vulnerable: el caso de mujeres embarazadas en paises en desarrollo

Availability and safety in use of drugs in vulnerable populations: the case of pregnant women in developing countries

DOCTORAL THESIS

UNIVERSITAT DE BARCELONA

ESPERANÇA JÚLIA PIRES SEVENE

2009

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FACULTAT DE MEDICINE

PROGRAMA DE DOCTORAT DE "MEDICINA"

GRUP DE RECERCA: FARMACOLOGÍA CLÍNICA

Disponibilidad y seguridad de medicamentos en población vulnerable: el caso de mujeres embarazadas en paises en desarrollo

"Availability and safety in use of drugs in vulnerable populations: the case of pregnant women in developing countries"

Memory presented by Esperança Júlia Pires Sevene to aspire to the degree of Doctor in Medicine and Surgery by the University of Barcelona, under direction of Professor Xavier Carné and Professor Clara Menéndez.

Barcelona, January 2009

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PRESENTATION

The present Doctoral Thesis is presented following the university recommendations on presentation of Doctoral Thesis by compendium of publications.

The studies presented in this Doctoral Thesis are part of a line of research. The results achieved by studies presented in this Doctoral Thesis provide relevant and novel information on the topic. The results were collected in three original articles and one review article, published in different journals with high international impact.

INTERNATIONAL PUBLICATIONS THAT COMPOSE THE DOCTORAL THESIS

1. **System and market failures: the unavailability of magnesium sulphate for the treatment of eclampsia and pre-eclampsia in Mozambique and Zimbabwe**
   E Sevene, S Lewin, A Mariano, G Woelk, A D Oxman, S Matinhure, J Cliff, B Fernandes and K Daniels
   BMJ 2005;331;765-769
   Impact factor: 9.723

2. **Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance**
   S Ward, E Sevene, I Hastings, F Nosten, R McGready
   Lancet Infect Dis 2007; 7:136–44
   Impact factor: 12.058

3. **Drug exposure and pregnancy outcome in rural Mozambique**
   E Sevene, A Bardají, A Mariano, S Machevo, E Ayala, B Sigaúque, P Alonso, X Carné, C Menendez
   PLOS One 2008; in revision

4. **Spontaneous adverse drug reaction reporting in rural districts of Mozambique**
   E Sevene, A Mariano, U Mehta, M Machai, A Dodoo, D Vilardell, S Patel, K Barnes and X Carné
   Drug Safety 2008; 31 (10): 867-876
   Impact factor: 3.536

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i. ACRONYMS AND ABREVIATONS

ACT- ARTEMISININ-BASED COMBINATION THERAPY

ADR – ADVERSE DRUG REACTION

AIDS – ACQUIRED IMMUNODEFICIENCY SYNDROME

CIMed – DRUG INFORMATION CENTRE

CIOMS - COUNCIL FOR INTERNATIONAL ORGANIZATIONS OF MEDICAL SCIENCES

CISM – MANHIÇA HEALTH RESEARCH CENTRE

CRESIB - CENTRE DE RECERCA EN SALUT INTERNACIONAL DE BARCELONA

HIV – HUMAN IMMUNODEFICIENCY VIRUS

ICH - INTERNATIONAL CONFERENCE OF HARMONIZATION

IPT - INTERMITTENT PREVENTIVE TREATMENT

IPTp - INTERMITTENT PREVENTIVE TREATMENT IN PREGNANCY

MDGs - MILLENNIUM DEVELOPMENT GOALS

MoH – MINISTRY OF HEALTH

NMCP – NATIONAL MALARIA CONTROL PROGRAMME

PV – PHARMACOVIGILANCE

UEM – EDUARDO MONDLANE UNIVERSITY

UNAIDS - UNITED NATIONS PROGRAMME ON HIV/AIDS

US – UNITED STATES OF AMERICA

WHO- WORLD HEALTH ORGANIZATION

RESUMEN

I. RESUMEN

La investigación relativa a los seres humanos debe realizarse dentro de unos estándares que promuevan la protección de sus derechos. Varios códigos han sido desarrollados y todos ellos coinciden unánimemente en los siguientes principios éticos: el respeto por las personas, la beneficencia y la justicia. La realización de estos principios debe asegurar la dignidad, los derechos, la seguridad y el bienestar de los participantes en una investigación biomédica sean preservados.

La necesidad de una protección especial hacia aquellos seres cuya autonomía sea limitada es un requerimiento común para todos los códigos. Las mujeres embarazadas están definidas como un grupo de población vulnerable dado el riesgo potencial de causar daño al feto. Además del riesgo para el feto, las mujeres embarazadas en los países en desarrollo son potencialmente más vulnerables, y suelen contar con desventajas a nivel económico y/o educativo. Su nivel de educación, por lo general bajo, les pone en una situación difícil, dificultando la comprensión de los formularios de consentimiento y la evaluación del riesgo-beneficio que prestan los investigadores.

En los últimos años, la medicina basada en la evidencia ha sido una meta muy importante a nivel internacional. Se están promoviendo mecanismos para respaldar el uso de la evidencia científica para la

definición de política de desarrollo de la salud. La investigación debe ser sensible a la vulnerabilidad potencial cuando se diseñan ensayos basados en la evidencia. Además, se debe asegurar que la población vulnerable esté siendo protegida.

Con la intención de proteger a esa población vulnerable, algunos grupos como los de mujeres embarazadas han sido tradicionalmente excluidos de los ensayos clínicos. Como resultado de esta exención, algunas mujeres embarazadas están siendo expuestas a medicamentos de los que no hay información basada en la evidencia en cuanto a su eficacia y seguridad. Este hecho las priva de los beneficios del tratamiento que debería protegerlas, a ellas y sus hijos, de un riesgo desconocido. Aunque está muy claro que proteger a una población vulnerable, particularmente a las mujeres embarazadas, es obligatorio en el diseño de un ensayo clínico, los retos de la implementación de este principio no deberían aumentar el vacío entre la introducción de un producto farmacéutico en el mercado y la disponibilidad de información sobre su seguridad para uso en el embarazo.

En los países en vías de desarrollo la mortalidad materna es un problema importante de salud pública. La mayoría de muertes maternas ocurren en los países más pobres, particularmente en África Subsahariana. En Mozambique el índice puede ser entre 408-1000 por 100000 nacidos vivos, dependiendo de la fuente de información.

Diferentes estudios han señalado diversas causas de mortalidad materna en África, encontrándose la eclampsia y la malaria entre las cinco primeras.

Existe una gran evidencia de la eficacia del sulfato de magnesio (MGSO4) en mujeres con pre-eclampsia y eclampsia, sin embargo el fármaco no está disponible en algunos países. El ejemplo del sulfato de magnesio se ha utilizado para describir el fracaso en el traslado de los resultados de la investigación a la práctica y/o política.

Para el tratamiento de la malaria, se consideró seguro el uso durante el embarazo de algunos fármacos incluyendo cloroquina, sulfadoxina-pirimetamina y quinina. La información sobre seguridad responde a una gran experiencia de uso. El aumento de resistencia de *P. falciparum* a estos fármacos está limitando su uso en la mayoría de las zonas endémicas. Actualmente se está recomendando el uso de los derivados de la artemisinina en combinación con otros fármacos antimaláricos. Los estudios preclínicos han mostrado sistemáticamente que la artemisina y sus derivados son embrioletales y teratogénicos en animales. La información disponible hasta la fecha no es adecuada para extrapolar los resultados de los animales a los humanos.

Los datos limitados en el perfil de seguridad de los fármacos antimaláricos durante el embarazo constituyen un desafío. Hoy en día, estos fármacos se usan en mujeres embarazadas basándose en una valoración retrospectiva acumulativa de riesgo-beneficio. Se

necesitarían mecanismos de monitorización prospectiva del uso de los fármacos para proteger a las mujeres de su riesgo potencial.

El objetivo de esta tesis es el de describir la disponibilidad o no disponibilidad de los fármacos y sus razones; describir la disponibilidad o no disponibilidad de información sobre la seguridad de estos fármacos que son de uso necesario en el sureste de África. Se pretende también proponer mecanismos efectivos para monitorizar la seguridad de los fármacos en el embarazo en los países en desarrollo.

Para alcanzar estos objetivos se llevaron a cabo cuatro estudios. El primero consistía en un estudio cualitativo de casos basados en entrevistas y en una revisión bibliográfica en Mozambique y Zimbawe. Se evaluaron los factores que afectaban a la disponibilidad o no disponibilidad del sulfato de magnesio. El estudio mostró que la evidencia científica respecto a la eficacia del sulfato de magnesio para el tratamiento de la eclampsia y la pre-eclampsia fue ampliamente conocida en los países del estudio. Sin embargo, el registro, aprobación, adquisición y distribución del sulfato de magnesio y como consecuencia, su disponibilidad para los médicos se vio afectada por fallos de mercado y de sistema. Este estudio concluye que el bajo coste del sulfato de magnesio, así como el mecanismo a través del cual se obtiene, significa que las fuerzas del mercado por si solas no pueden asegurar su disponibilidad. Los gobiernos y las organizaciones internacionales deben estar preparados para intervenir y para asegurar

una amplia disponibilidad de fármacos efectivos de bajo coste, críticos para mejorar la salud pública en África.

El segundo y tercer estudio mostraron que los fármacos antimaláricos se están usando en mujeres embarazadas sin contar con información sobre su perfil de seguridad en este grupo particular. Se necesita claramente una monitorización fuerte y segura en los países en vías de desarrollo para acompañar el despliegue de los nuevos fármacos, especialmente aquellos que conllevan un potencial riesgo teratogénico.

El cuarto estudio mostró que el sistema de notificación espontánea puede ser una herramienta para la monitorización de la seguridad de los fármacos. Este sistema se podrá usar para incrementar la consciencia en provedores de salud y en enfermos sobre las posibles reacciones adversas de fármacos. Ello permitirá desarrollar una cultura de notificación de estas reacciones. La notificación espontánea y los registros de embarazo se presentaron como ejemplos de mecanismos que podrían y deberían ser implementados. Las recomendaciones de cómo estos sistemas podrían ser implementados de forma efectiva en países con recursos limitados también fueron presentadas.

Todos estos estudios sugieren que la definición de vulnerabilidad de las mujeres embarazas en los países en desarrollo no se puede restringir a causa del riesgo potencial de daño al feto, o debido a la dificultad de entender por completo los formularios de consentimiento.

También son vulnerables por el riesgo elevado de morir por alguna causa relacionada o agravada por el embarazo. La implementación de estos principios éticos necesita tener en cuenta la necesidad de implementar fármacos diana efectivos y seguros para reducir la mortalidad y morbilidad materna.

SUMMARY

II. SUMMARY

Research involving human subjects must be performed with standards that promote protection of their rights. Several codes were developed and all are unanimous in the following ethic principles: respect for persons, beneficence and justice**.** The fulfilment of these principles will assure that the dignity, rights, safety and well-being of the participants in a biomedical research are guaranteed.

The need of a special protection to those with diminished autonomy is a common requirement to all codes. Pregnant women are defined as a vulnerable population because of the potential risk of harm of the foetus. Apart from the foetal risk, pregnant women in developing countries have additional potential for vulnerability, as in most of the cases they are economically or/and educationally disadvantaged individuals. Their generally low level of education may put them in a difficult situation to fully understand consent forms and the risk-benefit assessment provided by the researchers.

In recent years, the evidence-based medicine has been an important international goal. Mechanisms to support the use of research-based evidence in developing health policy are being promoted. The research must be sensitive to the potential for vulnerability when designing evidence-based trials and they have to assure that the vulnerable population are being protected.

With the intention to protect the vulnerable population, some groups such as pregnant women have being traditionally excluded from clinical trials. As a result of this exclusion, pregnant women are being exposed to medicines in situations where no evidence-based information is available on efficacy and safety. They are deprived of the benefits of treatment in order to be protected themselves and their offspring from an unknown risk. Although is very clear that protection of a vulnerable population, particularly the pregnant women, is mandatory in the design of any trial, the challenges of the implementation of this principle should be taken into account in order to not increase the gap between the introduction of a pharmaceutical product in the market and the availability of safety information for its use in pregnancy.

In developing countries maternal mortality is an important public health problem. Most maternal deaths occur in the poorest countries particularly in Sub-Saharan Africa. In Mozambique the rate could be between 408-1000 per 100 000 live births according to the source of information. Several studies have addressed different causes of maternal mortality in Africa, eclampsia and malaria being part of the five most reported.

There is strong evidence of the effectiveness of magnesium sulphate (MGSO4) in women with pre-eclampsia and eclampsia but the drug is not available in some countries. The example of MgSO4 has

being used to describe failure in translating results of research into policy and/or practice.

For malaria treatment few drugs were considered effective and safe for use during pregnancy including chloroquine, sulphadoxine-pyrimethamine and quinine. The information on safety comes from a long experience of use. The emergency of resistance of *P. falciparum* to these drugs is limiting its use in most of endemic areas. The artemisinin derivatives are being strongly recommended to be used in combination with other antimalarial drugs. Preclinical studies have consistently shown that artemisinin and its derivatives are embryolethal and teratogenic in animals. Current available information is not adequate to extrapolate the results in animals to humans.

Limited data on the safety profile of antimalarial drugs during pregnancy is a challenge. Nowadays these drugs are used in pregnant women based on retrospective cumulative risk-benefit assessment. Mechanisms of prospectively monitoring the drugs use are required to protect pregnant women from the potential risk.

The aim of this thesis is to describe the (un)availability of drugs and their reasons, as well as, the (un)availability of safety information on drugs needed to be used during pregnancy in Southern Africa, and to propose mechanisms to effectively monitor drug safety in pregnancy in developing countries.

In order to achieve this objective four studies were performed. In the first study a qualitative case-study based on interviews and bibliographic review was performed in Mozambique and Zimbabwe. Factors affecting the (un)availability of MgSO4 were assessed. This study showed that research evidence regarding the effectiveness of MgSO4 for the treatment of eclampsia and pre-eclampsia, was widely known in the study countries. However, the registration, approval, acquisition and distribution of MgSO4, and hence its availability to clinicians, was affected by market and systems failures. With this study we concluded that the low cost of magnesium sulphate, as well as the mechanisms through which it is procured, means that market forces alone cannot be relied upon to ensure its availability. Governments and international organizations must be prepared to intervene to ensure the wide availability of low cost, effective drugs critical to improving public health in Africa.

The second and the third studies shown that antimalarial drugs are being used in pregnant women even without information on its safety profile in this particular group. Robust safety monitoring systems are clearly needed in developing countries to accompany the deployment of new drugs, especially those with a potential teratogenic risk.

The fourth study showed that spontaneous reporting system may be a tool for drug safety monitoring. This system could be used to increase health care providers' and patients' awareness of possible

ADRs, and to develop a culture to report these reactions. Spontaneous reporting and pregnancy registries were presented as examples of mechanisms that could and should be in place. Recommendations on how these systems could be effectively implemented in resource constrained countries were also presented.

All these studies suggest that the definition of vulnerability of pregnant women in developing countries should not be restricted to the potential risk of harm of the foetus (harm-based definition) or to the difficulty of fully understanding consent forms (consent-based definitions). Women are also vulnerable because of the high risk of dying from any cause related to or aggravated by the pregnancy. The implementation of these ethic principles need to take into account the urgent need to implement effective and safe drugs targeted to reduce the burden of maternal morbidity and mortality.

INTRODUCTION

III. INTRODUCTION

1. Vulnerability and vulnerable population

1.1. Ethical principles

The advances in medical science were based on research involving human subjects. Since the atrocities perpetrated upon concentration camp inmates by Nazi Doctors, the issue of protection of participants in research has being arise. The Nuremberg code (1949) was developed during the Nuremberg War Crime Trial where physicians and scientists were judged for their involvement in criminal research on prisoner's camps [1].

In 1964 the 18th Would Medical Assembly adopted the Helsinki Declaration. This Declaration is being successively revised. The last revision (2000) of the Declaration of Helsinki states the following: "Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights" [2].

In 1979 the United States (US) National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, published the Belmont Report. This report attempts to summarize the basic ethical principles that should underline the conduct of biomedical and behavioural research involving human

subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles [3].

Several other bodies such as, the Council for International Organizations of Medical Sciences (CIOMS) and the World Health Organization (WHO) have established guidance to ensure that research involving human subjects would be carried out according to scientific and ethical highest standard. In 1982, CIOMS/WHO published the “proposed international guidelines for biomedical research involving human subjects” [4].

In the Helsinki Declaration as in the other codes and guidelines in ethics, the basic principles of ethics of research involving human subject are clearly presented: respect for persons, beneficence and justice [2]**.**

The respect for persons is a principle where the subject should be treated as an autonomous agent. Persons with diminished autonomy are entitled to a special protection. In the Belmont report, an autonomous person is defined as an individual capable of deliberation about personnel goals and of acting under the direction of such deliberation [3]. The informed consent relies on the concept of autonomy and consists on the individual voluntarily confirming his/her availability to participate in the study, after receiving information about the study and about his/her rights as a participant [2].

With the informed consent the participant has to receive the relevant information, understand correctly the received information, and be able to make a decision without coercion or intimidation [2]. Thus, the consent process can be analyzed as containing three elements: information, comprehension, willingfulness [3]. For a research subject who is legally incompetent, physically or mentally incapable of giving consent a legally authorized representative should give an informed consent. These groups should not be included in research unless the research is necessary to promote the health of the population represented, and this research cannot instead be performed on legally competent persons [3].

The principle of respect for persons also suggests that researchers have an obligation to honour the concerns of communities involved in their studies.

In the principle of beneficence persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well being. This principle gives rise to norms requiring that the risk of research be reasonable in the light of the expected benefits, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. The beneficence further proscribes the deliberate infliction of harm on person; this

aspect of beneficence is sometimes expressed as a separate principle, nonmaleficence based on the Hippocratic Oath that states “do not harm” [5]. For all biomedical research involving human subjects, scientists should maximize possible benefits and minimize possible harms [2, 6].

The principle of justice states that benefits and potential harm must be distributed equally for all participants in the research. Justice in selection of research subjects requires attention in two respects: the individual and the social. In individual justice, researchers should not offer potentially beneficial research to only some patients who are in favour or select only “undesirable” persons for risky research [3]. In social justice groups of subjects are involved. Equity requires that no group or class of persons should bear more than its fair share of the burdens of participation in research and similarly no group should be deprived of its fair share of the benefits of research [3].

The basic ethical principles are reflected in all codes and guidelines for development of biomedical research. The fulfilment of these principles will assure that the dignity, rights, safety and well-being of the participants in a biomedical research are guarantied and the results of research are more credible.

Although numerous codes and guidelines for ethical conduct in research have been promulgated, there are inconsistencies between them concerning the use of language and terminology; this has

implications for how the guidelines are used by investigators in the field.

Recently, reports of ethical misconduct during biomedical research have resulted in ongoing debates over issues such as appropriate standards of care, the use of placebo in clinical trials, and obligations to study participants and their communities [7, 8]. Challenges associated with informed consent to research conducted in diverse settings particularly in developing countries have also arisen [9-11]. In light of these debates, numerous governmental and nongovernmental organizations and agencies have published specific guidelines and recommendations to researchers. For example, in 2000, the Joint United Nations Programme on HIV/AIDS (UNAIDS) published the UNAIDS guidance document entitled *Ethical consideration in HIV preventive vaccine research* and the US National Bioethics Advisory Commission (2001) published a report entitled *Ethical and policy issues in international research: clinical trials in developing countries* [12, 13].

1.2. The need of special protection to the vulnerable

When discussing the ethical principles, the need of a special protection to those with diminished autonomy is a common requirement to all codes.

The need of identify and protect vulnerable populations arose out of the historic examples of unethical use of subjects in experiments like those performed with prisoners in Nazi camps or the “Tuskegee experiment”, in which over 600 black men were recruited to study syphilis; they were misinformed about the study and private of any treatment to know more about the natural history of the disease [14, 15].

The Nuremberg Code, the Declaration of Helsinki, and the Belmont Report address the concept of protection of vulnerable population. The need of protecting vulnerable population is clearly stated, what is still needed to raise a consensus is the definition of vulnerable [16].

The Belmont report defines a person as vulnerable when “his/her dependent status compromises the capacity for free consent” [3]. The CIOMS and the International Conference of Harmonization (ICH) define vulnerable as “those who are relatively (or absolutely) incapable of protecting their own interests” [5, 17]. These definitions are consent-based. Other definitions of vulnerable are harm-based and involve participants who are more “susceptible to harms”. This susceptibility is present when we become biologically weak and require additional protections [18].

In recent medical ethics, vulnerable populations are defined as those that are at risk of being misused in the course of medical

research, either by coercion or a lack of knowledge or understanding [19].

Recently, Hurst proposed the following definition of vulnerability in research and healthcare: “an identifiable increased likelihood of incurring additional or greater wrong”. With this definition he suggested that identify the vulnerable need to be linked with identification of the type of protection that they need [20].

Based on these different definitions, the list of vulnerable populations could be long, but the following groups are most commonly referred: pregnant women, human foetus, neonates, children, prisoners, physically handicapped, mentally disabled persons, economically or educationally disadvantaged individuals, racial minorities, very sick and institutionalized people.

1.3. Pregnant women in developing countries and their vulnerability

Pregnant women are defined as a vulnerable population because of the potential risk of harm of the foetus (harm-based definition).

The involvement of pregnant women in research is a challenge, as the risk-benefit assessment must take in account the foetal risk. Most of the time there is little information about this assessment as the pregnant women are frequently excluded from the clinical trials.

Apart from the foetal risk, pregnant women in developing countries have additional potential for vulnerability, as in most of the cases they are economically or/and educationally disadvantaged individuals. The economically disadvantage, could place them at risk of being misused in the course of medical research, by coercion.

Their generally low level of education put them in a difficult situation to fully understand consent forms and the risk-benefit assessment provided by the researchers (consent-based definitions).

Understanding informed consent, particularly when it involves randomized controlled trials is a challenge in developed countries and even more difficult in developing countries, due to the low level of education, lack of access to health care services, and the community understanding and perceptions of illness and health [21]. Although the researchers acknowledge the difficulty in obtaining informed consent, few practical guidelines exist on how to ensure that research participants in developing countries understand consent forms before enrolment [22, 23].

1.4. Evidence-based medicine and protecting the vulnerable

In recent years, the evidence-based medicine has been an important international goal. Mechanisms to support the use of research evidence in developing clinical practice guidelines, health

technology assessments, and health policy are being promoted. The WHO in 2004 provided a framework for appreciating the diversity and complementarities of many of these mechanisms in his World Report on Knowledge for Better Health [24].

Now is common acceptance that evidence-based research is critical for the progress of biomedical sciences. Different organizations are working to support the effort to link research to action at a country-level [25, 26].

The research must be sensitive to the potential for vulnerability when designing evidence-based trials and they have to assure that the vulnerable population are being protected.

With the intention to protect vulnerable population, some groups such as pregnant women have being traditionally excluded from clinical trials. As a result of this exclusion, pregnant women are being exposed to medicines in situations where no evidence-based information is available on efficacy and safety. They are deprived of the benefits of treatment in order to be protected themselves and their offspring from an unknown risk. In clinical practice, the decision on the use of drugs in pregnant women is based on an empirical assessment of the theoretical risk-benefit ratio to the mother and the foetus. Experience on decades of drug use, accumulates to the point at which a drug is thought to be safe for use. This unstructured approach to get safety

information of the drugs is shocking and opposed with the evidence-based medicine principles.

Although it is very clear that protection of a vulnerable population, particularly the pregnant women, is mandatory in the design of any trial, the challenges of the implementation of this principle should be taken into account in order to not increase the gap between the introduction of a pharmaceutical product in the market and the availability of safety information for its use in pregnancy.

On the other hand, few drugs have demonstrated efficacy to reduce maternal mortality in clinical trials but are not available. Ensuring the availability of these drugs for priority health problems remains a key public health issue in many African countries [27].

2. Maternal mortality

2.1. Definition of maternal mortality

In developing countries maternal mortality is an important public health problem, and its reduction has being included in the Millennium Development Goals (MDGs). The United Nations stated the goal of reducing by three-quarters the maternal mortality ratio between 1990 and 2015 [28].

According to the WHO, "A maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes" [29].

Although the definition is clear, measuring maternal mortality is difficult and complex and reliable estimates of the dimensions of the problem are not generally available.

Most maternal deaths occur in the poorest countries. Maternal mortality is highest by far in Sub-Saharan Africa, where the lifetime risk of maternal death is 1 in 16, compared with 1 in 2800 in rich countries [30].

The United Nations MDG regions have estimated that the maternal mortality ratio in 2005 was 400 per 100 000 live births globally and 900 per 100 000 live births in Sub-Saharan Africa [31].

2.2. Maternal mortality in Mozambique

Mozambique is a developing country situated in the oriental coast of Sub-Saharan Africa (figure 1), with a population of approximately 20.5 million inhabitants with 70% living below poverty line. In 2006 the expectance of live was 47.1 years, the illiteracy rate was 53.6%, the

mortality rate was 16.4/1000 and the infant mortality rate was 107.9/1000 [32].

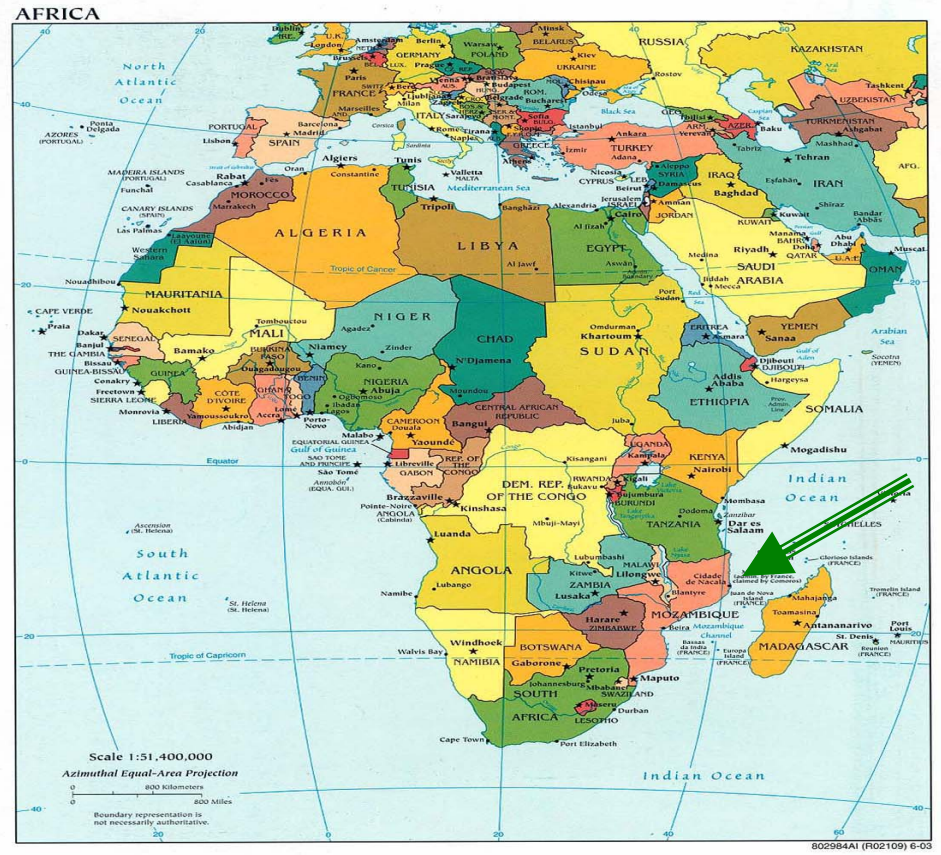

Figure 1: African Map indicating the location of Mozambique
Font: University of Texas in Austin, Perry-Castañeda Library Map Collection

The National Health Service in the country is based on primary health care, with a coverage rate of 50-60% of the population [33]. The prenatal care attendance is high with about 85% of pregnant women attending at list one visit. The rate of births taking place in Health Facilities is 48% (range from 34% in rural areas to 81% in urban areas) [33].

The prevalence of HIV infection among people aged 15 to 49 in 2004 was 16% (range 12-23%) and is higher among women [34].

Data on the maternal mortality ratio is not very accurate and different ratios can be found according to the source of information. The figures officially used in the country are derived from the data of some hospitals in the main cities not in the community [35]. The National Institute of Statisticians gives a rate of 408 per 100 000 live births but the WHO maternal mortality in 2000 report present a ratio of 1000 per 100 000 live births [32, 36]. According to WHO report, in 2005, the maternal mortality ratio in Mozambique was 520 per 100 000 live births [31]. The WHO data resulted from a complex informatics model analysing the impact of different factors in maternal mortality including the influence of the HIV pandemic, social and demographic factors, and factors related with the national health system [31, 36]. A hospital based study in Maputo City reported a maternal mortality ratio of 847 per 100 000 in 2004 [37].

These rates show how vulnerable the pregnant women are in Mozambique and reinforce the need of protecting this group by creating mechanisms of reducing maternal mortality.

In 1998 the needs for safe motherhood at national level were assessed, followed by an analysis of the causes of maternal death in the country. This led to the formulation of a national strategy to reduce maternal mortality in 2000 [38]. On this strategy the essential obstetric

care, the medicines and the equipment to be available at different health units to improve the diagnoses and treatment in order to reduce the maternal mortality were defined. Implementation of this strategy is in place and successes and challenges have being described elsewhere [39].

2.3. Malaria and eclampsia contribution for maternal mortality

As described before, the estimation of maternal death is a complex issue. It is even more complex to rank the causes of maternal death. Studies in Senegal, Nigeria and Gambia reported that haemorrhage, eclampsia and puerperal sepsis are the first causes of maternal mortality [40-42].

In Mozambique several studies have addressed different causes of maternal mortality. A hospital-based study in 7 provinces reported puerperal sepsis, haemorrhage and uterine rupture as the first's causes of maternal mortality in Mozambique, representing 83% of the deaths [39]. In a recent autopsic study, Menéndez and collaborators reported that infectious diseases mainly HIV/AIDS, pyogenic bronchopneumonia, malaria and bacterial meningitis were the leading causes of maternal mortality and represented 50% of all deaths [37]. Granja and collaborators, in a hospital based study, reported haemorrhage (31%), hypertensive diseases of pregnancy including

eclampsia (15%) puerperal sepsis (12%) and malaria (9%) as the first causes of death [43]. In other two studies malaria was an important cause of maternal mortality, particularly in adolescents followed by hypertension including eclampsia, puerperal sepsis and septic abortion [44, 45].

These data show that most of maternal deaths in Mozambique are due to avoidable or treatable causes. Malaria and eclampsia are constantly part of this list. Mechanisms to prevent, rapid diagnoses and adequate treatment must be in place to control these diseases.

3. Management of eclampsia and malaria to reduce the maternal mortality

3.1. Eclampsia

3.1.1. Definition and risk factors

Pregnancy-induced hypertension is part of the hypertensive syndrome which is a life-threatening condition both for mother and foetus. Pre-eclampsia and eclampsia are complications of hypertension in pregnancy. In pre-eclampsia, the woman has dangerously high blood pressure, swelling, and protein in the urine. If allowed to progress, this syndrome will lead to eclampsia, characterized by hyperreflexia and convulsions [46].

The diseases are most common in mothers under the age of 20, some studies describe a geographic variation in their incidence [47, 48]. Other risk factors include poverty, multiple pregnancies (twins, triplets, etc.), pre-existing chronic hypertension or kidney disease, diabetes, excess amniotic fluid, and a foetal nonimmune hydrops [49, 50]. The tendency to develop pre-eclampsia appears to be clustered in families. The daughters and sisters of women who have had pre-eclampsia are more likely to develop the condition [48, 51].

Pregnancy-induced hypertension syndrome can cause placental abruption, intracranial haemorrhage, liver lesions, acute renal disorders, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), hypervolemia and inhalation of gastric content, due to deep sedation [52].

Delivery is always an appropriate therapy for the mother, but may not be a good solution for the foetus. Standard treatment of pre-eclampsia-eclampsia includes: anticonvulsive therapy, antihypertensive therapy, generous fluid administration, and if necessary, management of oliguria, DIC, pulmonary oedema and recovery of liver function [52].

3.1.2. Magnesium sulphate in the treatment of eclampsia

Magnesium sulphate (MgSO4) is recommended for prevention of eclampsia and to treat the spasm. There is strong evidence of the efficacy of MgSO4 in women with pre-eclampsia and eclampsia. A large multi-centre trial where MgSO4 was compared either with diazepam or phenytoin showed that MgSO4 was superior to these two drugs in the treatment of eclampsia [53]. In other multi-centre study MgSO4 was compared with placebo in pre-eclampsia and was proved to be effective [54]. Three systematic reviews have shown the efficacy of magnesium sulphate in treating eclampsia and pre-eclampsia [55-57].

While the evidence of effective treatment for eclampsia is available since 1995, it is a matter of concern that this effective and low cost drug [MgSO4 costs was $0.35 (€0.29) per ampoule (40 ml of 10% magnesium sulphate; Central Medical Store, Mozambique, April 2005] is still not available in many countries while other less effective therapies are still being used in obstetric practices in one third of the world [53, 58, 59]. Magnesium sulphate appeared on the WHO essential medicines list since 1996 [60]. The example of MgSO4 has being used to describe the failure to translate results of research into policy and/or practice [61].

3.2. Malaria

3.2.1. Definition and risk factors

Malaria is the most important protozoan parasitic disease in the human being in terms of human suffering and economic implications, with current transmission in about 100 countries, affecting over 1000 million people and causing annually 1 to 3 million deaths, the majority of which are young children and pregnant women living in Sub-Saharan Africa [62, 63]. The real malaria burden is difficult to estimate, mostly due to the varying case definition as well as the ineffective case reporting system in most of endemic countries.

The disease is transmitted by the bite of an infected *Anopheles* mosquito who introduces motile organisms called sporozoites into the blood stream. Different species of parasites are responsible for the disease including *Plasmodium falciparum, ovale, vivax and malariae*. Infection with *P. falciparum* can result in high levels of parasitaemia because of its ability to invade erythrocytes of all ages and is responsible for the most severe forms of the disease [64].

The symptoms of malaria include headache, anorexia, malaise, fatigue, myalgias, fever and chills. Severe malaria cases could present with hypoglycaemia, convulsions, severe anaemia, acute renal failure, jaundice, pulmonary oedema, cerebral malaria, shock and acidosis [65].

There is broad evidence for the adverse effects of *P. falciparum* infection in pregnancy, particularly in areas of high transmission. Malaria, especially caused by *P. falciparum* infection, during pregnancy frequently leads to maternal anaemia, placental infection, stillbirth, prematurity, intrauterine growth retardation, and low birth weight. Severe anaemia in pregnancy is an important contributor to maternal and perinatal morbidity and mortality [66-68].

3.2.2. Malaria control

After World War II, strenuous efforts were made to eradicate malaria, and great attention was thrown into prevention programmes promoted during the 50's and 60's by the World Health Organization. Although these programmes were effective in certain areas of the world, the emergence of resistance to insecticides from mosquitoes, and to antimalarials from the parasite (specifically to chloroquine) obliged the WHO, in 1972, to abandon their global malaria eradication programme and focus on treatment rather than prevention. This situation, however, failed to bring adequate solutions, as in the last 25 years of the 20th century, among the 1393 new chemical entities marketed in the world, only 4 were antimalarials [63].

The first effective treatments against malaria were reported during the 17th century, and were based on the bark extracted from the

Peruvian cinchona tree. However, it would take more than two centuries (1820) until quinine, its active principle, would be isolated from that same tree. Quinine, a quinoline-arilmethanol, is still used nowadays as the first line treatment for severe malaria in many parts of the world.

Chemotherapy and prophylaxis of different forms of malaria have become progressively more complex and less satisfactory, primarily due to selection of drug-resistant strains of *P. falciparum* in areas of extensive antimalarial use [69]. Any guideline should be appropriately reviewed according to the status and habitat of the patient, the geographic origin, the prevalent species, the drug resistance profile of the likely infecting parasites, and the agents used locally for malaria control.

a) Prevention

Prevention and control of malaria morbidity relies on the use of personal protection against mosquito bites (avoiding exposure to mosquitoes at dusk and dawn, usually times of maximal feeding; sleeping under insecticides treated bednets; wearing long-sleeved clothes; using insect repellents); vector control measures: using indoor-residual house spraying and larvicides [70-72].

Chemoprophylaxis is recommended for travellers to endemic areas and chloroquine, mefloquine, proguanil-atovaquone or doxyciclyne are examples of drugs widely used according to the patient and to the specific endemic area [73].

Various strategies using anti-malarial drugs for prevention of malaria in endemic areas have been recommended especially during pregnancy. Studies in pregnant women on endemic malaria areas have shown significant effect of chemoprophylaxis in increasing birth-weight, maternal haemoglobin levels and in reducing parasitaemia prevalence even in multigravidae [74, 75]. However, this intervention has rarely been implemented on any significant scale and some of the reasons have being described as: sustainability, compliance, safety, cost, impairment of the development of natural immunity and induction of drug resistance [76]. Proguanil associated with chloroquine is considered a safe combination for malaria prevention during pregnancy but compliance was a concern as the drugs should be taken in a daily basis during throughout the pregnancy. The risk-benefit should be performed to start prophylaxis in endemic areas [77].

Recent studies have shown benefits of a new control strategy: the intermittent preventive treatment (IPT). It consists on the administration of antimalarial drugs to asymptomatic individuals regardless of the presence of parasitaemia, at pre-determined time points [78]. As pregnant women and children are at highest risk of the most severe

forms of malaria and its complications, they have been selected as the target groups for the IPT. IPT in pregnancy (IPTp) consists on the administration of two to three doses of antimalarial drugs to pregnant women through the antenatal clinic visits.

At present, sulphadoxine-pyrimethamine (SP) is the antimalarial with the best overall effectiveness for IPT of malaria in pregnancy in areas with stable *P. falciparum* transmission [78-80]. This combination contains two substances which have potential drawbacks, hypothetical risk of kernicterus in the newborn and serious skin reactions [81]**.** Nevertheless studies have never shown harmful effects in pregnant women when IPTp with SP was given in the second and third trimesters [78-80]. With increasing risk of emerging *P. falciparum* parasites resistant to SP, other drugs need to be studied as alternatives for IPTp.

An anti-malarial vaccine is unlikely to be available before the end of this decade but recently, a new malaria vaccine has shown efficacy in infants and it has a potential to prevent malaria in pregnancy [82-84].

b) Treatment

Most antimalarial drugs are targeted against the asexual erythrocytic stage of the parasite by disturbing the polymerisation, and/or the detoxification by any other way, of heme, thus killing the

parasite with his metabolic waste. The main classes of schizontocides are 4-aminoquinolines, aryl-methanol's (including quinoline-methanol's), antifolate compounds that inhibit the synthesis of parasitic pyrimidines and the newest class based on the natural endoperoxide artemisinin and its hemisynthetic derivatives and synthetic analogs [65]. Some antibiotics like doxyciclyne, tetracycline, clyndamicin and azithromycin are also used, generally in association with quinoline-methanol's [85-87]. Few compounds are active against gametocytes and intra-hepatic stages of the parasite (e.g. primaquine).

Prompt effective treatment of confirmed or suspected malaria cases continues to be the cornerstone of malaria control [88]. Chloroquine was used since prior to the Second World War as the drug of choice for treating malaria. Chloroquine was the main treatment for the erythrocytic stages of *P. vivax*, *P. ovale*, *P. malariae* and chloroquine-sensitive *P. falciparum*. The dormant hepatic stages of *P. vivax* and *P. ovale* also require further treatment with primaquine.

Chloroquine was very cheap, widely available, and extremely effective but its use is now limited by the increase of *P. falciparum* resistant parasites in most endemic areas [69]. Resistance of P. vivax to chloroquine was first observed in Papua New Guinea and after in Indonesia, Myanmar and Vanuatu, then other countries reported resistance of *P. falciparum* to chloroquine [89, 90].

Amodiaquine has been found to be significantly more effective than chloroquine in terms of parasite cleaning on day seven in *P. falciparum* uncomplicated malaria in children. It is generally effective against chloroquine-resistant *P. falciparum* infections and this drug is used as a first or second-line drug in many African countries in combination with other antimalarial drugs [91, 92].

Sulphadoxine-pyrimethamine, alone or in combination, is also used to treat uncomplicated malaria in areas where resistance to SP remains low [91, 93, 94]. Mefloquine is highly effective in the treatment of chloroquine-resistant *P. falciparum* malaria but resistance to mefloquine has appeared and the exact mechanism is still unknown [95]. Quinine, alone or in combination with other drugs, is the indicated drug for the treatment of severe malaria in chloroquine-resistant *P. falciparum* areas, although other drugs are been reporting efficacy [96].

Increasing drug resistance of *P. falciparum* and the resurgence of malaria in tropical areas have affected a change in the treatment of malaria in the last two decades. The beginning of the 21st century is witnessing an era of renewed effort in terms of malarial chemotherapy and prophylaxis, and many are the candidate molecules that are currently designed and assessed for malaria.

Combination therapy is now recommended in vast areas of the world, due to its potential to rapidly decrease parasitaemia, and also because the synergic effect of the combination could improve the

clinical cure, provide a way in which resistance can be combated, and may also reduce malaria transmission [97-99]. The probability of resistance developing simultaneously to two chemotherapeutic agents with independent mechanisms of action is extremely low, of the order of once in 10^{12} treatments (being this frequency, the product of the probabilities of the acquisition of a resistant mutation to each drug multiplied by the number of parasites in a typical infection) [100].

The artemisinin derivatives are being strongly recommended to be used in combination with other antimalarial drugs. Artemisinin-based combination therapies (ACTs) are the first line treatment recommended by the WHO in *P. falciparum* endemic areas [101]. However, the relatively high cost and erratic supply of the natural parent compound of artemisinin implies an urgent need for the development of new synthetic and cheap endoperoxide-based antimalarials [101].

Following the WHO recommendation, by May 2008, 76 countries from Africa, Asia and Latin America have adopted ACTs as first or second line treatment, but only 58 were deploying the drugs (Jackson Sillah, WHO African Region, personal communication) (Figure 2).

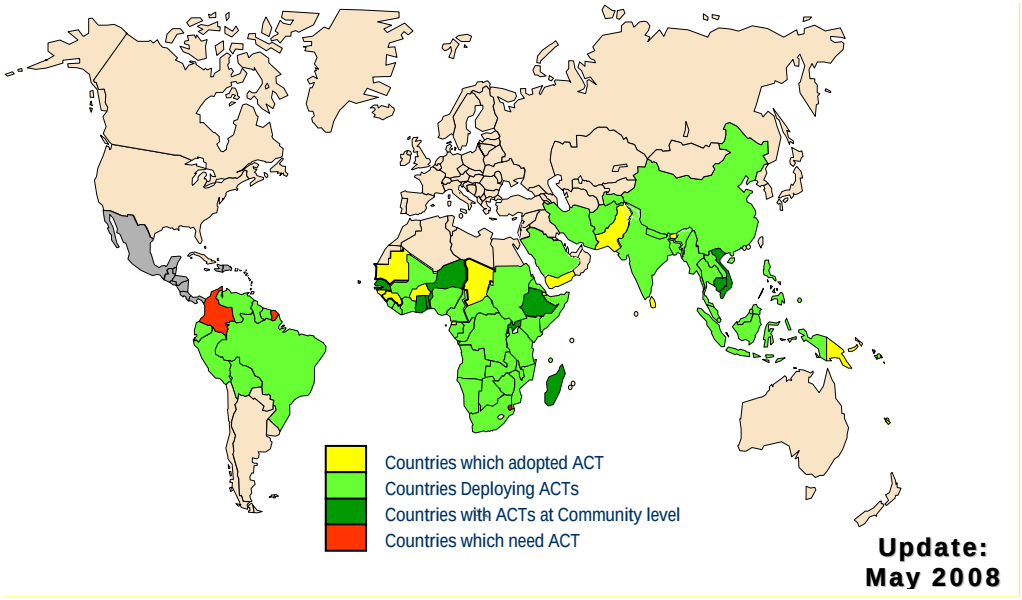

Figure 2: Countries adopted ACTs as first or second line treatment for malaria
Font: WHO African Region

Recently, a new policy in the treatment of malaria was adopted by the Ministry of Health in Mozambique [102]. The current line treatment for uncomplicated malaria is artesunate plus sulphadoxine-pyrimethamine and the second line is artemether-lumefantrine. Quinine is recommended for severe malaria or for uncomplicated malaria when other alternatives are contra-indicated or not available [102].

3.2.3. Safety profile of antimalarial drugs in pregnancy

Chloroquine seems to be the safest antimalarial drug in pregnancy and was extensively used in this group of the population**.** Congenital ototoxicity, retinal toxicity and mental retardation have been reported in children whose mothers took large doses of chloroquine during

pregnancy for other diseases. However, these risks have not been observed during the treatment of malaria at recommended doses [103, 104].

Currently, there is no evidence to contraindicate amodiaquine based on its safety profile for malaria treatment during pregnancy [105]. However, the risk of agranulocytosis and severe hepatitis related to amodiaquine have been described years ago [106]. It was withdrawn from the WHO essential medicines list during 1990-1996 but later reinstated (1996) after the 19th Expert Committee on Malaria, stating that “amodiaquine could be used for treatment if the risk of infection outweighs the potential for adverse drug reactions” [107]. Recent studies suggest that the drug is safe when used in second and third trimesters [108].

Primaquine is not recommended in pregnancy because of potential risk of haemolysis in the foetus [81, 104]. If a radical cure with primaquine is indicated, it is suggested that symptoms must be suppressed with chloroquine until delivery, and administer primaquine after delivery.

Quinine has been used historically as an abortifacient, but it is considered safe in pregnancy and not responsible for abnormalities in the foetus except in large doses [109]. Its use is, therefore, recommended during pregnancy. However, its tolerance when given

orally is poor and it is associated with increased risk of hypoglycaemia when given parenterally [110].

Mefloquine is teratogenic in animals at high doses [111]. In pregnant women, its use for malaria treatment was associated with an increased risk of stillbirth in a retrospective study in the western border of Thailand [112]. This result was not found in other studies.

Some abnormalities were observed in animals when halofantrine was given at high doses and there is not enough safety information when used in humans [113]. For the related drug lumefantrine there is no information on safety in pregnancy [109].

There is no evidence that proguanil is harmful at prophylactic doses during pregnancy [81]. Neither atovaquone nor proguanil are known to have teratogenic, embryotoxic or mutagenic activity. Pregnancy is currently listed as a contra-indication to the use of the atovaquone-proguanil combination but studies are in place to confirm its safety profile [114].

Teratogenicity and embryotoxicity of sulphadoxine-pyrimethamine has been demonstrated in animals [115, 116]. This effect has been reversed by folinic acid. The teratogenic potential in humans is not known. Sulphadoxine and pyrimethamine are excreted in breast milk. The manufacturers recommend that pregnant women at term and nursing mothers should, therefore, abstain from using the combination or refrain from breast feeding since sulphonamides may cause

kernicterus in the newborn. However, the risk of *kernicterus* with doses used for malaria treatment is considered to be very low, and has not been observed in many carefully carried out trials [117].

Preclinical studies have consistently shown that artemisinin and its derivatives (artesunate, dihydroartemisinin, artemether and arteether) are embryolethal and teratogenic in animals [118]. In rats and other rodents they exhibit embryolethality and teratogenic activity consisting of cardiovascular and skeletal defects (shortened and/or long bones) [119]. *In vitro* studies demonstrated that there was a marked depletion of embryonic blood cells followed by heart deformation, retarded growth, and embryonic death suggesting that hypoxia resulted from embryonic anaemia may be responsible for embryotoxicity in rats and other rodents. The time of exposure is critical to the development of the embryotoxicity and was between day 10 and 14 postcoitum [120, 121].

In studies conducted in *cynomolgus* monkeys with doses of 4, 12 or 30 mg/kg of artesunate on days 20 to 50 postcoitum, embryo death occurred after 12 to 20 days of treatment at 12 and 30 mg/kg/day. No malformations were observed in these studies but the sample size was not adequate to conclude that artesunate is not teratogenic in monkeys [122, 123].

Current available information is not adequate to extrapolate the results in animals to humans. Although the mechanisms are suggesting that the same process could occur in humans, the time window of

sensitivity, the equivalent dosage and duration of exposure is not known and further data are clearly needed [124]. Based on the preclinical studies, artemisinins are not recommended during the first trimester of pregnancy [88]. There are new synthetic artemisinin derivatives currently in development phase [125].

Limited data on the safety profile of antimalarial drugs during pregnancy is a challenge. Nowadays these drugs are used in pregnant women based on retrospective cumulative risk-benefit assessment. Mechanisms of prospectively monitoring the drugs use are required to protect pregnant women from the potential risk.

4. Pharmacovigilance System to monitoring drug use

4.1. The need of pharmacovigilance

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems [126].

In early 1960s Dr William McBride (Australia) reported 20% increase in foetal abnormalities and significant increase of *phocomelia* in relation with thalidomide [127]. This drug was given to pregnant women to prevent “morning sickness”. After this incident, drug safety monitoring gained world-wide attention.

During the last decades it has been demonstrated by several studies that drug related morbidity and mortality is a major public health problem. In US it is estimated that adverse drug reactions represent the 4th or 5th cause of death [128]. A recent study reported that adverse drug reactions result in 250 000 hospital admissions a year in the United Kingdom [129].

Preclinical drug studies and formal phase I, II, and III clinical trials are generally accepted to have serious limitations in terms of establishing safety [130]. A functional pharmacovigilance system is necessary for the prevention of drug-related human suffering and also to avoid the human and financial costs associated with adverse drug reactions.

4.2. Spontaneous Reporting System

Spontaneous reporting is a relatively new phenomenon in the history of medicine. The first national ADR reporting schemes were set up in the 1960s. The United Kingdom started the yellow card system in 1964. The WHO established the programme for International Drug Monitoring in 1968 in Alexandria, USA with ten countries participating including Australia, Canada, Denmark, Germany, Ireland, Netherlands, New Zealand, Sweden, United Kingdom and US. A WHO drug monitoring centre situated within WHO Headquarters was established

in 1971. In 1978 the operational activities were transferred to Uppsala, Sweden, where a WHO collaborating Centre for International Drug Monitoring was established [131].

By 2008, only 12 out of the 86 full members countries of the WHO International Drug Monitoring Programme were African countries including Morocco, South Africa, Tanzania, Tunisia, Zimbabwe, Ghana, Egypt, Nigeria, Mozambique, Uganda, Togo and Ethiopia [132].

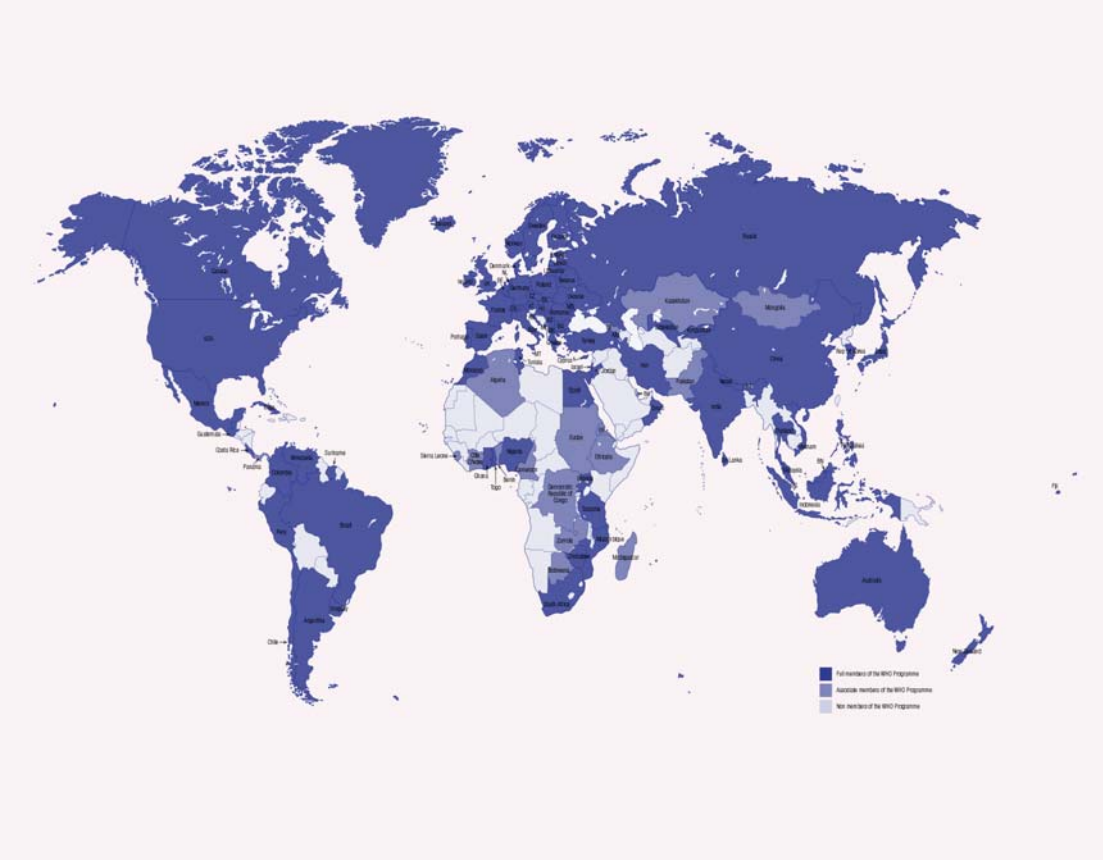

Figure 3: Countries participating in the WHO International Pharmacovigilance System by October 2008. Official Member Countries (dark blue), Associate Member Countries (medium blue), countries in pale blue are not members of the WHO Programme.
Font: http://www.who-umc.org

A national PV programme can contribute significantly towards ensuring the safety use of medicines within a country. Signals of previously unknown or poorly understood adverse drug reactions (ADR) and drug-related problems can be detected and assessed through spontaneous reporting systems [131, 133].Once the national regulatory authority is made aware of the problem, the necessary regulatory actions can be taken.

Unlike any other monitoring system, spontaneous reporting is able to oversee the safety of all drugs, all the time. Covers a large population and can quickly produce a signal of previously unknown ADR, which may have resulted from preventable or inherent risks associated with the use of a drug/s [134]. It is an effective tool in identifying new risks associated with medicines, provided that all levels of health staff throughout the country support this activity and recognize its importance in patient care. The Pharmacovigilance system should be able to find early signals of drug problems and determine the risk benefit profile [135].

Implementation of spontaneous reporting in developing countries is particularly problematic in settings where other pressing health priorities exist and challenges like remote location, poor telecommunication services, and low level of education of health professionals are common.

The introduction of new policies and the accessibility of drugs for the treatment of malaria, tuberculosis and HIV/AIDS, thus, offer a number of challenges to health services in resource-poor countries. There are new drugs and new drug combinations whose efficacy and safety have not been adequately monitored under conditions of large-scale use in these settings. Healthcare personnel are required to ensure correct prescription, effective distribution channels, and the fostering of compliance by patients. Systems to promote this should be in place or may require strengthening.

Appropriate PV systems to monitor the potential occurrence of unexpected ADRs in these countries are needed for monitoring these treatments. In case those PV systems are not available, simple techniques to promote and facilitate reporting of unusual clinical events are recommended [136].

WHO is starting to promote the introduction of Pharmacovigilance in Public Health Programs (PHP) in developing countries. As PHP are well established, operate according to standard guidelines and are well supported nationally and internationally, there is an opportunity to interact with pharmacovigilance. To address this issue, five African countries (Burundi, Democratic Republic of Congo, Mozambique, Zambia and Zanzibar) have designed action plans to introduce Pharmacovigilance Systems, in the context of the implementation of new antimalarial therapy [137].

4.3. Pregnancy registry

During implementation of pharmacovigilance systems, special attention should be given to specific risk groups, particularly pregnant women. The first trimester of pregnancy is of highest risk of foetal adverse reactions and some women are being accidentally exposed to medicines during this period because they are not aware of pregnancy or they do not declare the pregnancy.

Although it is known that pregnancy is a physiological process, advances in medicine increasingly mean that the condition is associated with increasing exposure to medicines with a high prevalence of drug use during pregnancy being described in different studies [138, 139].

Causality assessment is difficult in pregnant women as some adverse reactions can only be identified after delivery. There is a need to consider different factors in determining the strength of the association between the medicine and the reaction including specific and possibly unique pathognomonic defects, plausible temporal exposure, consistency of the observed evidence, dose-response relationships and duration of exposure as well as confounding factors like other exposures (drugs, environmental, chemical and traditional medicines).

Pregnancy registries are increasingly being recognized as one method for detecting major risks associated with a drug or biologic exposure during pregnancy [140]. These registries could be used to follow-up a specific product or as a routine way to follow-up the use of any medicine in pregnancy. At the time of pregnancy registry, information is collected on the drug exposure, maternal disease status, and other factors that may affect pregnancy outcome. An active follow-up of these pregnancies, including outcome of the pregnancy and the infant, are performed using a variety of approaches, including maternal interviews, medical record abstraction or a combination of these methods in order to avoid recall bias [141].

These registries are widely used in the U.S. and Europe to provide useful information to health care providers and policymakers on the outcomes of pregnancy following exposure to drug therapy. Examples of classes of medications that are systematically monitored through pregnancy exposure registries are antiretroviral drugs, antiepileptic drugs, antipsychotic drugs, asthma medicines, cancer regimens, and immunosuppressants [142, 143]. From this system accurate data should be recorded in order to calculate prevalence of adverse reactions, identify risk factors, better estimate the magnitude of risk of exposure and detect long-term reactions such as delayed development, other neurological impairments, or any effects that might be detected in older children with at least one year of age previously

exposed to drug in the uterus. Pregnancy registries may also be useful to evaluate products suspected of causing harm during pregnancy based on animal reproductive toxicology studies, structure-activity relationships, pharmacological class, or human case reports.

These surveillance mechanisms can experience under-reporting, selection of reporting (some pregnancy will not be registered), selection of birth defects (some defects will not be diagnosed at birth and there will be some loss to follow-up) and could be difficult to link specific maternal exposures to foetal anomalies enhanced by lack of quality baseline data on birth outcomes in some countries. Despite limitations of these methodologies, they have been used to supplement animal toxicology studies and clinical trials, and to generate signals of risk in order to help health care providers to weighing the risk of using medicines in pregnant women.

With these data it is clear that pregnant women in developing countries are vulnerable. There is a need to create mechanisms **to promote the availability of drugs** with proved efficacy and safety in pregnancy. When the drugs are available **pharmacovigilance systems to monitor its use should be in place**.

HYPOTHESIS

IV. HYPOTHESIS

Pregnant women in developing countries are defined as vulnerable populations because of the potential risk of harm of the foetus and their being economically or/and educationally disadvantaged. For these reasons they are frequently excluded from the clinical trials.

Maternal mortality rate is high in developing countries particularly in Sub-Saharan Africa. Different factors contribute to the high rate of maternal mortality being eclampsia and malaria always present among the first five causes described by most of the studies.

Although, clinical trials and meta-analyses demonstrate that magnesium sulphate (MgSO4) is effective for the treatment of eclampsia, the drug is not available in some countries. Being a cheap drug, the reason for this low use remains unclear. With the emergence of *P falciparum* resistance to different antimalarials, new drugs or new combinations of drugs are being used for treatment of malaria in pregnant women as in other groups. There are limited Information on efficacy and safety profile of these drugs during pregnancy and interpretation of the results from pre-clinical studies in animal models is a challenge. In the evidence-based era this is a real concern as no evidence will be available for policy decision-making.

Our working hypothesis was that “it is possible, in low resource countries, to identify and mitigate the factors that contribute to

vulnerability of pregnant women in developing countries by promote implementation of effective and safe drugs for reduction of maternal mortality?”

Eclampsia and malaria during pregnancy and problems related to the effective and safety use of drugs for these conditions, are good examples that highlight the importance and complexity of the use of drugs in pregnant women in developing countries and the need for action.

OBJECTIVES

V. OBJECTIVES

In order to answer the above mentioned hypothesis the following objectives are proposed:

1. General Objective:

The aim of this thesis is to describe the (un)availability of drugs and their reasons, as well as, the (un)availability of safety information on drugs needed to be used during pregnancy in Southern Africa, and to propose mechanisms to effectively monitor drug safety in pregnancy in developing countries.

2. Specific Objectives:

1. To explore the factors affecting the (un)availability of magnesium sulphate (MgSO4) for the treatment of eclampsia and pre-eclampsia in Mozambique and Zimbabwe.

2. To describe the (un)availability of appropriate safety information for important therapeutic groups of antimalarial drugs during pregnancy.

3. To describe the level of drug exposure during pregnancy and its relation to pregnancy outcomes in a rural area of Mozambique with high malaria endemicity.

4. To describe the feasibility of creating an adverse drug reaction spontaneous reporting system in two rural districts in Mozambique where remote location, poor communication services, and low level of formal education of health professionals are the rule.

METHODOLOGY AND RESULTS

VI. METHODOLOGY AND RESULTS

1. First article

System and market failures: the unavailability of magnesium sulphate for the treatment of eclampsia and pre-eclampsia in Mozambique and Zimbabwe

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BMJ 2005;331;765-769

SUMMARY

Evidence from randomized controlled trials shows that magnesium sulphate, a low cost drug, is effective for the treatment of eclampsia and pre-eclampsia. The drug is still not available widely in many low and middle income countries. The objective of this study was to explore the policy level factors affecting the availability of magnesium sulphate for the treatment of eclampsia and pre-eclampsia in Zimbabwe and Mozambique.

A qualitative case-study based on interviews and bibliographic review was performed in publicly funded health sectors in Mozambique and Zimbabwe. Thirty three policy actors, including ministry of health

senior officials, clinicians, pharmacists, pharmaceutical company representatives and researchers were interviewed. The participants were selected using a purposive and snowballing approach, based on respondents' involvement in policy making or procurement for magnesium sulphate.

Research evidence regarding the effectiveness of MgSO4 for the treatment of eclampsia and pre-eclampsia is widely known in the study countries. However, the registration, approval, acquisition and distribution of MgSO4, and hence its availability to clinicians, was affected by market and systems failures. Market failure was a result of positive external effects, a single national consumer for the drug and information asymmetries. The low cost of the drug had other unexpected effects: the small profits to be made from it provided little economic incentive for pharmaceutical companies to incur drug registration costs in Zimbabwe or to market the drug in Mozambique.

Systems failures included poor communication between clinicians and central pharmacy suppliers; the absence of a coherent drug registration mechanism in Mozambique; and the low priority given to the drug within the national formularies in both countries.

In conclusion, the low cost of magnesium sulphate, as well as the mechanisms through which it is procured, means that market forces alone cannot be relied upon to ensure its availability. Governments and international organizations must be prepared to intervene to ensure the

wide availability of low cost, effective drugs critical to improving public health in Africa.

System and market failures: the unavailability of magnesium sulphate for the treatment of eclampsia and pre-eclampsia in Mozambique and Zimbabwe

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Summary points

Removing user fees for primary care is important in offering financial protection to poor African households

Fee removal must be accompanied by increased national budgets for health care to protect the quality of health care in the face of increased utilisation

Careful and deliberate implementation strategies are needed to ensure that fee removal achieves its objectives

National action must be supported by international action that is sensitive to national circumstances and underpins the sustained mobilisation of resources

Health in Southern Africa, EQUINET, and HEPNet, the Health Economics and Policy Network in Africa). It responds to current calls, such as those of the Africa Commission, for the removal of primary care user fees in Africa. An earlier, substantively different, version of this piece was prepared by the authors as an editorial for the electronic newsletter of EQUINET.

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System and market failures: the unavailability of magnesium sulphate for the treatment of eclampsia and pre-eclampsia in Mozambique and Zimbabwe

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Low cost and effective drugs, such as magnesium sulphate, need to be included in initiatives to improve access to essential medicines in Africa

Ensuring the availability of effective drugs for priority health problems remains a key public health issue in many African countries.[1] Market deficiencies in ensuring drug development for "neglected" diseases affecting developing countries are well described,[2 3 w1] and several global initiatives are attempting to tackle this.[4 w2] Even when low cost, effective treatments exist, however, drug availability for many common health problems remains poor in many settings, limiting progress towards achieving the millennium development goals.[5]

One such health problem is the management of pre-eclampsia and eclampsia, important causes of maternal and infant morbidity and mortality. Over 63 000 women die annually after eclamptic convulsions, with 99% of these deaths occurring in low and middle income countries.[6 7 w3]

Evidence is strong for the effectiveness of magnesium sulphate in treating and preventing eclampsia.[8–10 w4 w5] Magnesium sulphate costs $0.35 (£0.19; €0.29) per ampoule (40 ml of 10% magnesium sulphate; Central Medical Stores, Mozambique, April 2005) and has appeared on the World Health Organization's essential medicines list since 1996.[11] It is of great concern that this effective and low cost drug is

Details of drug regulation, web references w1-w9, and Table 2 are on bmj.com

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TELIN VOEREN/PANOS

A pregnant woman has a check up at a clinic in a camp for internally displaced people

still unavailable in many countries.[12 15 w6 w7] We describe problems with the registration, approval, acquisition, and distribution of magnesium sulphate, and hence its availability to clinicians, in Mozambique and Zimbabwe, two countries with high maternal mortality ratios (table).[14–16] We draw on a range of sources, including a bibliographical review of policies concerning magnesium sulphate over the past 25 years and qualitative data collected as part of a case study of policy making and procurement for magnesium sulphate in the two countries (box 1),[17] to argue that drug availability has been affected by system and market failures.

Why is magnesium sulphate not widely available in Mozambique and Zimbabwe?

Mozambique

Magnesium sulphate has been used in Mozambique's Maputo Central Hospital since 1981, well before rigorous evidence of its effectiveness became available. An obstetric guideline published in 1985 described magnesium sulphate as the first line drug for treating eclampsia. Until recently, however, it was unavailable outside the hospital, and other drugs, including diazepam, continue to be used as first line treatment.

The key reasons for this lie in the complex mechanisms of approval, acquisition, and distribution of drugs in Mozambique (see bmj.com). The national formulary of medicines lists the essential drugs that can be acquired by, and distributed through, Mozambique's national health system. The 1980 edition did not include magnesium sulphate and this was not updated until 1999. In this period the Central Medical Stores compiled a list of purchases that included both the medicines listed in the formulary and other drugs that clinicians regarded as necessary. Magnesium sulphate had not been requested by clinicians, however, and was therefore not included. This meant that it had to be ordered locally, but this was only done by the Maputo Central Hospital, and only when funds were available. During this period, economic constraints resulting from the war affected the availability of many drugs, particularly those not on the list of the Central Medical Stores. In addition, pharmaceutical companies were poorly represented in Mozambique at this time and participated only in international competitive tenders.

When the formulary was updated in 1999 it was decided that medicines for specialist and hospital use would be included in a special appendix to better control their use. Although magnesium sulphate was seen as important for the management of eclampsia, there was consensus that it should appear only in this list. For reasons that remain unclear, this appendix was not included in the Central Medical Store's list of purchases when the new formulary came into force. Medicines in this appendix could still be acquired, but required special import procedures, including a request by clinicians, review by the Therapeutic Commission, and authorisation from the Ministry of Health. This was a major barrier to procurement.

Maternal mortality ratios in Mozambique and Zimbabwe

Country	Maternal mortality ratio*	Proportion of mortality attributable to eclampsia (%)
Mozambique	1000	3.2 to 11.3[15 w6]†
Zimbabwe	1100	6.9[16]

*Number of maternal deaths per 100 000 live births.[14]
†Robust national estimates are not available. Range given is based on estimates provided in listed studies.

Box 1: Methods used for case study of policy making and procurement for magnesium sulphate in Mozambique and Zimbabwe

Data collection approach

- In-depth, semistructured qualitative interviews and informal discussions covering:
  - The structure and process of policy making for the management of eclampsia and pre-eclampsia
  - Factors affecting the implementation of policies on the issues of interest
  - Individual's knowledge of evidence related to the use of magnesium sulphate in the treatment of eclampsia and pre-eclampsia

Summary of methods used for case study of magnesium sulphate policy making and procurement in Mozambique and Zimbabwe

Characteristics of respondents

Position	No in Mozambique	No in Zimbabwe
Clinicians or researchers	5	7
Senior Ministry of Health officials	4	2
Therapeutic Commission	2	2
Medicine Control Authority	2	2
Pharmacist	1	3
Pharmaceutical company representatives	—	3

Sampling

- Purposive and snowballing approach, based on respondents' involvement in policy making or procurement for magnesium sulphate

Data analysis

- All interviews audio recorded and transcribed
- Categories emerging from the data identified and a coding frame developed
- Coding frame applied to all transcripts
- Country level themes compared and similarities and differences identified

Discussions in 2001 between clinicians, Ministry of Health departments, and the Therapeutic Commission culminated in authorisation for the central purchasing of magnesium sulphate. Since 2003 the drug has been distributed to peripheral units, but again only when requested by the local clinicians. Routine data show that these requests have been sporadic.

In discussing these ongoing problems with the approval, acquisition, and distribution of magnesium sulphate since the publication of the landmark collaborative eclampsia trial in 1995, obstetrician respondents claimed that although they had contributed to the development of guidelines for obstetric care, including the management of eclampsia, and had trained health professionals in using magnesium sulphate, they did not have the authority to ensure a countrywide implementation of the guidelines.

Respondents from Central Medical Stores, however, noted that these problems were the result of obstetricians not requesting the drug. Poor communication between the two groups seemed, then, to be an important obstacle to improving drug availability. Even after formal approval of the drug, difficulties with distribution and management gave the impression to clinicians that the drug was still unavailable. As a result, they continued to use alternative treatments and did not request magnesium sulphate from the Central Medical Stores or the pharmacy in their own health unit.

Zimbabwe

Magnesium sulphate has long been used for the treatment of eclampsia in Zimbabwe, including at Harare Central Hospital since at least 1984-5 (see table on bmj.com). It is still not registered for this use, however, and was listed in 2000 in the essential drugs list as a second line therapy for eclampsia. Respondents cited four key reasons for this. Firstly, the effects of insufficient capacity and resources within the Ministry of Health and Child Welfare: as foreign currency resources are limited, the ministry decided that local (that is, hospital based) arrangements should be made to acquire what they described as "orphan" drugs—those required mainly by hospital based specialists. Priority for central purchasing is given to first line drugs used at all levels of the health service. It was also suggested that the Ministry of Health and Child Welfare does not have sufficient qualified clinicians to monitor drug use or even to prescribe the drug in peripheral hospitals.

Secondly, the ministry and professional obstetric organisations failed to ensure the registration of magnesium sulphate with the Medicine Control Authority of Zimbabwe: the drug was not seen as a priority because it was perceived to be slow moving and because pharmacists at the Ministry of Health and Child Welfare thought that other drugs, such as diazepam, could be substituted.

Thirdly, pharmaceutical companies lacked financial incentives to push for registration and importation: several respondents noted that the low cost of magnesium sulphate, coupled with the low potential volume of use, resulted in low returns. It is unclear to what extent drug registration fees, currently Z$5m (£277; $500; €409) for Zimbabwean applicants per drug or US$1000 for foreign applicants per drug, are a barrier. Although relatively low by international standards,[18] these fees, together with the costs of preparing a submission and bureaucratic barriers, may dissuade commercial companies from applying for registration in this small market.

Finally, clinicians' perceptions of the dangers of magnesium sulphate may have contributed to the drug's non-use. Respondents acknowledged that the international trials in which Zimbabwe collaborated showed clearly that the drug saves lives. They also noted, however, that the belief of many Zimbabwean clinicians in the drug's effectiveness is tempered by their perceptions of its dangers to women. This was seen to contribute to its second line listing in the essential drugs list.

Respondents highlighted several other factors affecting the availability of magnesium sulphate. These included the lack of a clinical champion, poor communication between clinicians and pharmacy staff, the ambiguity of clinical guidelines from the Ministry of Health and Child Welfare on the use of magnesium sulphate, inadequate dissemination of guidelines, clinicians' long use of other drugs to manage eclampsia, and constraints on human resources. Consequently, diazepam continues to be used by many clinicians in Zimbabwe as first line therapy for the management of eclampsia.

Although magnesium sulphate remains unregistered, clinicians have since convinced the Medicine Control Authority of Zimbabwe, the Ministry of Health and Child Welfare, and the National Drug and Therapeutic Policy Advisory Committee of its usefulness. It can, therefore, be used without registration but still has to be requested by clinicians from their local pharmacy—a process that depends on the availability of local resources.

System and market failures in ensuring the availability of magnesium sulphate

The issues affecting the availability of magnesium sulphate can be divided broadly into the two categories of system and market failures. We identified several key system failures. Firstly, issues related to drug registration were important in both countries. In Zimbabwe,

Box 2: Criteria for and barriers to the operation of a free market for magnesium sulphate in Mozambique and Zimbabwe

Many independent producers and consumers
Only one major consumer of the drug—the central government purchaser—is responsible for national acquisition

Full information on both sides about prices and quality
Asymmetries in information exist as the central purchaser does not assess need for the drug among clinicians and is therefore unaware of demand.

The central purchaser also does not receive information from the producers on drug effectiveness

No external effects (that is, costs or benefits accruing to individuals or groups other than those undertaking the activity)
If a pharmaceutical company marketed a low cost generic dug such as magnesium sulphate, this could increase the market share of other companies producing the drug—that is, positive external effects. In contrast, branded products have higher profit margins as other companies are legally prevented from selling the same drug. Marketing thus increases the sales of the branded product only.

Incentives are few under a central tendering system for companies to market drugs to clinicians

Box 3: Recommendations to improve the availability of magnesium sulphate

- Governments need to ensure that:
  Bureaucratic processes do not obstruct the delivery of low cost, effective drugs
  Mechanisms are put in place for improved communication between clinicians and agencies responsible for drug procurement and supply at country level
- WHO, international professional organisations such as FIGO (International Federation of Gynaecology and Obstetrics), and international donor agencies, should take a more active role in ensuring that all essential medicines are registered and available in developing countries
- Pharmaceutical companies need to be engaged in initiatives to ensure the supply of low cost, effective drugs for common conditions in Africa; financial and other incentives for marketing these drugs need to be considered by international agencies
- When the conditions for a functional market for pharmaceuticals are not met, governments must be prepared to intervene to support public health, and international organisations should support them in this

long delays in registration were described. In Mozambique, the absence of a registration mechanism before 2001 resulted in the development of a complex drug procurement process, with many opportunities for failure. Secondly, long delays occurred in both countries in including magnesium sulphate in their national formularies. Because drug purchasing is based on these formularies, any failure to include effective drugs such as magnesium sulphate is critical. Thirdly, the numerous opportunities for communication failure within the bureaucratic processes of drug registration, inclusion in the formulary, acquisition, and distribution further contributed to the poor availability of magnesium sulphate. The earlier and current economic difficulties in Mozambique and Zimbabwe, respectively, also affected the procurement of drugs.

As magnesium sulphate is a cheap generic drug, its cost should not be a barrier to its availability in a free market. For a free market to operate, several criteria need to be fulfilled (box 2).[19] It is not unusual for some or all of these criteria not to be met, but the more marked the departure from these criteria, the less likely that a market can function. Several of these criteria were not met for magnesium sulphate in Mozambique or Zimbabwe (box 3), suggesting that market failure contributed to the poor availability of the drug. Similar failures have been described for other pharmaceuticals elsewhere,[5 20 w8] including for other cheap, effective drugs such as thiazides[w9] and ibuprofen.[20]

The low cost of magnesium sulphate had several paradoxical effects. It was suggested that its price retarded its registration in Zimbabwe, as the potentially small profits provided little economic incentive for companies to incur registration costs. Respondents in Mozambique noted similarly that because the drug was cheap and the potential profits from it low, pharmaceutical companies did not actively market it or promote it to the central purchaser.

These problems seem to have been compounded by the lack of economies of scope for the drug. The market for magnesium sulphate is relatively small and the drug is not widely used for other conditions. Economies of scale are also unlikely, given that eclampsia is relatively uncommon and that the drug is already low cost. Economies of scope are important to both the health system and the manufacturer—they give additional incentives to the purchaser to consider the drug and they increase the size of the market (and hence opportunities for profit) for the manufacturer. Alternative drugs for the treatment of eclampsia, while substantially less effective, are also cheap and used widely for other conditions. They are therefore generally available at health unit level, and pharmaceutical companies do not incur costs in promoting them.

Conclusions

The complexity of drug approval, acquisition, and distribution mechanisms in Mozambique and Zimbabwe results in many opportunities for system failures. Cost is also an important factor in the availability of magnesium sulphate, but not because the drug is expensive. Rather, its low cost means that market forces cannot be relied on to ensure its availability in these settings. Box 3 outlines several recommendations to address these system and market failures.

As initiatives are developed to ensure wider access to expensive drugs critical to improving public health in Africa, low cost and effective drugs such as magnesium sulphate for treating eclampsia, should not be forgotten.

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Contributors and sources: This article arose from discussions within our research team while conducting a study of the use of research evidence in policy making in Mozambique, South Africa and Zimbabwe. GW, JC, and SL designed the study. SM, ES, and AM collected the data. ES, SM, AM, JC, and GW led the

Summary points

Evidence from randomised controlled trials shows that magnesium sulphate, a low cost drug, is effective for the treatment of eclampsia and pre-eclampsia

The drug, like many other effective treatments, is still not available widely in many low and middle income countries, but the reasons for this remain unclear

Failures in the registration, procurement, and distribution mechanisms for magnesium sulphate contribute to its poor availability in Mozambique and Zimbabwe

In addition, the low cost of magnesium sulphate means that market forces cannot be relied on to ensure its availability

Governments and international agencies must be prepared to intervene to ensure the availability of low cost, effective drugs in developing countries

analysis, to which the other authors contributed. ES, SL, and ADO led the writing of the paper, to which the other authors contributed. ES and SL are guarantors.

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2. Second article

Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance

Stephen A Ward, Esperança J P Sevene, Ian M Hastings, François Nosten, Rose McGready

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SUMMARY

Use of medicines during pregnancy is always a concern as the risk for the mother and for the foetus should be taking into account. Before a recommendation for antimalarial drug use in pregnancy is made, it is essential that we understand the potential risks involved and have mechanisms in place to monitor this risk during treatment. This requires data on drug disposition during pregnancy and potential toxicological liabilities to the developing foetus and to the mother.

In this article a review of the reproductive toxicology of the main antimalarial drug classes in use or under development was presented. Data for this review were identified by search of Medline, Current Contents, and references from relevant articles. The search was systematic performed using predefined search terms.

Clinical data indicated that chloroquine, quinine, and sulphadoxine-pyrimethamine are safe when used for malaria treatment during pregnancy. The concern on use this drugs is the widespread of *P falciparum* resistance in most areas of the world although, quinine remains the most effective and can be used in all trimesters of pregnancy. Amodiaquine is weakly mutagenic and induces bone-marrow toxic effects in mice, but recent studies indicates that it is safe during second and third trimester. Skeletal and muscular malformations in animals were described for mefloquine and in a retrospective clinical study, stillbirth was reported. Pre-clinical studies indicate embryo and foetal toxicity with halofantrine. There is low safety information and limited experience of use in human pregnancy of atovaquone-proguanil and piperaquine. For artemisinins, the most promise drug, several pre-clinical studies demonstrated induction of embryo loss, apparent as abortions and resorptions, cardiovascular malformations and syndrome of skeletal defects. These toxicities were observed in rats and rabbits. Recent studies indicate the same results in *Macaca cynomologus*. There is no information on teratogenic potential of the artemisinins in human beings.

Additionally, in this review, the lack of appropriate pharmacokinetic and dose optimization studies of antimalarial drugs in pregnancy was highlighted and mechanisms that could be used to capture data on risk after drug treatment in pregnancy were suggested.

Antimalarial drugs and pregnancy: safety, pharmacokinetics, and pharmacovigilance

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Before a recommendation for antimalarial drug use in pregnancy is made, it is essential that we understand the potential risks involved and have mechanisms in place to monitor risk during treatment. This requires data on drug disposition during pregnancy and potential toxicological liabilities to the developing fetus and mother. In most cases this information is not available. We review the reproductive toxicology of the main antimalarial drug classes in use or under development. Preclinical data are presented if appropriate, but as human experience overrides such data, in instances in which preclinical studies do not correlate with the human experience the data are reviewed only briefly. Additionally, we highlight the lack of appropriate drug disposition data in pregnancy and suggest mechanisms that can be used to capture data on risk after drug treatment in pregnancy.

Introduction

Despite the clear need for safe and effective antimalarial drugs for use in pregnancy, the pharmaceutical industry is reluctant to develop drugs specifically for this indication, and in almost all cases in which a new drug is being developed, use in pregnancy is contraindicated. This situation indicates the difficulties, risks, and costs associated with proving human safety throughout pregnancy by the use of traditionally designed clinical trials. In the case of malaria in pregnancy, the assessment of risk caused by drug administration is further compounded by the lack of quality baseline data on birth outcomes within the target populations. In practice, clinicians make decisions to use drugs in pregnancy on the basis of their pragmatic assessment of the risk–benefit ratio to the mother and the unborn child. In this way, experience of drug use in a specific clinical setting, gathered sporadically over many decades, accumulates to the point at which the drug is thought to be safe for use. A good example of such a process has been the acceptance of chloroquine as a drug suitable for use in all three trimesters of pregnancy, before its fall from favour because of parasite resistance. This unstructured approach to securing safety data in pregnancy is no longer acceptable because we anticipate the development and use of new antimalarials and antimalarial combinations at a time when treatment options for pregnant women are so limited (table).

Preclinical and clinical drug safety

Preclinical toxicology and, more importantly, preclinical reproductive toxicology (including embryotoxicology and teratogenicity), a pre-requisite to modern-day drug registration, provides some measure of potential human risk. However, these models are not always predictive and can never replace clinical experience.

4-Aminoquinolines

Chloroquine, extensively used in pregnancy, is generally thought to be safe for mother and fetus at the therapeutically recommended dose.[2] Treatment of *Plasmodium falciparum* malaria in pregnancy in Kenya[3] and Tanzania[4] have indicated the drug to be safe, although with the problem of treatment failure because of parasite resistance. A previous review provided details of all studies in which chloroquine has been used in pregnancy, including 755 first trimester exposures.[5] These studies, although generally indicating safety, did include cases of ototoxicity and retinal toxicity from the older literature.[6,7] These risks are not substantiated by recent data. Data secured from the use of hydroxychloroquine for non-malaria indications indicate that this 4-aminoquinoline analogue is safe in pregnancy.[8,9] The other clinically available drug in this class, amodiaquine, is generally thought to be safe for use in pregnancy, although there are almost no data to support this view.[5]

As an example of the potential shortcomings of relying on preclinical data to assess human risk, studies with chloroquine indicate that it has toxicological liabilities in the developing rat fetus,[10] whereas amodiaquine is weakly mutagenic and genotoxic in preclinical tests.[11] However, for both of these compounds there is a lack of any clinical evidence to suggest that this risk is carried forward to women who take the drug during pregnancy. Support for the safety of amodiaquine when used in the second and third trimester has been recently reported in a controlled clinical trial.[1]

The use of chloroquine and amodiaquine in pregnancy may be acceptable, but widespread resistance in *P falciparum* severely limits their use in most areas of the world. Use against other malaria species is possible, although recent reports of chloroquine-resistant *Plasmodium vivax* in southeast Asia needs careful monitoring.

Quinoline methanols and related drugs

The preclinical toxicity of quinine, including reproductive toxicity, has been studied in various species with some evidence of genotoxicity reported in the mouse.[12] Studies in rats, dogs, and primates have generally concluded that quinine does not have selective toxic effects on the fetus and does not induce malformations,[13–15] with the exception of one study reporting congenital malformations in the pups of female rats treated with quinine.[16] Although

	Main kinetic properties	Comments on the use in human pregnancy
4-Aminoquinolines		
Chloroquine	Limited pharmacokinetic data in pregnancy; very long half-life (>25 days).	Considered safe in all trimesters. Recent suggestions of preclinical embryotoxicity, but no signals raised with extensive experience over previous 60 years in human pregnancy (use for systemic diseases). Human data overrides animal models.
Amodiaquine	No data in pregnancy, medium half-life for metabolite (2–7 days).	Weakly mutagenic and induces bone-marrow toxic effects in mice. Recent publication suggestive of safety in second and third trimesters.[4]
Piperaqine	No pharmacokinetic data in pregnancy; very long half-life (>25 days).	No reliable preclinical data to date, but reproductive toxicology is being studied as part of the combination drug development (combined with dihydroartemisinin). No data on safety in pregnancy.
Quinoline methanols		
Mefloquine	Reduced concentrations in pregnancy; long half-life (7–25 days).	Skeletal and muscular malformations in animals. Over 1000 documented exposures in human pregnancy. One study reported an excess in stillbirths, although this was not found in other studies. Recommended by US CDC for prophylaxis in pregnant women.
Lumefantrine	Reduced concentrations in pregnancy; medium half-life (2–7 days).	No sign of toxicity in animal studies. Only available in combination with artemether, twice a day for 3 days with fat.
Antifolates		
Sulfadoxine-pyrimethamine	No pharmacokinetic data; half-life of sulfadoxine long (7–25 days).	Embryotoxic at high doses; use impaired by resistance.
Chlorproguanil-dapsone	No pharmacokinetic data; short half-life (8 h to 2 days) of combination proguanil (an analogue of chlorproguanil); biotransformation is reduced in pregnancy; medium half-life (2–7 days).	Dapsone not teratogenic but causes haemolytic anaemia. Cycloguanil toxic at ovum cleavage stage. Concerns over dapsone toxicity if dosage has to be increased because of the reduced biotransformation of cycloguanil.
Atovaquone proguanil	Reduced blood concentrations	No concerns raising from animal studies; very expensive.
Artemisinins	Reduced blood concentrations; very short half-life (<8 h).	Embryotoxic and teratogenic in rats and rabbits, and embryolethal in non-human primates at doses close to therapeutic range. The susceptible time window for these effects is in the first trimester, corresponding to 2–6 weeks pregnancy in human beings. Implications for use in human beings unclear. Safety data available in over 1000 carefully documented second and third trimester exposures. Limited first trimester data (about 100 late first trimester pregnancies).

Table: General characteristics of antimalarial drugs with potential for use in pregnancy

quinine has been used historically as an abortifacient, use of the drug in pregnancy is generally thought safe. A recent review of the clinical data on quinine use in pregnancy concluded that there was no evidence of poor birth outcomes in several hundred women treated with quinine during pregnancy, including almost 400 treated in the first trimester.[5]

Although somewhat limited, there are clinical data on mefloquine exposure in pregnancy in several thousand women when used for prophylaxis and treatment.[5] These data include over 1000 first-trimester exposures. The data support the view that the drug is safe, does not result in negative birth outcomes, and did not induce malformations. However, in one retrospective study in Thailand, mefloquine was associated with an increased incidence of stillbirth compared with women given quinine, other antimalarials, or women without malaria.[17] These data support the view that mefloquine use in pregnancy should be avoided unless there is clear benefit to the mother or fetus, if there are no alternatives, or until this question is resolved.

There are no data on the use of halofantrine in pregnant women, but preclinical data in rabbits indicate embryotoxic effects and identified skeletal abnormalities at doses of 60–120 mg/kg per day (gestational days 7–19). The related drug lumefantrine is in clinical use in combination with artemether, but there are no reported safety data on the use of the drug in pregnancy. Reassuringly, and by contrast with artemether, preclinical data with lumefantrine alone failed to show any embryotoxicity.

Atovaquone-proguanil

Preclinical data suggest that atovaquone-proguanil does not cause selective toxic effects on the developing fetus, although maternal toxicity-related fetal toxic effects were reported in rabbits.[5] Clinical experience of this drug in human pregnancy is limited.[18,19]

Antifolates

Sulfadoxine-pyrimethamine has been used extensively in pregnancy, including in intermittent preventive therapy strategies, but formal safety studies in pregnancy are limited. Preclinical studies indicate embryotoxic effects including cleft palate in rat pups exposed to suprapharmacological doses of pyrimethamine and other toxic effects associated with antifolate action.[20–22] A compilation of the available safety data on sulfadoxine-pyrimethamine use in pregnancy indicates that, from over 2000 pregnant women treated with the drug in the second and third trimesters, the drug did not increase the risk of malformations or other adverse events in the fetus.[5] The main concerns associated with use of the drug were clinical failures because of parasites resistant to antifolate combinations.

A new antimalarial combination of dapsone and chlorproguanil with the same mechanism of action as sulfadoxine-pyrimethamine retains activity against resistant parasites carrying a triple mutation in the dihydrofolate reductase gene *DHFR*. There are no clinical data on the use of this drug in pregnancy. Dapsone in pregnancy when used in the treatment of leprosy is

thought to be safe, although there are only 19 reported cases of dapsone exposure in the first trimester.[5] One study in Kenya reported the use of dapsone and chlorproguanil in pregnant women and no adverse events were reported, although birth outcomes were not documented.[23]

Artemisinins

The artemisinin-based peroxidic antimalarials are currently our most important class of antimalarial drugs, because they are effective against drug-resistant parasites. The malaria community has argued that the use of artemisinin-based combination chemotherapy is the only practical solution to controlling malaria and limiting the evolution and spread of resistance. As a consequence of these recommendations, WHO's Roll Back Malaria programme predicted a requirement of up to 210 million artemisinin-based treatment doses in 2005–2006 alone. Implicit in this strategy is the assumption that these drugs are safe for use in all clinical settings, including women of childbearing age. Although clinical experience to date indicates artemisinins to be safe, the area of reproductive toxicology demands special consideration. Data from the early Chinese literature indicated that the artemisinins were embryotoxic and potentially teratogenic in several animal species.[24–26] Importantly, these effects were seen in the absence of maternal toxic effects or impaired fertility. An investigation into the developmental toxicity of artesunate in the rat and rabbit according to regulatory International Conference on Harmonization standards has been done and confirmed the Chinese data.[27] The hallmark effect of artesunate exposure seen was a dramatic induction of embryo loss, apparent as abortions and resorptions. Additionally, low incidences of cardiovascular malformations and a syndrome of skeletal defects were induced at or close to embryolethal doses in both species. These effects were seen mainly in the absence of any apparent maternal toxic effects, at doses approximating those used in human exposure and at blood concentrations equivalent or less than those seen in human beings.[27] Further preclinical studies in the rat have shown that the heart and bone defects can be induced by a single oral administration of 10 mg/kg artesunate or other related artemisinins (including artemisinin, artemether, and dihydroartemisinin).[28] These observations prompted a response from WHO Tropical Diseases Research Programme, who have also concluded that the developmental toxicity of the artemisinins is a priority area for further research.[29]

One important aspect of the recent studies is that the critical window for drug exposure is approximately 10–14 days in the rat. At this developmental stage, rats and rabbits differ from human beings in their reliance on the visceral yolk sac rather than the placenta as the main maternofetal exchange system.[30,31] Recently, it has been shown that dihydroartemisinin causes a dose-dependent reduction in the number of fetal red cells circulating in the visceral yolk sac with a concomitant reduction in angiogenesis.[32] These primitive red cells appear at gestational day 10 in rats, which agrees with the critical window studies by Clark and co-workers.[27] The reliance on the inverted yolk sac in rats and rabbits might mean that these toxic effects would not be seen in primates. To address this hypothesis, a primate reproductive toxicity study (in *Macaca cynomolgus*) has been done, although the results are yet to be reported.[33]

The teratogenic potential of the artemisinins in human beings is unknown. In total, less than 1000 cases

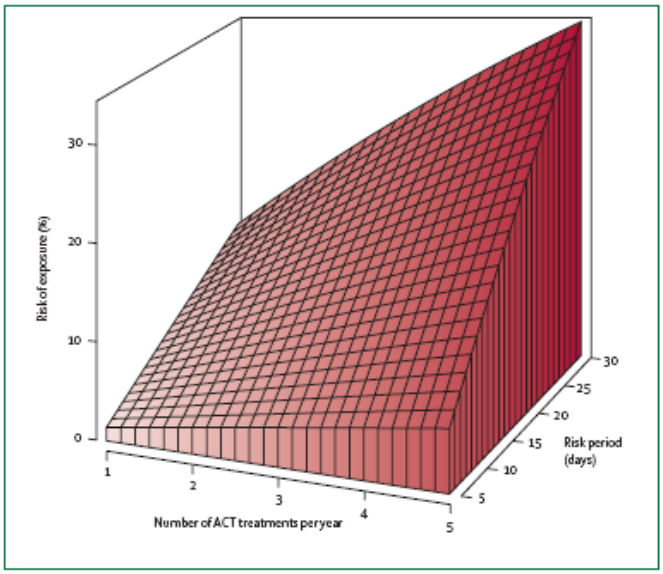

Figure: Calculated risk of artemisinin exposure during the critical pregnancy period
The probability that an embryo will encounter artemisinins during the critical phase of its development can be calculated. If the critical period is t days (eg, from days 20 to 40 of gestation then $t=21$) and the period of persistence of artemisinin is p days (usually 3 days because artemisinin-based combination treatments [ACTs] are normally deployed as a 3-day regimen and have a very rapid elimination), then the embryo is at risk if a mother starts an ACT during the period of $t+p$ days. If the mother takes x courses of ACTs per year, which may be on confirmed malaria or taken presumptively, then the calculation is simple: $x/365$ is the probability that a mother does start ACT on any given day; $1-x/365$ is the chance she does not start ACT on any given day; $(1-x/365)^{t+p}$ is that chance of not taking ACT during the at-risk period; and $1-(1-x/365)^{t+p}$ is the chance that the mother does take ACT during the embryo's at-risk period. For example (assuming $p=3$), if the embryo is at risk for a critical 5-day period of its development and the mother takes one ACT course per year, then the chance of an embryo being treated during the at-risk period is 2%. More pessimistically (and realistically), if the critical period is 20 days and the mother take on average three ACT courses per year, then an embryo has a 17% chance of being treated during the at-risk period (ie, 17% of all embryos will have encountered artemisinins during their critical development period). A more direct, but approximate, calculation can be used. If the at-risk period is 23 days and the mother takes three ACTs per year, then the expected number of ACTs falling in the critical period is $(23/365)\times 3=0{\cdot}19$ per embryo, assuming a maximum of one treatment per embryo gives the proportion treated as 19%. The true chance of treatment is slightly lower (17%, see above), because this approximate calculation includes double and triple treatments per embryo; using the Poisson distribution, the chance of being treated is $1-e^{-0{\cdot}19}=17\%$, regaining the result above. Note that the percentage of ACTs that actually encounter an at-risk embryo will be much smaller. For example, if 20% of treatments are given to women of reproductive age, who have a pregnancy on average every 3 years, and the window of risk is 24 days, then the probability of any single ACT treatment hitting an at-risk embryo is $0{\cdot}2\times 24/(3\times 365)=0{\cdot}004$ or 0·4%. A disparity between risks occurs because the risk per treatment course is low, but there are so many treatments being deployed that the risk per embryo may be substantial.

of monitored artemisinin exposure during pregnancy have been reported (250 exposures to artemether-lumefantrine); reassuringly, these data show no differences in birth outcomes compared with community controls, and no evidence of teratogenic or other embryotoxic events.[5] However, the number of pregnant women exposed to artemisinins during the first trimester of pregnancy, the sensitive period by extrapolation from our critical window studies (figure), is less than 100, which is far too small a dataset on which to base a claim for safety. Extrapolation from rat data would indicate a sensitive period in human beings of weeks 2–6 of pregnancy. Malaria during pregnancy is itself associated with substantial mortality and morbidity to the mother and the unborn child,[34] and so we need to balance the risk–benef it ratio of artemisinin use. However, it is essential that all efforts are made to measure the true risk, because most women receive their antimalarials in an unsupervised way, most will not be aware of their pregnancy (if the extrapolated critical window from the rodent is correct), and most antimalarial treatments in adults are not given to true malaria cases. However, the detection of fetal toxic effects so early in pregnancy will be very difficult to achieve.

Pharmacokinetics

The need for accurate pharmacokinetic data on antimalarials in pregnancy is one of the highest priority areas for research on malaria and pregnancy. Host defences against malaria are impaired in pregnancy, and pregnancy itself creates huge physiological changes—increased volume of distribution, reduced gut motility, increased renal blood flow, hormonal changes, and increased protein binding—all of which can alter drug disposition and metabolism. Unfortunately, when pharmacokinetic studies are done, they usually only include adult men. The number of pregnant women treated with antimalarials who have been included in drug pharmacokinetics studies worldwide is less than 100 (table).[5]

Incorrect dosing could result in maternal and fetal toxic effects, therapeutic drug failures resulting in poor pregnancy outcomes or maternal death, and could increase the risk of drug resistance with large-scale deployment of intermittent preventive treatment. There are few pharmacokinetic and toxicity studies of antimalarials in pregnancy, which makes this review diminutive. The problem for pharmacokinetic studies is that, to understand the pregnancy effects on antimalarials, comparable controls are needed. Future studies need to make a serious effort to address this by finding concurrent controls matched by sex, malaria, and age, or alternatively, by having the same woman return for sampling in the 2–3-month post-partum period. The methods of drug analysis (eg, HPLC, drug bioassay) and drug dosages also need to be consistent.

Artemisinins

Pregnant women who are infected with *P falciparum* are at particular risk and need to be treated with effective antimalarials. The artemisinin derivatives are now recommended for the treatment of *P falciparum* malaria in the second and third trimesters of pregnancy. In severe malaria at any time in gestation, intravenous artesunate is the drug of choice.[35] The recommendations for dosing of artesunate used in monotherapy and artemisinin-based combination therapies (ACTs) have mainly been derived empirically.[36] Artesunate is rapidly hydrolysed in vivo to dihydroartemisinin, which has equivalent antimalarial activity. Thus, in terms of biological (ie, antimalarial) effect kinetics, plasma concentrations of both compounds are assessed.

There is one preliminary report of artesunate and dihydroartemisinin pharmacokinetics in 24 pregnant women with acute uncomplicated *P falciparum* malaria from the Thai-Burmese border.[37] As with other pharmacokinetic studies, artesunate was very rapidly eliminated. The maximum dihydroartemisinin drug concentration (C_{max}) and area under the concentration–time curve for time 0–24 h (AUC_{0-24}) values were 4·2 and 1·8 times lower in Karen pregnant women (dose 4 mg/kg) than in non-pregnant Thai adults given less than half that dose (1·79 mg/kg).[38] The dihydroartemisinin apparent volume of distribution and oral clearance in non-pregnant Asian patients were 2·3 and 2·7 times lower than Karen pregnant women. Pregnant women had C_{max} and AUC_{0-24} values that were nine and four times lower than in non-pregnant adults, respectively, assuming dose linearity and correcting for dose. Although the lower plasma concentrations of dihydroartemisinin could be explained by reduced absorption, it is more likely that the physiological changes of pregnancy, resulting in a larger volume of distribution and more rapid clearance, are responsible.

The fixed combination of artemether and lumefantrine is the result of research undertaken by Chinese scientists. Artemether-lumefantrine is the only coformulated ACT currently manufactured to European Union Good Manufacturing Process standards and widely registered. The combination has proved safe and effective against multidrug-resistant infections on the Thai-Burmese border.[39,40] In 13 pregnant women in the second or third trimester with acute uncomplicated *P falciparum* malaria from the same area, artemether-lumefantrine was used for treatment.[41] Again, artemether was rapidly hydrolysed to dihydroartemisinin, which in turn was rapidly eliminated. Pharmacokinetic variables for artemether C_{max} and AUC_{0-8} were approximately 50% lower, and for dihydroartemisinin C_{max} and AUC_{0-8} were approximately 20% and 40% lower, respectively, than in non-pregnant women.[41]

The kinetics of dihydroartemisinin and artemether are modified by pregnancy. The plasma concentrations of the active antimalarial metabolite dihydroartemisinin are lower than reported previously in non-pregnant adults.[38]

These findings are also consistent with the lower cure rates observed with artesunate in pregnancy compared with non-pregnant patients. Dose-optimisation studies in pregnant women are needed.

4-aminoquinolines

Even chloroquine, which has been consumed worldwide by pregnant women in vast quantities, is poorly described by current pharmacokinetic data. Chloroquine readily crosses the placenta in human beings.[42] Two African studies, in which malaria status was not known, suggested that chloroquine clearance is increased in the third trimester, and that higher doses should be studied.[43,44] Pharmacokinetic variables after treatment with chloroquine (10 mg/kg on days 1 and 2, 5 mg/kg on day 3) in four Nigerian women with slide-confirmed uncomplicated *P falciparum* malaria did not show lower concentrations in plasma.[45] The pharmacokinetic data on the related 4-aminoquinoline, amodiaquine, in pregnancy are non-existent.

Quinoline methanols and related drugs

It is ironic that mefloquine, the best characterised drug in terms of pharmacokinetics in pregnancy, is one of the least used. In a dose-finding pharmacokinetic study, mefloquine clearance was increased in pregnancy with lower resultant blood mefloquine concentration for a given dose.[46] A subsequent study also found that the peak concentrations of mefloquine were lower, and the apparent volume of distribution larger, so that treatment doses lower than 25 mg/kg may lead to suboptimum circulating drug concentrations.[47]

The pharmacokinetics of quinine in uncomplicated malaria in pregnancy have not been examined. A study in third-trimester pregnant women with severe malaria, who were treated with a quinine loading dose of 20 mg/kg, showed a smaller volume of distribution and more rapid elimination of the drug than non-pregnant adults.[48] Characterisation of the pharmacokinetics of quinine is very important because there are so few drugs known to be safe in the first trimester of pregnancy, and because the physiological changes of pregnancy are proactive (ie, not proportional to the size of the fetus), so that by the end of the first trimester many body systems are actually functioning at levels close to term.

In the study on artemether-lumefantrine,[41] it was possible to compare pharmacokinetic data of lumefantrine collected in pregnant and non-pregnant Karen adults. Lumefantrine AUC values were substantially lower in pregnant than in non-pregnant women with uncomplicated *P falciparum* malaria, and this was because of more rapid elimination in pregnant women. Pregnant women who smoked had substantially reduced AUC values. Low concentrations of lumefantrine in combination with artemether are likely to lead to reduced cure rates because the residual lumefantrine in the third and subsequent post-treatment cycles must be sufficient to remove all residual parasites. Low lumefantrine concentrations in combination with artemether present a substantial problem for a fixed combination drug. There is no point increasing the dose to be given over 3 days because lumefantrine absorption is rate limited and can increase toxic effects to the mother and fetus; extending the dosing regimen to 5 days treatment can decrease compliance. Urgent work is necessary, since many countries now use artemether-lumefantrine as first-line therapy.

Antifolates

Sulfadoxine-pyrimethamine seems to have been widely deployed in Africa for intermittent preventive treatment on the basis of the assumption that the dose in non-pregnant adults is correct for pregnant women. There are also no pharmacokinetic data on the efficacy of sulfadoxine-pyrimethamine when used for case management in pregnancy. Chlorproguanil is thought to be the safest of all antimalarial drugs. Proguanil is metabolised to the triazine cycloguanil, mediated by the cytochrome P450 enzyme CYP2C19. As a result, some pharmacokinetic data has been derived from the use of proguanil in pregnancy and the plasma concentrations are lower than would be predicted from literature data in non-pregnant adults. Pregnancy reduces the conversion of proguanil to the active metabolite.[49] Chlorproguanil has been combined with dapsone, which has been found to be more active than sulfadoxine-pyrimethamine against resistant *P falciparum* in East Africa.[50] In a recent review, very limited safety data and no pharmacokinetic data were found on the use of dapsone for any indication in pregnant women.[51] The changes in the disposition of proguanil in pregnancy (lower plasma concentrations) are likely to be very similar for chlorproguanil. This has important implications for the use of dapsone-chlorproguanil in pregnancy. Increasing the dose of chlorproguanil in the fixed combination could result in toxicity problems from dapsone. The dose is likely to require optimisation, which is problematic for all fixed combinations.

Atovaquone-proguanil

The pharmacokinetics of atovaquone and proguanil were examined as part of a treatment study on atovaquone-proguanil-artesunate combination therapy for multidrug-resistant *P falciparum* malaria in pregnant women in the second and third trimesters.[52] A previous study found no interaction between atovaquone-proguanil and artesunate.[53] Plasma concentrations for atovaquone were less than half, and for proguanil approximately two-thirds of those in non-pregnant patients with malaria who were given the same dose. Cycloguanil concentrations were substantially lower than reported in non-pregnant patients with malaria, but this impaired conversion in pregnancy is unlikely to be of therapeutic relevance because the parent

compound, not cycloguanil, synergises with atovaquone. The triple combination was effective in this preliminary study; nevertheless, the dose for optimum cure rates in pregnancy probably needs to be increased. Similar findings were reported in a subsequent study in eight Thai and 18 Zambian women in their third trimester of pregnancy treated with malarone alone.[53] This study suggested that the C_{max} and AUC were approximately halved by pregnancy status.[53]

Dihydroartimisinin-piperaquine

There are currently no data on the use of dihydroartimisinin-piperaquine in pregnancy. The data in non-pregnant individuals are limited.

Antibiotics

Antibacterial drugs can have substantial antimalarial activity, although they are not sufficient to use on their own to treat malaria. There are no pharmacokinetic studies in women with malaria. However, antibiotics can provide an important adjunct when treatment options are limited, such as in pregnancy (eg, clindamycin has been shown to enhance the efficacy of quinine in multidrug-resistant *P falciparum* infections in pregnancy).[54] Clindamycin given to full-term pregnant women before caesarean section showed concentrations in the normal range compared with decreased concentrations for gentamicin.[55] Azithromycin pharmacokinetic studies in full-term pregnant women showed a rapid serum half-life and high-sustained antibiotic concentrations within the myometrium, adipose, and placental tissue.[56] Azithromycin, an antimalarial with activity in vitro, has been disappointing in vivo when used in malaria as a monotherapy (Nosten F, unpublished data).

Drug interactions

Antimalarial drug interactions are important to define. For example, inducers of the cytochrome P450 enzyme CYP3A4, such as rifampicin and anticonvulsant drugs, accelerate the clearance of quinine and mefloquine with resultant lower drug concentrations and hence a greater chance of treatment failure. Studies of the synergy or antagonism between antiretrovirals and antimalarials are also essential to ensure effective and safe malaria case management, intermittent preventive treatment, and HIV treatment for pregnant women.

Pharmacovigilance

WHO defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse reactions or any other possible drug-related problems.[57] The major aims of pharmacovigilance studies are the early detection of unknown safety problems, the detection of increases in frequency of known adverse drug reactions, the identification and quantification of risk factors for adverse reactions, and the prevention of unnecessary risk to the patient by promoting the rational and safe use of medicines. Preclinical drug studies and formal phase I, II, and III clinical trials are generally accepted to have serious limitations in terms of establishing safety.

Antimalarial drugs

Spontaneous reporting is a relatively new phenomenon in the history of medicine. The first national reporting schemes for adverse drug reactions were set up in the 1960s in ten countries after the thalidomide disaster.[58] However, only a few African countries have implemented a reporting mechanism.[59]

Implementation of spontaneous reporting in low-income countries is particularly problematic because of other pressing health-care priorities and specific challenges such as geographical remoteness of many of the health facilities, poor telecommunication systems, and inadequate education of health professionals and patients. Additionally, problems with availability of drugs, caused by lack of funds and failures in systems and markets,[60] could also interfere with the reporting process. Since most of these countries have well established (although often overstretched) public-health programmes, which operate according to standard guidelines and are supported at both national and international level, there is an opportunity for these structures to interact with pharmacovigilance initiatives. WHO is promoting the introduction of pharmacovigilance into public-health programmes, and some countries have started to implement their monitoring systems in collaboration with malaria control programmes.[61,62]

Recently, a new policy in the treatment of malaria, with ACTs, was adopted by several countries. The therapeutic profile of these artemisinin-based drugs seems to be good under well-conducted clinical trials, but their efficacy and safety have not been adequately monitored in large-scale use in populations outside southeast Asia.[63,64] Safety monitoring is important in all countries, but especially in African populations in which the presence of comorbid conditions such as HIV/AIDS, malnutrition, and tuberculosis could be important issues. As mentioned previously, there are concerns related to the safety of ACTs during the first trimester of pregnancy.[22,65] Use of artemisinin combined with amodiaquine or sulfadoxine-pyrimethamine has raised different concerns over dermatological, haematological, and hepatic toxicity.[63]

To address the issue, five African countries (Burundi, Democratic Republic of Congo, Mozambique, Zambia, and Zanzibar), supported by WHO Roll Back Malaria, participated in a training course in which they designed action plans to introduce pharmacovigilance systems, together with the implementation of new antimalarial therapy.[61] In each of these countries, mechanisms are being established to collect information about adverse reactions, and some of them have become members of a WHO monitoring programme.[59] In addition, Ghana[66] and South Africa[67] are reinforcing established pharma-

covigilance systems to better monitor the safe use of antimalarial drugs. Nevertheless, none of these activities have focused on safety monitoring of drugs used during pregnancy. However, some have included safety monitoring of antimalarial drugs used during the implementation of intermittent preventive treatment during pregnancy. These studies were designed to monitor adverse events in the mother rather than the unborn child, and have not produced any signals of significant risk.[68]

Antimalarial drug use in pregnancy

During implementation of the pharmacovigilance systems, special attention should be given to specific risk groups, particularly pregnant women. The first trimester of pregnancy carries the highest risk of fetal adverse reactions, and some women are exposed to medicines during this period because they are unaware that they are pregnant or do not declare their pregnancy. Recently, studies have described drug exposure prevalence of 86–97%,[69,70] with an average of 2·9–4·2 drugs per woman. The most commonly prescribed medicines are antimicrobials, analgesics, anti-emetics, tranquilisers, vitamins, mineral salts, and vaccines. In areas of high malaria prevalence, this list also includes antimalarial drugs.

Indiscriminate use of medicines in pregnancy is not recommended because of the risk of adverse reactions in the mother and fetus, and the possibility of irreversible effects. The decision to give drugs to pregnant woman must be made based on a balance between risk and benefits. In particular, the potential benefits must outweigh the potential risk to the fetus. The adverse consequences of malaria in pregnancy are well described: untreated malaria poses a far greater risk than treatment, although the mechanism for monitoring pregnant women exposed to these drugs is limited.

Causality assessment is difficult in pregnant woman because some adverse reactions can only be identified after delivery. Date of the last menstrual period, or some other reliable method of gestational age, is notoriously difficult to obtain in low-income countries, but is crucial in determining first trimester exposures. Different factors should be considered to estimate the strength of the association between the drug and the reaction, including specific and possibly unique pathognomonic defects, plausible temporal exposure, consistency of the observed evidence, dose-response relations, duration of exposure, and confounding factors (eg, drugs, environmental factors, chemicals, and traditional medicines).

Pregnancy registries are recognised as one method for detecting major risks associated with a drug or biological exposure during pregnancy. At the time of pregnancy registration, information is collected on drug exposure, maternal disease status, gestation, and other factors that may affect pregnancy outcome. An active follow-up of these pregnancies including outcome of the pregnancy and the infant are done using various approaches, including maternal interviews, medical record abstraction, or a combination of these methods to avoid recall bias. From this system, accurate data should be recorded to calculate the prevalence of adverse reactions, identify risk factors, better estimate the magnitude of exposure risk, and detect long-term reactions such as delayed development, neurological impairment, or any effects that might be detected in older children of at least 1 year who might have been exposed to antimalarial drugs in the uterus.

These surveillance mechanisms are susceptible to under-reporting, selection bias (some pregnancies will not be registered, and some defects will not be diagnosed at birth), and loss to follow-up, and there may be difficulties linking specific maternal exposures to fetal anomalies. Despite limitations of these methods, they have been used to supplement animal toxicology studies and clinical trials, and to generate signals of risk to help health-care providers assess the risk of antimalarial drug use in pregnant woman. Single methods should not be used alone to identify increases in the prevalence of adverse events, particularly in pregnant women. Combinations of different methods are needed for the early detection of any safety issue.

Panel: **Research priorities**

Preclinical and clinical drug safety

- Unified design strategy for clinical trials to capture safety data in all phases of pregnancy.
- Validated baseline data on birth outcomes in target populations.
- Assessment of safety and tolerability of all drugs and drug combinations proposed for use in pregnancy for case management and intermittent preventive treatment.
- Investigation of the prescribing practices of antimalarials in Africa: are women of childbearing age routinely asked about possible pregnancy?
- Critical artemisinin exposure period in relevant species needs to be defined.
- Metabolic profiling of artemisinins in relevant species need to be determined to assess whether parent drug or metabolites are correlated with toxic effects.
- Embryotoxicity of non-semisynthetic peroxides needs to be addressed.

Pharmacokinetics

- Pharmacokinetics and metabolic fate of all antimalarials used in pregnancy need to be further studied (at different gestational periods, and when used for case management or intermittent preventive treatment during pregnancy).
- Population pharmacokinetic/pharmacodynamic models need to be developed for use in pregnancy.
- Pharmacokinetic interactions of antimalarials with highly active antiretroviral therapy in HIV/AIDS should be studied.

Pharmacovigilance

- Feasibility of spontaneous reporting systems and pregnancy registries in low-income countries.

Conclusions

P falciparum malaria remains a potentially lethal yet treatable disease. However, we remain ignorant of the best treatments. Use of antimalarial drugs in pregnant

Search strategy and selection criteria

Data for this Review were identified by searches of Medline, Current Contents, and references from relevant articles; numerous articles were identified through searches of the extensive files of the authors. Search terms were "malaria and pregnancy", "malaria chemotherapy", "antimalarial drug toxicity", "antimalarial drug safety", "antimalarial pharmacokinetics", "pharmacovigilance". English language papers were reviewed. The search was not restricted by date.

women continues to be a problem in which the risks to the woman and fetus are not completely known. More information on the correct doses to be given to pregnant women is desperately needed. Large-scale trials and post-market surveillance systems to monitor drug safety in pregnancy are required (panel).

Conflicts of interest

All authors contributed equally to the manuscript and have no conflicts of interest.

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3. Third article

DRUG EXPOSURE AND PREGNANCY OUTCOMES IN RURAL MOZAMBIQUE

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SUMMARY

Drug exposure during pregnancy is worrisome. Most of the drugs administered to pregnant women are given to treat acute and chronic diseases. The decision to give drugs to pregnant woman must be made based on a balance between risk and benefits. In malaria endemic areas antimalarial drugs are often used during pregnancy, and thus they should always be considered in any drug exposure assessment in these areas. This study aimed to describe the level of drug exposure during pregnancy in a rural area of Mozambique and its relation to pregnancy outcome.

3105 pregnant women were interviewed in a retrospectively and prospectively cohort study. Information on disease episodes and treatments received during pregnancy was collected, as well as on the pregnancy outcome. Additional information was completed through

revision of antenatal and admission files, drug prescriptions, and any other relevant, available documents at the maternity and antenatal clinic. Newborns were examined at birth for clinical signs, birth weight, gestational age and presence of any congenital malformation.

Malaria episodes and sexually transmitted diseases (STD) were the most frequently reported diseases (30.5% and 24.1%, respectively). Forty one percent (1276/3105) of participants reported at least one drug exposure. Average number of drugs taken per pregnant woman was 3.9 (SD ± 2.1, range 1-14). Antibiotics were the most commonly (41.2%) reported followed by antimalarial drugs (23.8%). Thirty five percent of the women reported to have taken drugs of FDA pregnancy risk categories C and D. There were more spontaneous abortion and stillbirth ($p<0.001$) among those who reported to be exposed to drugs compared to none exposed. Statistical significant difference in spontaneous abortion and stillbirth ($p=0.002$) was also observed in pregnant women reported the use of antimalarial drugs. Polydactyly was the most frequent malformation observed (57.4%).

In conclusion, drug exposure during pregnancy, including drugs with recognised potential pregnancy risk, was high in this rural area of southern Africa. Antibiotics and antimalarials were the most frequently prescribed drugs in accordance with the high prevalence of both malaria and STDs in this population. The association of abortions and stillbirths with drug exposure might be a consequence of the disease that led to drug administration, although a direct causality of the drugs

cannot be excluded. These findings emphasise the need of reinforcing pharmacovigilance systems in rural Africa, especially or at least in pregnant women.

DRUG EXPOSURE AND PREGNANCY OUTCOME IN RURAL MOZAMBIQUE

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ABSTRACT

Background: Drug exposure during pregnancy is worrisome. This study aimed to describe the level of drug exposure during pregnancy in a rural area of Mozambique and its relation to pregnancy outcome.

Methods: 3105 pregnant women were interviewed in a cohort study. Information on disease episodes and treatments received during pregnancy was collected, as well as on the pregnancy outcome. Newborns were examined at birth for clinical signs, birth weight, gestational age and presence of any congenital malformation.

Results: Malaria and sexually transmitted diseases (STD) were the most frequently reported disease (30.5% and 24.1%, respectively). Forty one percent (1276/3105) of participants reported at least one drug exposure. The average number of drugs taken per pregnant woman was 3.9 (SD ± 2.1, range 1-14). Antibiotics were the most commonly (41.2%) reported followed by antimalarial drugs (23.8%). Thirty five percent of the women reported to have taken drugs of FDA pregnancy risk categories C and D. There were more spontaneous abortion and stillbirth ($p<0.001$) among those who reported to be exposed to drugs compared to none exposed. A significant increase in spontaneous abortion and stillbirth ($p=0.002$) was also observed in pregnant women reporting the use of antimalarial drugs. Polydactyly was the most frequent malformation observed (57.4%).

Conclusion: Drug exposure during pregnancy, including drugs with recognized potential pregnancy risk, was high in this rural area of southern Africa. The association of abortions and stillbirths with drug exposure might be a consequence of the disease that led to drug administration, although a direct causality of the drugs cannot be excluded. These findings emphasize the need of reinforcing

pharmacovigilance systems in rural Africa, especially or at least in pregnant women.

INTRODUCTION

Drug exposure during pregnancy is increasing with advances in medicine. Studies in the United States have shown prevalence of pregnant women exposed to drugs that varied between 59% and 64% [1,2]. Several studies reported an average of 2.3 to 3.3 different drugs prescribed per woman [3,4,5], being antimicrobials, analgesics, anti-emetics, tranquilisers, vitamins, mineral salts and vaccines the most commonly prescribed. Moreover, in another study in Canada it was reported that 19.4% of pregnant women were exposed to drugs considered with potential risk according to the US Food and Drug Administration (FDA) pregnancy risk classification (categories C, D and X) [6].

In general, most of the drugs administered to pregnant women are given to treat acute and chronic diseases. In some cases, drugs are prescribed inadvertently before the pregnancy is recognized [1]. The decision to give drugs to pregnant woman must be made based on a balance between risks and benefits. Unfortunately, these decisions are often made with very limited information and in the absence of mechanisms for safety monitoring.

Causality assessment between drug exposure and pregnancy outcome is difficult to make, since some adverse reactions can only be identified after delivery, and other factors could also be involved including other drugs and diseases [7].

In developing countries the assessment of drug exposure in pregnancy is complicated by several factors. First, pregnant women are more likely to present concomitantly clinical complaints of several diseases, which are prevalent in resource poor settings, thus requiring

drug prescription. Secondly, recording of drug exposure during pregnancy on routine clinical records is frequently inadequate. Thirdly, there is a lack of quality baseline data on birth outcomes within the target population to be used as a comparator in causality assessment. Finally, in most areas there are no pharmacovigilance systems in place.

In malaria endemic areas antimalarial drugs are often used during pregnancy, and thus they should always be considered in any drug exposure assessment in these areas. In a study in Nigeria, 11.2% of all prescribed drugs in pregnancy were antimalarials, representing the third most prescribed drug in this group [4]. Antimalarial drug combinations that include artemisinin derivatives (ACTs) are now recommended by World Health Organization (WHO) for treatment in most malaria endemic areas [8]. Although this recommendation includes pregnant women, there is still very little information on the safety of these drug combinations in pregnancy [9].

The aim of this study is to describe the level of drug exposure during pregnancy and its relation to pregnancy outcomes, in a rural area of Mozambique with high malaria endemicity.

METHODS

Study area and population

The study was carried out in Southern Mozambique by the Manhiça Health Research Centre (CISM) between August 2004 and September 2006. Details of the District of Manhiça and CISM have been presented elsewhere [10]. The study area has a population of approximately 82,000 inhabitants under continuous demographic surveillance for vital events and migrations. Adjacent to the CISM is the Manhiça District Hospital, a 110 bed health facility that offers preventive and curative services. Malaria transmission is perennial, with some seasonality,

mostly attributable to *P. falciparum*. *Anopheles funestus* is the main vector and the average entomological inoculation rate was 38 infective bites per person per year in 2002 [11]. In 2005, the fertility rate was 4.8 and the maternal mortality ratio was 750 per 100,000 live births [12]. About 80% of pregnant women have an institutional delivery and more than 90% attend the antenatal clinic (ANC) at least once during pregnancy [13].

In 2002, data from this area showed that amodiaquine (AQ) in children had a therapeutic efficacy (adequate clinical response) of 92% while sulfadoxine-pyrimethamine (SP) had 83% and Choroquine (CQ) had 47% [14]. During the study period the national policy recommended SP and AQ as first line treatment, arthemeter-lumefantrine (AL) as second line, and quinine as third line. In late 2005 the malaria treatment policy changed to SP and artesunate as first line treatment [15]. ACTs were not used in this area until the end of the study, due to the time lag that often occurs in the implementation of policy recommendations in rural Africa.

HIV seroprevalence in pregnant women in the area was 23% in 2004 [16]. An operational plan to control the HIV/AIDS pandemic was designed in 2004 but antiretroviral therapy was not yet available in the area until the end of the study [17].

Study design

This is a descriptive retrospective and prospective cohort study. The information was obtained through participant questionnaires. Additional information was completed through revision of antenatal and admission files, drug prescriptions, and any other relevant, available documents at the maternity and antenatal clinic.

Pregnant women were recruited after written informed consent was given, during hospital admission for any illness during pregnancy, or

after delivery at the maternity between August 2004 and September 2006. Some women were interviewed both during hospital admission and after delivery.

At each time a standardised questionnaire was filled in. Apart from demographic data and obstetric history, information on past malaria episodes and malaria treatment during pregnancy was collected. The participants were queried about other disease episodes and treatments that they might have received. Information on the current episode of disease was registered, including the treatment administered and the pregnancy outcome at the time of discharge. If a new hospital admission occurred, information related to the interval between the admissions was also gathered.

At delivery, a new questionnaire was administered. Information was collected on the delivery and pregnancy outcomes, and on past malaria episodes, as well as other disease episodes and treatments that might have occurred during this pregnancy. The newborn was assessed at birth for clinical signs, birth weight, gestational age and presence of any congenital malformation.

Diseases were classified according to the International Diseases Classification (ICD-10) and drugs according to the Mozambican National Drug Formulary [18,19]. Data on the US FDA classification of medicines according to risk to the foetus were based on the Physician's Desk Reference and on the drug safety website [20,21]. According to this classification, the groups of drugs with the highest risk are C, D, and X. Group C drugs, are those in which studies in animals have shown adverse effects on the foetus, and there are no controlled studies in women. However, these drugs may be recommended in pregnancy despite their potential risk. Group D drugs, are those with positive evidence of human foetal risk. These drugs should be given only if the potential benefit justifies the risk to the foetus. Group X

drugs, are those in which studies in animals or human beings have demonstrated foetal abnormalities or there is evidence of foetal risk based on human experience. In this last case, the risk of the use of the drug in pregnancy clearly outweighs any possible benefit [22].

Statistical methods

Double data entry, validation and cleaning were done using Microsoft Visual FoxPro 5.0 and statistical analysis was performed using Stata 9.2 (Stata Corporation, College Station, TX, USA). Differences in prevalence were estimated with the x^2 test and proportions with the Fisher's exact test. Continuous values were evaluated with t-test and non-parametric Wilcoxon test. Data on women with a multiple delivery (twins or triplets) were also included in the analysis. Missing values were coded as such and excluded from analysis.

The study was approved by the Mozambican Ministry of Health and by the National Bioethics Committee.

RESULTS

3105 pregnant women were recruited into the study. Ninety two percent (2856/3105) were recruited at delivery and 8% (249/3105) during hospital admission. Mean age was 25 years (SD ± 7.0) and 14.7% (457/3105) were women in their first pregnancy (table 1).

Disease episodes during pregnancy

Nearly 44% (1359/3105) of the women reported to have had at least one episode of disease during their current pregnancy. A total of 1866 disease episodes were reported by the study women.

Malaria during pregnancy was reported by 17.3% (538/3105) of the participants (table 1). Of these, 18.2% (98/538) said to have had

malaria during the first trimester of the pregnancy. Nearly a third of the women [29.6% (159/538)] had confirmed malaria during the current hospital admission. Malaria episodes represented 30.5% (570/1866) of total diseases episodes during pregnancy. Malaria was also reported concomitantly with other diseases by 8.8% (273/3105) of the women.

Table 1 shows the list of diseases reported. Diseases other than malaria were reported by 35.3% (1094/3105) of the women. Sexually transmitted diseases (STDs) were the second most frequent disease, reported by 24.1% (449/1866) of the women.

Drug exposure during pregnancy by maternal characteristics

Forty one percent (1276/3105) of participants reported at least one drug exposure during their pregnancy. The average number of drugs taken per pregnant woman was 3.9 (SD ± 2.1), with a range of 1-14 drugs (table 1). Most of the women who reported to have taken drugs, did so during the second [51.0% (651/1276)] and third [50.1% (639/1276)] trimesters, whilst 6.8% (87/1276) reported drug exposure during the first trimester.

Antibiotics were the most commonly reported drug, being prescribed in 41.2% (2033/4936) of episodes of drug exposure (table 2).

Antimalarial drugs were the second most frequent drug prescribed, being reported in 23.8% (1176/4936) of drug exposure episodes (table 2). In 62.8% (738/1176) of these episodes, antimalarials were reported to have been taken as monotherapy. The drugs reported were quinine (304), CQ (231), SP (195), halofantrine (7) and AQ (1). Combination therapy was reported to be taken in 25.5% (300/1176) of antimalarial drug exposure. The combinations used were SP + CQ (182), SP + quinine (106), quinine + CQ (11) and quinine + AL (1). In 11.7% (138/1176) of the cases the antimalarial was not specified.

There were 13 drugs reported to have been taken in association with antimalarial drugs. These drugs were prescribed for symptomatic treatment, or for treating other concomitant diseases. Paracetamol, acetylsalicylic acid, ferrous sulphate and folic acid were those drugs most frequently prescribed.

The other most commonly reported drugs were analgesics [18.2% (896/4936)], minerals and vitamins [10.4% (513/4936)] (table 2).

According to the FDA classification of teratogenic risk, women were exposed to drugs from category A [14.5% (717/4936)], B [50.4% (2488/4936)], C [19.1% (943/4936)] and D [16% (788/4936)] (table 2).

Table 3 presents maternal age, gravidity, place of interview, and pregnancy outcome by drug exposure. There were differences in gravidity among those who reported drug exposure. More primigravidae reported drug exposure than those who reported no-exposure (17.3% versus 12.9%, p value=0.001). During hospital admission there were more women reporting drug exposure than those who reported no-exposure (17.9% versus 1.1%, p value<0.001) (table 3).

Table 4 shows the comparison of maternal variables and pregnancy outcome between women exposed to antimalarials and those exposed to other drugs. Although not statistically significant, women who received antimalarial drugs tended to be younger than those who received other drugs (p=0.055). Primigravidae were more likely to receive antimalarial drugs than other drugs (23.4% versus 12.7%, p<0.001), while multigravidae were more likely to receive other drugs than antimalarials (76.6% versus 87.3%, p<0.001). Women admitted to hospital received more antimalarial drugs than any other drug (p<0.001) (table 4).

Drug exposure and pregnancy outcome

There was one maternal death out of the 3105 participants recruited. She was a 24 year-old woman, with 24 weeks of gestational age, admitted with diagnosis of premature placental abruption.

There were more spontaneous abortions and stillbirths among women who reported drug exposure compared to those who reported no-exposure ($p<0.001$) (table 3). Women experiencing an abortion or stillbirth also reported more exposure to antimalarial drugs ($p=0.002$) (table 4). Nine women were admitted with malaria and subsequently had a spontaneous abortion. They all received quinine, alone (3) or in combination with SP (6), to treat their disease episode.

There were 2 early neonatal deaths. The two cases presented severe and multiple congenital malformations. The mothers of these children did not report any diseases or drug exposure during pregnancy.

Mean birth weight was 3034.8 gr. (SD ± 468.0). About 14% of the women had a pre-term delivery and/or a newborn with low birth weight. There were no statistically significant differences with regard to drug exposure between those women who had a pre-term and/or low birth weight delivery compared with those who had a term and normal weight delivery ($p=0.500$) (table 3). No differences were observed either, between women reporting exposure to antimalarials and those exposed to other drugs, in relation to the prevalence of pre-term and/or low birth weight delivery ($p=0.781$) (table 4).

Forty four newborns out of 2856 (1.5%) had at least one congenital malformation. Polydactyly was the most frequent malformation observed (57.4%). Other limb and feet defects were observed including, calcaneovalgus and equinovarus deformity (3) and arthrogryposis (2). Five newborns presented multiple malformations. Two of them died soon after delivery. Table 5 shows the different malformations diagnosed by clinical examination.

There was no difference in relation to drug exposure between women who had newborns with congenital malformations and those who did not (p=0.637), nor between those exposed to antimalarials and those exposed to other drugs with regard to the presence of malformations (p=0.624).

DISCUSSION

This study has shown that drug exposure in pregnancy is high in this rural area of Southern Africa. More than forty percent of the study women reported exposure to at least one drug during their pregnancy. The average number of drugs reported to have been taken per woman was also high with a maximum of 14 drugs reported by one woman. Nearly a third (30.5%) of the women said to have received 3 or more drugs during their pregnancy. This average was slightly greater than that reported in other studies, with more women taking a high number of drugs (>10) in this study [3,4,5]. This could be explained by the need to treat concomitant diseases, as well as the presence of multiple disease episodes during pregnancy. In this study, more than a third (35%) of the pregnant women exposed to drugs, was so to drugs classified by the FDA of teratogenic risk C and D.

Of those women exposed to drugs, nearly 7% reported have taken drugs during the first trimester of pregnancy. This proportion, although not high, reinforces the need for pharmacovigilance systems being tailored to capture early pregnancy drug exposure. This is especially relevant in developing regions, where most pregnant women attend antenatal clinics from the second trimester, and thus recall bias might be important [13]. In malaria endemic countries, functioning pharmacovigilance systems have become a real need given the current WHO recommendation of artemisinin derivatives for malaria treatment [8]. It is likely that in these countries, an increasing number of pregnant women will be exposed to these drugs even during the first trimester

[13]. Preclinical studies have shown that artemisinin and its derivatives exhibit embryotoxicity or teratogenic activity in different animal species [23,24]. The latest WHO assessment on the safety of artemisinin derivatives for pregnancy, stresses that more research in this area is needed to clarify the implications of the animal findings for humans [25].

Antibiotics were the most frequently reported drugs. This may be explained by their prescription for the treatment of infectious diseases, particularly STDs. Except in the case of syphilis, a syndromic approach was the recommended clinical management of STDs during the study. STDs were treated with at least three or four drugs (penicillin G benzathine, kanamycin, erythromycin and metronidazole), following empirical treatment. Improvement in the diagnosis of STDs, and targeted treatment with one or two efficacious therapies could reduce the use of these drugs at least in pregnancy.

As it may be expected in a malaria endemic area, antimalarials were the second most reported drug prescribed. The reported use of antimalarials did not necessarily follow the national policy for malaria treatment in Mozambique. Thus, all antimalarial drugs available in the area were reported to have been taken. These drugs were also taken as monotherapy and not just in combinations as recommended [15]. For example, CQ was no longer recommended to treat uncomplicated malaria, but was still taken during pregnancy, alone or in combination with other antimalarial drugs. Antimalarials were also prescribed presumptively without parasitological confirmation. It is well established that the inappropriate use of antimalarial drugs is associated with treatment failure, and increases the risk of the emergence of drug resistant strains of *P. falciparum* [26,27].

Apart from antibiotics and antimalarials, analgesics, minerals and vitamins were the other most reported drugs. This observation is in

agreement with other studies that described these drugs as the most frequently taken during pregnancy [3,4,5]. Only 10.4% of the pregnant women in this study reported have taken minerals and vitamins, although ferrous sulphate and folic acid are routinely prescribed during antenatal visits. More information is needed with regard to the perception of women about anaemia prophylaxis during pregnancy in developing countries, in order to improve the effectiveness of this intervention.

Traditional medicines were reported to have been taken by just one woman, although this practice is common in the area (K Munguambe personal communication). Fear to report the use of these medicines to the nurses at the ANC may explain this observation, since nurses are trained to advise pregnant women not to take them during pregnancy.

This study showed that spontaneous abortion and stillbirth were associated to drug exposure during pregnancy. In particular, spontaneous abortion was even more related to antimalarial drug exposure. It has been suggested that placental malaria infection may be associated with a higher risk of stillbirth, and thus the infection and not the drug to treat it, might be the actual cause of this poor outcome [28]. However, this can not be concluded and therefore, more information on the association of antimalarial exposure and spontaneous abortion and stillbirth is critically needed.

Associations between reported drug exposure and maternal deaths, early neonatal death, pre-term delivery, low birth weight and newborn congenital malformation was not observed in this study. A higher number of subjects being followed are required to exclude any of these associations.

The most frequently clinically observed malformation was polydactyly. Some studies have described a high incidence rate of polydactyly in African populations [29,30,31]. Genetic factors have

been postulated to explain this high frequency [31,32]. However, more studies may be needed to rule out the influence of environmental factors, including diet and use of pesticides [33,34]. The number of cases with specific congenital defects was low, and thus, did not allow the assessment of a statistical relationship with drug exposure.

The objective of this study was not to do a causality assessment of exposure to each drug with each pregnancy outcome, but to describe the characteristics and pregnancy outcome of women exposed to drugs during pregnancy and explore the potential statistical associations.

Intrinsic to pharmacovigilance studies, especially in pregnancy, the main limitation of this study is that most information was collected retrospectively. Therefore, its reliability is clearly dependent on the women's recall of what happened during her pregnancy. In order to minimise this bias, all reported information was cross-checked with data recorded in the antenatal card, and in the admission file for those women reporting to have been admitted during the current pregnancy. Information on drug exposure was prospectively recorded in women who were admitted at the time of study recruitment.

Robust safety monitoring systems are clearly needed in developing countries to accompany the deployment of new drugs specially those with a potential teratogenic risk. Some examples should be avoided such as that of selective serotonin reuptake inhibitors, whereby it took almost 20 years to confirm their teratogenicity in humans despite the fact that these drugs were widely prescribed [35].

In conclusion, this is one of the few studies on drug exposure in pregnancy in Africa, and to our knowledge, the first one using a prospective methodology and assessing the relationship with the pregnancy outcome. The study highlights the high level of drug exposure, even to drugs of potential teratogenic risk, of pregnant

women living in a rural area of Mozambique. This is of special concern given the weaknesses and limitations of health systems in rural Africa to establish adequate safety monitoring programs. It also emphasises the need of reinforcing pharmacovigilance systems in Africa, especially or at least in pregnant women.

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ANNEX

Table 1: Characteristics of study women at recruitment and description of their drug exposure

N = 3105[*]		
Age (years), mean (SD)[¶]	25.0	(7.0)
Gravidity, n (%)		
Primigravidae	457	(14.7)
1 to 3 pregnancies	1664	(53.6)
4 or more pregnancies	984	(31.7)
Diseases reported during pregnancy, n (%)[‡]		
None diseases	1746	(56.2)
Malaria	265	(8.5)
Other diseases	821	(26.5)
Malaria + other diseases	273	(8.8)
Reported drug exposure during pregnancy, n (%)		
None	1829	(58.9)
1-2	329	(10.6)
3-5	734	(23.6)
6-9	186	6.0
≥ 10	27	(0.9)
Number of drugs reported per pregnant woman, mean (SD)[¶]	3.9	(2.1)

* Total of pregnant women recruited during hospital admission and at delivery time
¶ Standard Deviation
‡These participants reported **1866** diseases episodes: malaria (570), sexual transmitted diseases (449), general
Symptoms and signs (358), anaemia (195), respiratory tract diseases (81), gastrointestinal tract diseases (78),
obstetric diseases (75), skin diseases including Zoster Herpes (20), pre-eclampsia/eclampsia (18), Acquired
Immunodeficiency Syndrome (9), urinary tract infection (5), tuberculoses (4), hepatomegaly and splenomegaly (4)

Table 2: Drugs reported and prescribed to the study pregnant women‡

N = 4936*	n	(%)
Antibiotics	2033	(41.2)
Antimalarials	1176	(23.8)
Analgesics	896	(18.2)
Minerals and vitamins	513	(10.4)
Antifungals	172	(3.5)
Antihypertensives	50	(1.0)
Antiasthmatics	35	(0.7)
Antihistamines	16	(0.3)
Uterotonic agents	14	(0.3)
Antiacids	12	(0.2)
Antihelmintics	8	(0.2)
Corticosteroids	8	(0.2)
Antivirals	1	(0.0)
Antitussive	1	(0.0)
Traditional Medicines	1	(0.0)
FDA pregnancy risk categories#		
A	717	(14.5)
B	2488	(50.4)
C	943	(19.1)
D	788	(16.0)
X	0	(0.0)

‡ Information on prescribed drugs was collected during admission
*Pregnant women could have more then one episode of drug exposure.
More then one drug could be prescribed in one episode
The 5 most reported drugs in each category:
A: Ferrous sulphate, folic acid, nystatin vaginal tablets, hydroxocobalamin, multivitamins
B: Penicillin G benzathine, erythromycin, paracetamol, metronidazole, Amoxycillin
C: Sulfadoxine-pyrimethamine, cotrimoxazole, acetylsalicylic acid, gentamicin, chloramphenicol
D: Kanamycin, doxycyclin, tetracycline, captopril, povidone iodine

Table 3: Reported drug exposure according to the characteristics of study women and pregnancy outcome

	Drug exposure		
	Yes (N = 1276)	**No (N = 1829)**	**p-value**
Age (years), mean (SD)*	24.8 (7.0)	25.2 (7.0)	0.081
Gravidity, n (%)			
Primigravidae	221 (17.3)	236 (12.9)	0.001
Multigravidae	1055 (82.7)	1593 (87.1)	
Recruited			
During hospital admission	228 (17.9)	21 (1.1)	<0.001
At delivery	1048 (82.1)	1808 (98.9)	
Pregnancy outcome, n (%)			
Maternal death	0 (0)	1 (0)	1.000
Spontaneous abortion¶	18 (1.4)	2 (0.1)	<0.001
Stillbirth‡	10 (0.8)	4 (0.2)	
Live birth	1248 (97.8)	1823 (99.7)	
Low birth weight and Pre-term delivery¥	151 (14.4)	244 (13.5)	0.500
Normal weight and term delivery	896 (85.6)	1561 (86.5)	

*Standard deviation
¶Birth weight < 500 g
‡Birth weight ≥ 500 g
¥Low birth weight: weight <2500 g; pre-term delivery: birth < 37 weeks of gestation. **N = 2852**

Table 4: Reported antimalarial drug exposure according to the characteristics of study women and pregnancy outcome

N = 1276	**Drug exposure**		
	Antimalarials (N = 551)	**Other drugs (N = 725)**	**p-value**
Age (years), mean (SD)*	24.4 (7.0)	25.1 (7.0)	0.055
Gravidity n (%)			
Primigravidae	129 (23.4)	92 (12.7)	<0.001
Multigravidae	422 (76.6)	633 (87.3)	
Recruited			
During hospital admission	186 (33.8)	42 (5.8)	<0.001
At delivery	365 (66.2)	683 (94.2)	
Pregnancy outcome n (%)			
Abortion¶	15 (2.7)	3 (0.4)	0.002
Stillbirth‡	5 (0.9)	5 (0.7)	
Live birth	531 (96.4)	717 (98.9)	
Low birth weight and Pre-term delivery¥	54 (14.8)	97 (14.2)	0.781
Normal weight and term delivery	310 (85.2)	586 (85.8)	

*Standard deviation
¶Birth weight < 500 g
‡Birth weight ≥ 500 g
¥Low birth weight: weight <2500 g; pre-term delivery: birth < 37 weeks of gestation. **N = 1047**

Table 5: Description of congenital malformation in the babies of the study women

N = 68*

	n	(%)
Polydactyly	39	(57.4)
Limb and feet defects	6	(8.8)
Facial defect including cleft lip and/or palate	6	(8.8)
Genital defects	3	(4.4)
Spine bifida and other spinal cord defects	3	(4.4)
Abdominal wall defect	2	(2.9)
Anal and urethra atresia	2	(2.9)
Arthrogryposis	2	(2.9)
Cardiac defects	1	(1.5)
Hydrocephaly	1	(1.5)
Marfan syndrome	1	(1.5)
Supernumerary nipple	1	(1.5)
Vascular facial tumour	1	(1.5)

*Some babies presented more then one congenital malformation

4. Fourth article

Spontaneous adverse drug reaction reporting in rural districts of Mozambique

EJP Sevene, ARE Mariano, U Mehta, MJ Machai, ANO Dodoo, D Vilardell, SM Patel, KI Barnes, X Carné

Drug Safety 2008; 31 (10): 867-876

SUMMARY

The introduction of new policy recommendation for drug treatment of poverty-related diseases, such as malaria, tuberculosis and HIV/AIDS, calls for the deployment of responsive pharmacovigilance systems to permit identification of signals of rare or even common adverse reactions. In developing countries, particularly in Africa, these systems are mostly absent due to shortage of human, financial and technical resources.

The aim of this study therefore was to examine the impact of training of all categories of health workers, monitoring and supervisory visits as well as the availability of telecommunication and transport facilities on the implementation of a pharmacovigilance system in Mozambique.

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 low level of education of health professionals are ongoing challenges was performed. 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 in these districts were trained to diagnose, treat and report adverse drug reactions to all medicines using a standardised yellow card system. There were routine site visits to identify and clarify any problems in filling 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 telecommunication and transport was assessed.

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 (certain, probable or possible) linked to the reaction. Most reported ADRs were dermatological reactions (83.1%). Antimalarial drugs (chloroquine, amodiaquine, quinine, artesunate and sulphadoxine-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 between the districts.

In 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.

ORIGINAL RESEARCH ARTICLE

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Spontaneous Adverse Drug Reaction Reporting in Rural Districts of Mozambique

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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

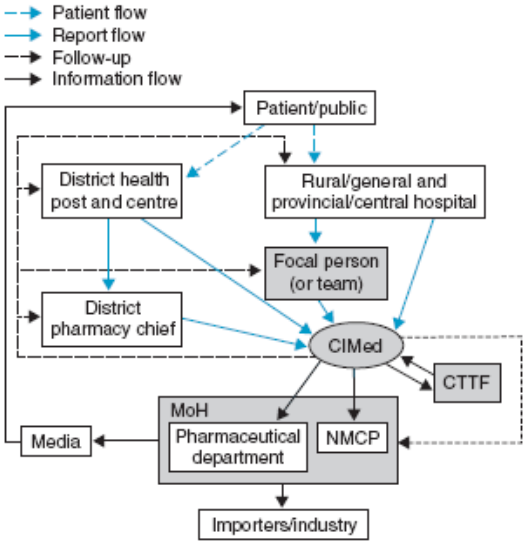

Fig. 1. Description of the flow of information in the CIMed (Drug Information Centre) pharmacovigilance system. In this system, the patients report their symptoms to health facility staff in District Health Centres (patient flow). At the district level, the health facility staff send the forms to district 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.

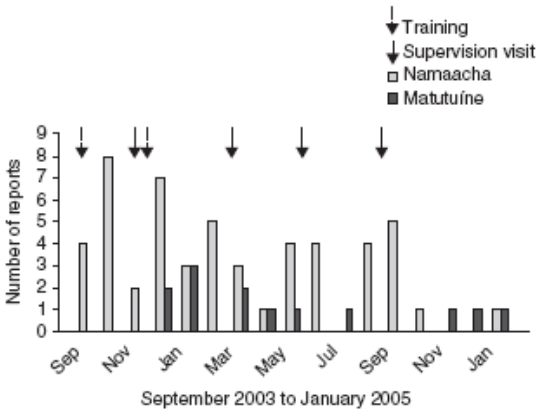

Fig. 2. Distribution of the reports from Namaacha and Matutuíne according to the date of report.

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 Matutuíne, 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 Matutuíne 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.

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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.

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DISCUSSION

VII. DISCUSSION

The objective of the first study was to explore the policy level factors affecting the availability of magnesium sulphate for the treatment of eclampsia and pre-eclampsia. The study shows that the approval, acquisition and distribution of MgSO4 encountered multiple barriers in both Mozambique and Zimbabwe. The factors reducing the availability of MgSO4 can be divided broadly into two groups: market and systems failures.

Several key system failures were identified. Firstly, issues related to drug registration were important in both countries. Secondly, long delays occurred in both countries in including magnesium sulphate in their national formularies. Because drug purchasing is based on these formularies, any failure to include effective drugs such as magnesium sulphate is critical. It is interesting that the presence of the drug in the WHO Essential Medicines List of 1996 did not appear to influence the decision to include MgSO4 in these countries lists. Thirdly, the numerous opportunities for communication failure within the bureaucratic health system processes contributed to the poor availability of magnesium sulphate.

As magnesium sulphate is a cheap generic drug, its cost should not be a barrier to its availability in a free market. The low cost of magnesium sulphate had several paradoxical effects. It was suggested

that its price retarded its registration in Zimbabwe, as the potentially small profits provided little economic incentive for companies to incur registration costs [144]**.** Respondents in Mozambique noted similarly that because the drug was cheap and the potential profits from it low, pharmaceutical companies did not actively market it or promote it to the central purchaser. If a pharmaceutical company marketed a low cost generic drug such as magnesium sulphate, this could increase the market share of other companies producing the same drug. In contrast, branded products have higher profit margins as other companies are legally prevented from selling the same drug. Marketing thus increases the sales of the branded product only. Incentives are few under a central tendering system for companies to market drugs to clinicians.

In evidence-based medicine all efforts to linking research to action is promoted [26]. Challenges on how to translate the results of clinical trials to policy actions are being described. These challenges are related to the judgments about the quality of research, the impact on public health, the health policy topics and its applicability in the different available contexts [145, 146]. In Mozambique and Zimbabwe, clinicians, researchers and policymakers were all aware of the evidence of efficacy of MaSO4 in the treatment of eclampsia. The policy was easily defined, but this study shows that implementation of a defined policy could be affected by complex factors related with the health system and the market of the drug. As a result, alternative

treatments more costly and with poor evidence continue to be used for the management of eclampsia and pre-eclampsia. This is disturbing coming more than ten years after the publication of the Eclampsia Trial findings [53].

Governments need to ensure that: bureaucratic processes do not obstruct the delivery of low cost and effective drugs, particularly for drugs that could reduce maternal mortality. Mechanisms for improving communication between clinicians and the agencies responsible for drug procurement and supply at country level must be in place. WHO, international professional organizations such as FIGO (International Federation of Gynaecology and Obstetrics), and international donor agencies, should take a more active role in ensuring that all essential medicines are registered and available in developing countries. Pharmaceutical companies need to be engaged in initiatives to ensure the supply of low cost and effective drugs for common conditions in Africa. Financial and other incentives for marketing these drugs need to be considered by international agencies. When the conditions for a functional market for pharmaceuticals are not met, governments must be prepared to intervene in order to support public health, and international organizations should support them in this purpose.

In the second study a review on the safety, pharmacokinetics and pharmacovigilance of antimalarial drugs is presented. This review

shows that chloroquine, quinine and sulphadoxine-pyrimethamine are considered safe for use during pregnancy. These are old drugs and the information on safety comes from a long experience of use. For other antimalarial drugs there are same safety concerns raised from pre-clinical studies in animals. Several pre-clinical studies in different animals' species have demonstrated that artemisinin derivatives may induce embryo loss, cardiovascular malformations and a syndrome of skeletal defects. The time window of sensitivity observed in animal studies would correspond in humans to part of the first trimester during which organogenesis takes place [147]. The current available information is clearly inadequate to predict the risk in humans.

Malaria during pregnancy is itself associated with substantial mortality and morbidity to the mother and the foetus, and thus we need to carefully balance the risks and benefits of artemisinin use. Currently, artemisinin derivatives are the most effective drugs for malaria treatment, particularly when associated with other antimalarials and they are considered an important tool for the reduction of maternal morbidity and mortality [88]. The absence of safety information has challenged its use during pregnancy, particularly in the first trimester. In the evidence-based medicine era it is unacceptable to gather this information only by collecting observational data after long time experience of use in humans. In developing countries, most antimalarial treatments are not given to confirmed malaria cases; often

antimalarial drugs are administered without laboratorial confirmation of the presence of the parasite [148]**.** It is essential that all efforts are made to measure the true risk, because most women will use the drugs in an unsupervised way and will not be aware of their pregnancy. Mechanisms to ensure better diagnosis of malaria cases will help to improve the benefits of drug use, particularly in pregnant women [148].

The other important issue addressed in this review is the lack of pharmacokinetic data for antimalarials during the pregnancy. Pregnancy creates huge physiological changes, which can alter drug disposition and metabolism. Incorrect dosing could result in maternal and foetal toxic effects. Therapeutic drug failure can result in poor pregnancy outcomes or maternal death, and could increase the risk of drug resistance. The few pharmacokinetic studies available indicate that the plasma concentration of the drugs in pregnant women is lower then in non pregnant women [149-151]. Implications of these studies are not known, but are likely to lead to decrease cure rates. More studies are needed to increase dose optimization and to further understanding the implication of pharmacokinetic variables in the final outcome.

The aim of the third study was to describe the level of drug exposure during pregnancy and its relation to pregnancy outcomes, in a rural area of Mozambique with high malaria endemicity.

The study has shown that drug exposure in pregnancy is high in rural areas of Southern Africa. More than forty percent of the study women reported an exposure to at least one drug during their pregnancy. The average number of drugs reported to have been taken per woman was also high, with a maximum of 14 drugs reported by one woman. Nearly a third (30.5%) of the women said to have received 3 or more drugs during their pregnancy. Of those women exposed to drugs, nearly 7% reported having taken drugs during the first trimester of pregnancy. This proportion, although not high, reinforces the need for pharmacovigilance systems being tailored to capture early pregnancy drug exposure. This is especially relevant in developing regions, where most pregnant women attend antenatal clinics from the second trimester onwards and thus, recall bias might be important [148].

In this study, antibiotics were the most frequently reported drugs. This may be explained by their use on the treatment of infectious diseases, particularly Sexual Transmitted Diseases (STDs). As it may be expected in a malaria endemic area, antimalarials were the second most reported drugs taken. The use of antimalarials did not necessarily follow the national policy for malaria treatment in Mozambique. Thus, all antimalarial drugs available in the area were reported to have been taken. Most of these drugs were also taken as monotherapy and not just in combination as recommended [102]. It is well known that the

inappropriate use of antimalarial drugs may increase the risk of treatment failure and the risk of emergence of drug resistant strains of *P. falciparum* [152, 153]**.** Apart from antibiotics and antimalarials, analgesics, minerals and vitamins were the other most reported drugs. This observation is in agreement with other studies that described these drugs as the most frequently taken during pregnancy [154, 155].

The study shows that spontaneous abortion and stillbirth are associated to drug exposure during pregnancy. In particular, spontaneous abortion was highly associated with antimalarial drug exposure. It has been suggested that placental malaria infection may be associated with a higher risk for stillbirth, and thus the infection and not the drug to treat it, might be the actual cause of this poor outcome [156]. However, more information about antimalarial drug exposure and spontaneous abortion and stillbirth is critically needed.

The most frequently clinically observed malformation was polydactyly. Some studies have described a high incidence rate of polydactyly in African populations [157, 158]. Genetic factors have been postulated to explain this high frequency [159, 160]. However, more studies may be needed to rule out the influence of drugs and other environmental factors, including diet and use of pesticides [161, 162]. The number of cases with specific congenital defects was quite low, and thus, precluding the assessment of statistical relationships with specific drug exposures.

The objective of this study was not to perform a causality assessment of exposure to each drug with each pregnancy outcome, but to describe the characteristics and pregnancy outcomes of women exposed to drugs during pregnancy and to explore the potential statistical associations.

In the forth study the aim was to examine the impact of training and monitoring a group of healthcare workers, making supervisory visits to the sites and the availability of telecommunication and transport facilities on the implementation of a pharmacovigilance system in Mozambique.

The study has shown that it is possible to implement a reasonably successful pharmacovigilance system in two resource constrained districts in southern Mozambique. The implemented strategy included training of healthcare personnel supplemented with routine visits, monitoring and feedback as well as 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.

The health staff in the two pilot districts included personnel of varying levels of education, ranging from medical doctors to health technicians with medium level training, and nurses and “health agents” with a basic degree. They were all able to fill in the ADR forms. The

active support and contributions of the basic clinical health staff during 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 PV system in the study areas. We believe that a similar approach would be feasible in other developing countries or areas with similar (very limited) resources.

Of the sixty-five ADR reports, antimalarials were the most commonly reported class of drugs. The change in first line antimalarial therapy at the beginning of the study period and its association with this pilot programme could have contributed to this reporting trend. Another drug that was frequently mentioned in the reports was co-trimoxazole, which is widely used for 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. This is an expected finding in a rural primary health care setting with limited access to diagnostic equipment and clinical expertise. Skin reactions are more easily recognized reactions and thus more frequently reported [134]. Other reactions with more subtle manifestations are more likely to be overlooked, particularly when laboratory tests and special clinical expertise are needed to confirm the diagnosis as is often the case for neurological, haematological, renal and hepatic effects.

The study focused on the feasibility of the PV systems and on the reports obtained spontaneously. The obtained results indicate that the system had been accepted and well received by healthcare workers in the two districts. The sustainability of the PV system is an important challenge for developed as well as for developing countries. Underreporting has being described as a major drawback of these systems [163]. The trainers need to follow-up implementation at district level in order to sustain reporting over time. In addition, feedback to reporters on a case by case basis is crucial, and must be a routine exercise performed by the focal personnel at provincial and district levels. We believe that the strengths of our approach to successfully implement the PV system in Mozambique was the development of a reporting and information flow system which 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.

The first study, demonstrated how the unavailability of an affordable drug to reduce maternal mortality resulted from systems and market failures. The second and the third studies showed that antimalarial drugs are being used in high proportion in pregnant women even without information on its safety profile in this particular group. With the current WHO recommendation of artemisinin derivatives for malaria

treatment it is likely that an increasing number of pregnant women will be exposed to these drugs even during the first trimester.

Robust safety monitoring systems are clearly needed in developing countries to accompany the deployment of new drugs, specially those with a potential teratogenic risk. Some examples should be avoided such as that of selective serotonin reuptake inhibitors, whereby it took almost 20 years to confirm their teratogenicity in humans despite the fact that these drugs were widely prescribed [164].

The fourth study presents spontaneous reporting system as a tool for drug safety monitoring. This system could be used to increase health care providers' and patients' awareness of possible ADRs, and to develop a culture to report these reactions. Although, the study shows that implementation of this system in resource constraint settings is feasible, it is not the most appropriated method to monitoring the safety use of drugs in pregnancy.

Pregnancy registry is a better method of monitoring drug exposure during pregnancy. Women with and without exposure to the treatment of interest should be enrolled in the studies as early as possible, and before the outcome of pregnancy is known. This avoids the limitation mentioned in the third study of recall bias when the information is collected after delivery. All information on drug use and other factors that can affect the pregnancy outcome, including demographic date, obstetric and medical history, family history, social or illicit drugs,

smoking and diseases are prospectively collected. Women need to be followed up to term and birth outcomes should be recorded: abortion, stillbirths, live births, neonatal deaths and presence of malformations [147].

Pregnancy registries involve complex methodological considerations and challenges at the time of recruitment, confirmation of exposure to the drug of interest, timing of exposure, detection of the congenital malformation, and data analysis for elimination of confounding factors (co-morbidities, concomitant treatments, and prophylactic treatments). In developing countries this challenges could be more difficult to address as other factors should be added to the list, including late declaration of the pregnancy, less and irregular attendance to antenatal care, few births taking place in health facilities, and lack of medical and prescription records. Implementation of this system will require resources, selection of sentinel sites were demographic surveillance system or other follow up mechanism are in place, and training must be continuous and repeated at regular intervals.

These studies highlight how complex is the use of drugs in pregnant women. Selection of effective and safety drugs is difficult, as there is no information or the drugs needed are not available. Traditionally, as pregnant women are considered vulnerable population, they were frequently excluded from most clinical trials. However, the need of

especial protection of this group should not imply a systematic exclusion from clinical trials, as they become even more vulnerable when exposed to drugs that are not evidence-based recommended or when they are private of the potential benefit of a drug with a poorly studied suspected risk.

Safety concerns are always part of the process of drug use in pregnancy and these studies have shown that antimalarial drugs are not an exception. Apart from the information based on clinical trials, other mechanisms to intensively monitor the safety use of antimalarials in pregnancy are needed. Spontaneous reporting and pregnancy registries were presented as examples of mechanisms that could and should be in place. Recommendations on how these systems could effectively be implemented in resource constrain countries were also presented.

Intrinsic to many pharmacovigilance systems, especially in pregnancy, the main limitation of these studies is that most information is based on the opinion and perceptions of the interviewers, and some data were collected retrospectively.

All these studies suggest that the definition of vulnerability of pregnant women in developing countries should not be restricted to the potential risk of harm of the foetus (harm-based definition) or to the difficulty of fully understand consent forms (consent-based definitions). Women are also vulnerable because of the high risk of dying from any

cause related to or aggravated by the pregnancy. The implementation of these ethic principles need to take into account the urgent need to implement effective and safety drugs targeted to reduce the burden of maternal morbidity and mortality.

CONCLUSIONS

VIII. CONCLUSIONS

1. Exclude pregnant women from clinical trials is not the appropriate way to protect them from their vulnerability as there is a great need of evidence-based information on drugs in this population in order to reduce the currently high maternal and offspring mortality.

2. There are few studies in pregnant women providing evidence on effective drugs. It is a concern that in the few instances where this evidence exists it is not transferred to policy and implementation. When the evidence exists, all mechanisms to ensure the availability of the drugs to the target population should be in place.

3. For the case of magnesium sulphate there is evidence-based information on efficacy and safety, but the drug has not been available for the treatment of eclampsia in Mozambique and Zimbabwe due to system and market failures.

4. The complexity of drug approval, acquisition, and distribution mechanisms in Mozambique and Zimbabwe results in many opportunities for system failures. Cost is also an important factor

in the availability of magnesium sulphate, but not because the drug is expensive. Rather, its low cost means that market forces cannot be relied on to ensure its availability in these settings.

5. There is no sufficient information available on the best antimalarial drug treatment for pregnant women. The decision on which antimalarial drug should be use in pregnant women continues to be a problem given the fact that the risks to the woman and foetus are not completely known. More information on the adequate doses to be given to pregnant women is also desperately needed.

6. In spite of the limited available information on these drugs, drug exposure during pregnancy (including those with recognised potential pregnancy risk) was high in rural Mozambique. Antibiotics and antimalarials were the most frequently reported drugs in accordance with the high prevalence of both malaria and other infectious diseases.

7. Pharmacovigilance systems can be established in resource-limited countries in Africa where malaria is endemic, 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.

8. The use of alternative ways of communication, like the use of focal person and the ambulance to send the report could contribute to improve the reports. Regular training, monitoring and feedback are key success factors in such an enterprise.

9. Large-scale trials and post marketing surveillance systems to monitor drug safety are required. Specific methodologies, selecting vulnerable groups like pregnant women and drugs with potential of risk could be an alternative for pharmacovigilance when weaknesses and limitations of health systems in rural Africa are of special concern.

10. Governments, donors and international agencies must be prepared to intervene to ensure the availability of low cost, effective and safety drugs in developing countries. Particularly, for pregnant women, these initiatives could be a step forward to reduce maternal mortality, an important contributor factor to their vulnerability.

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