Master's thesis submitted to the Universite Victor Segalen Bordeaux2 in partial fulfillment of requirements for the award of **Troped- European Master of Science in International Health** (Track-1 Tropical Medicine and Disease Control, 2005-06) by Ms. Revati Keshao Phalkey**.**

Watch Out …….**ACT** now!

"Pharmacovigilance for Artemisinin based Combination Therapies in Africa"

Safety profile assessment of amodiaquine (AQ) + artesunate (AS) co-administration for the treatment of uncomplicated *falciparum* malaria in Africa to support formulation of a pharmacovigilance system.

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List of Abbreviations

ACT	Artemisinin Combination Therapy
ACTs	Artemisinin based Combination Therapies
ADRs	Adverse Drug Reactions
AE	Adverse Effects
ALAT	Alanine aminotransferase
AQ	Amodiaquine
AR	Artemisinin
AS	Artesunate
ASAT	Aspartate aminotransferase
AS+AQ	Artesunate +Amodiaquine co-administration
CDC	Centre for Disease Control and Prevention
CME	Continuing Medical Education
COPS	Community Owned Pharmacovigilance System
COSTART	Coding Symbols for a Thesaurus of Adverse Reactions Terms
CRF	Case Report Form
CQ	Chloroquine
DALY	Disability Adjusted Life Years
DIT	District Investigation Team
GDP	Gross Domestic Product
GP	General Practicioner
Hb	Haemoglobin
HIV	Human Immunodeficiency Virus
ICD	International Classification of Diseases Terminology
ICH	International Conference on Harmonization
MedDRA	Medical Terminology for Drug Regulatory Authorities
NOAEL	No Observed Adverse Effect Level
P. Falciparum	Plasmodium Falciparum
RBM	Roll Back Malaria
SADH	South African Development Community
SAE	Serious Adverse Effects
SP	Sulfadoxine-Pyrimethamine
SPC	Summary Product Characteristics

TB	Tuberculosis
TDR	UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases
UNDP	United Nations Development Fund
UNICEF	United Nations Children's Fund
WHO	World Health Organization
WHO-ART	WHO Adverse Reaction Terminology

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I. Executive Summary

This document aims to investigate the safety profile of the *artemisinin* based combination: *amodiaquine* (AQ) and *artesunate* (AS) as a treatment for uncomplicated *falciparum* malaria in view of the expected co-formulation due to be registered in 2006. Currently the two drugs are administered as separate formulations as a single dose for three days.

The method used was systemic review of the information obtained from 30 monitored studies conducted between 1999-2006 in 19 African countries for safety of *artesunate* and *amodiaquine* (AS+AQ) co-administration as treatment for uncomplicated *falciparium* malaria obtained from published and unpublished sources (This section of the document is a part of the World Health Organization (WHO) report **"**Artesunate and amodiaquine for the treatment of uncomplicated falciparum malaria: an inventory of clinical studies and systematic review of safety and efficacy data.**"**- P. Olliaro, M. Valliant, P. Mussano, R. Phalkey).

The analyses suggested that although a substantial number of studies did report safety, the information was fragmented and not standardized. Summary of the data was difficult. Although all the studies reported the combination as "well tolerated and safe" and no Serious Adverse Effects (SAE) were reported in any of the study, results should be interpreted with great care for various reasons. The results from the analyses highlight the necessity to implement continued post marketing surveillance for the *Artemisinin based Combination Therapies (ACTs)* owing to the limitations of the clinical trials and due to overall scarcity of adequate safety information about the combination from African countries.

In order to stress the need and importance for a comprehensive monitoring system before the co-formulation is launched, a community based pharmacovigilance system model has been proposed. Furthermore the document also proposes a pictorial Adverse Effects (AE) case reporting form (CRF) to assist in facilitated reporting of Adverse Drug Reactions (ADRs) through community persons irrespective of their educational background.

II. Background Introduction

- ***Malaria: Disease Burden***

Malaria is emerging as a significant challenge for the world health initiatives today despite being both preventable and curable. Caused by a single cell parasite of the genus *plasmodium* and transmitted by the bite of a infected female *anopheles* mosquito, it is a disease known to man since many a decades. 95% of all severe cases of malaria are attributable to *plasmodium falciparum* which is the most severe and life threatening form of the disease. Malaria had a widespread occurrence but was successfully eliminated from few countries in the 20th century. Today the tropical and the sub-tropical regions are mainly affected, particularly sub-Saharan region of the African subcontinent, where 90% of malaria related deaths occur. 40% of the world population lives in 100 malaria endemic countries and regions (Gakuba and Van Den Ende, 2004), of which 370 million people live in endemic areas of Africa alone (Grandesso, 2004).

The disease causes an estimated 300-500 million acute illnesses and about 1 million deaths annually (RBM, 2003, Gakuba and Van Den Ende, 2004). 7% of the children and 5% of adults who survive cerebral malaria have residual permanent neurological deficits. It is a leading cause for under 5 mortality (20%) in the sub Saharan region and it is estimated that every30 seconds Africa experiences a malaria related child death (RBM, 2003).

Pregnant women are the second highest risk group for malaria. 40% of the worlds pregnant women are exposed to malaria during pregnancy (Lang et al., 2006) which contributes to low birth weights, anaemia, maternal mortality and also epilepsy and learning difficulties in children. The situation is further compounded by issues such as malnutrition and the emerging twin epidemic of Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) infections particularly in the African context.

United Nations Development Fund (UNDP), The United Nations Children's Fund (UNICEF), the World Bank and the World Health Organization (WHO) launched *Roll Back Malaria* (RBM), a global partnership, in 1998 as an attempt to control the disease effects and its economical costs. In 2000, all African heads pledged for the Abuja declaration which aims to halve the burden of malaria in Africa by 2010 (Simooya, 2005, RBM, 2003). Although substantial efforts have been made, the burden persists, mainly due to lack of awareness about the existence of effective measures and public accessibility to them (RBM, 2002).

- ***Economic Burden***

Malaria is described as a disease of poverty and a cause for poverty (RBM, 2003). "Where malaria prospers most, human societies have prospered least" (Heemskerk et al., 2006). It affects the most vulnerable and hence the economic manifestations of the disease due to the direct and indirect costs incurred are enormous. Malaria constitutes 10% of total disease burden of the African continent and accounts for about 40% of the public health expenditure, upto 30-50% of inpatient admissions and roughly 50% of outpatients visits (RBM, 2002). The situation in sub Saharan Africa is marked with complexities such as poor access to health care, inadequate health infrastructure and limited financial and human resources (RBM, 2002).

Economists estimate a US$ 12 billion loss in terms of Gross Domestic Product (GDP) in Africa and a "growth penalty " of upto 1.3% in some African countries due to malaria, besides the loss of human resources due to the disease (Adjuik et al., 2002, RBM, 2003, Heemskerk et al., 2006). The disease burden is estimated at about 50 million Disability Adjusted Life Years (DALYs) (Heemskerk et al., 2006).

Furthermore, in the absence of effective first line treatment, the system gets overburdened with cases that would ideally have been cured the first time (Grandesso, 2004) and so the choice of first and second line treatments have significant economic manifestations.

- ***Antimalarials and the History of Drug Resistance***

There is a multifold increase in malaria specific mortality in children between 0-4 yrs following *chloroquine* (CQ) resistance. It is of particular relevance in Africa as 75% of the cases have been identified here. It is rather difficult to quantify the disease burden of malaria caused specifically by the resistance to available antimalarials. *Chloroquine* resistance *falciparum* malaria was first reported from Africa in 1978. "Recent estimates based on the best available data from Africa suggest that the demise of *chloroquine* is *the most plausible single factor contributing to the change in malaria specific mortality*". This has doubled in the last 15 years (Yeung et al., 2004).

In the 1950-1960's malaria eradication seemed achievable since there was a single human reservoir for the disease. *Quinin*e, extracted from the bark of the *Cinchona* tree was introduced for malarial treatment, drawing on the knowledge of the native populations of South American as early as 1632. It was the only known anti-malarial agent until the 19th

century, to which resistance was identified almost 278 years later - in 1957 (Talisuna et al., 2004).

Chloroquine (CQ) was discovered by a German scientist Hans Andersag, in 1934 at Bayer I.G. Farbenindustrie A.G. laboratories in Eberfeld, Germany. British and American scientists established it as an effective and safe antimalarial in 1946 (CDC, Centre For Disease Control and Prevention). Resistance to *chloroquine* was first identified in Asia - in the Thai-Cambodia border in 1959, and was seen in South America in 1960. In 1976 Papua New Guinea reported 2 confirmed cases. Similarly drugs introduced later, such as *proguanil, sulfadoxine pyrimethamine, mefloquine* and *atovaquone* have all demonstrated resistance within 1 to 5 years of introduction. By 1983, a number of countries reported resistance to anti-malarial drugs and this contributed to the thinking and making of the hypothesis that resistance spread from South-east Asia to Africa possibly through population movements. This was, to an extent supported by the genetic similarities in parasite strains found in the two continents and its difference from the South American and Papua New Guinea strains.

The associations between isolated genetic mutations and *chloroquine* remain uncertain. *Chloroquine* resistance is related to decreased drug uptake (Le Bras and Durand, 2003). A set of mutations of the *PfCRT gene* located on chromosome 7 is found in all natural isolates from clinical *chloroquine* treatment failures and *in vitro* in isolates with *chloroquine* resistant phenotypes. Four independent geographically varying mutation profiles are seen: Asia-Africa, Papua, South America 1 and 2. Thus, the emergence of *chloroquine* resistant mutants, selected by drug pressure in the 1950's is a major event in the history of drug resistance in antimalarials (Le Bras and Durand, 2003). These have spread to 90% of the areas of *Plasmodium falciparum* in the last 40 years.

Thailand was the first country to change the first line of treatment of malaria in 1973. In 1988, South Africa changed to *sulfadoxine pyrimethamine* (SP). Malawi was the first country to change its national drug policy following the resistance appearance. By 1997, a number of countries in the African continent had reviewed and changed their policies as well (Talisuna et al., 2004). By 1987, *Plasmodium vivax*, the second predominant strain, came with resistance.

In the developing countries , second line drugs are not readily available and failure of the first line drugs in these situations often can lead to a direct increase in morbidity and

mortality (Yeung et al., 2004). The isolation of *artemisinin* by the Chinese scientists in 1972 was an essential breakthrough in the time of failing available drugs. However, knowing from the past adaptive behavior of the *falciparum* parasite it is likely that it develops resistance to any drug that is widely used. This is further contributed to by the indiscriminate, irrational, incomplete and inappropriate drug use. To date, no resistance to *artemisinin or artemisinin* derivatives has been reported, although some decrease in sensitivity *in vitro* has been detected in China and Viet Nam (WHO, RBM Factsheet).

Resistance can be attributed to a number of factors such as population drug selection, pattern and frequency of drug use, drug elimination half- life, malaria transmission intensity, parasite biomass and migration of humans or vectors. Mass drug administration campaigns in the late 1950's and early 1960's along with residual spraying as an attempt to eradicate malaria (World Health Organization) can be possibly contributing factors to the current situation (Talisuna et al., 2004). It is evident that use of combination therapies delays initial resistance emergence (Yeung et al., 2004). However malaria control programs often do not change to combination therapies firstly because of the cost implications and also unless resistance develops, there is no "evident" need to do so.

Thus, drug-resistance is co-produced, naturally and socially in the field. The problem of drug resistance has prompted the search for safe, good quality, affordable, acceptable, new therapies with long lasting clinical cure (Koram et al., 2005). In this catch 22 situation the only solution is development of drugs with novel mechanism of action or an easier alternative is to use combination therapies (Olliaro et al., 2001). Currently, the availability of *artemisinin* used in combination is a solution for the sustainable treatment of malaria. All possible care should be taken to preserve them and prevent the development of parasite resistance

- ***Artemisinin based Combination Therapy (ACT)***

The principle of *combination treatments* is the varying half lives of the two drugs. It is a symbiotic relationship where both the drugs protect each other from resistance development. For example the rapidly eliminated drugs like *artemisinin* have a short half life but they rapidly and effectively reduce the parasite density and gametocyte carriage rate. Thus the partner drug is efficacious in clearing the remaining parasites as its concentration is still high. This reduces the likelihood of the parasites being exposed to sub-optimal levels of the longer acting drug thus protecting it from resistance development. Use of the longer acting

drug reduces the risk of recrudescence due to rapid elimination of the *artemisinin* and also shortens treatment time to three days as against minimum 5 days (Barennes et al., 2004). Together the two drugs achieve effective parasitological and clinical cure and also reduce the rate of transmission of the disease (Koram et al., 2005, Martensson et al., 2005, Rwagacondo et al., 2004, Heemskerk et al., 2006). The probability that both the drugs develop resistance together is very low, one in 10^{12} treatments and this is the main advantage of combining treatments (Gakuba and Van Den Ende, 2004).

Choice of the partner drug

There is to a greater extent an inverse relationship between baseline resistance of the partner drug and efficacy of the combination (Sowunmi et al., 2005). Addition of *artemisinin* even to a reasonably failing partner drug is not useful (Guthmann et al., 2005, Mutabingwa et al., 2005). Therefore, the best time to switch from traditional monotherapies to a *Artemisinin based Combination Therapy (ACT)* is when the baseline resistance to the component drugs is still low (Barennes et al., 2004). *Chloroquine* resistance is wide spread and the resistance to the second line drug *sulfadoxine-pyrimethamine* is also emerging in Africa (Olliaro et al., 2001). High baseline resistance to *amodiaquine* and *sulfadoxine-pyrimethamine* resistance severely limits the available choice (Martensson et al., 2005). However the Thai-Myanmar experience suggests that the use of *artemisinin* with *mefloquine* (MQ) has increased to an extent its *in vitro* sensitivity (Olliaro et al., 2001). The critical question still remains when to change and what combination to choose (Martensson et al., 2005).*:*

Rational for Artemisinin use

(Abacassamo et al., 2004, Barennes et al., 2004, Durrani et al., 2005, Guthmann et al., 2005, Guthmann et al., 2006, Koram et al., 2005, Martensson et al., 2005, Mutabingwa et al., 2005, Rwagacondo et al., 2004, Sowunmi et al., 2005, Staedke et al., 2004, Yeka et al., 2005, Gakuba and Van Den Ende, 2004**)**

As against the other available antimalarials the *artemisinin* drugs have the following advantages:

- improved cure rates, reduced treatment failures
- reduction in the rate of resistance development
- delay in resistance development
- rapid efficacy and fever resolution and hence reduction in the use of antipyretics

- rapid resolution of parasitemia due to reduced parasite clearance time
- Anti-Gametocytic activity: reduced number and infectivity of gametocytes and thus reduced transmission of the disease
- rapid anaemia resolution
- few reported Adverse Drug Reactions (ADRs)
- currently not prey to resistance

Artesunate + amodiaquine as an Artemisinin based Combination Therapy

The dose for the co-administration of the drugs is 4 mg/Kg/day of *artesunate* (AS) and 10mg/Kg/day of *amodiaquine* (AQ) given orally for three days (Gakuba and Van Den Ende, 2004). *Artesunate + amodiaquine* (AS+AQ) is currently available as either separate or blister packaged tablets. A fixed dose combination is being developed and should be registered for use in 2006. Advantage with AS+AQ like other *Artemisinin based Combination Therapies (ACTs)* is rapid resolution of symptoms and a shorter 3 day regimen. In vivo observations suggest that *amodiaquine* resistance develops at relatively slower rate, however genotypic basis of *amodiaquine* resistance is the missing link (Hamour et al., 2005). The global *sulfadoxine-pyrimethamine* resistance pattern suggests that *artesunate+amodiaquine* (AS+AQ) combination is likely to have a relatively longer therapeutic life.

Most of the current *Artemisinin based Combination Therapy (ACT)* safety experience comes from Asia. Africa experiences different rates of transmission of the disease, endemicity, pattern of drug use, genetic predisposition and so there is a greater need for investigating these drugs in the African context (Bukirwa et al., 2006). Also, studies specifically to examine the drugs in different age groups and different populations is essential (Sowunmi et al., 2005).

Challenges with Artemisinin Combination Therapies (ACTs)

The main challenge with *Artemisinin based Combination Therapies (ACTs)* remain the prohibitive costs which keeps it away from the people who actually need it. Others include inadequate clinical and preclinical safety/toxicology information, drug supply shortage, unavailability at peripheral levels and logistic issues with policy implementations (Barennes et al., 2004, Bukirwa et al., 2006, Durrani et al., 2005). There is limited information on the performance of *Artemisinin based Combination Therapies (ACTs)* in areas with varying

transmission intensity (Yeka et al., 2005). There is limited information about these drugs in large populations and for a long time (Grandesso et al., 2006). Due to the current unavailability of fixed dose combinations, adherence to complex dosing patterns is also an issue (Koram et al., 2005, Mutabingwa et al., 2005).

Future drugs

10 years of time and around 800 million dollars of investment is what we need to have a new drug (Heemskerk et al., 2006). More than finances the time will take a toll on human lives. Although there are 21 projects currently under research from molecules in early inception to phase three trials with the Medicines for Malaria Venture (MMV) it will be some time before they are available for public use (Heemskerk et al., 2006).

Artemisinin based Combination Therapies (ACTs) are the way forward as endorsed by the *Roll Back Malaria (RBM)* initiative and all possible care should be taken to maintain its efficacy, prolong the therapeutic lifespan and save the drug from resistance development by ensuring its rational use as it would directly equate to saving lives!! (Guthmann et al., 2006).

Sustainability for Artemisinin based Combination Therapies (ACTs)

- Drugs be available at prices similar to previous antimalarials
- Monotherapy stopped immediately
- Ineffective drugs be withdrawn from market immediately in view of cross resistance development and loss of entire class of drugs
- private health bare providers, public health care programmes all should have access to subsidized drugs
- ACTs should be available at all places where previously drugs were available
- Correct prescription practices, effective distribution channels and assured compliance
- unit dose user friendly packaging for increased adherence, co-formulation would be an ideal solution.

- ***Artesunate and Amodiaquine***

Malaria treatment has become a great challenge owing to the rapid development and spread of resistance to cheap and effective antimalarials like *chloroquine* (CQ), *sulfadoxine-*

pyrimethamine (SP) and *amodiaquine* (AQ) due to complex factors as discussed before. An ideal treatment drug should be effective against all stages of the parasite , have short regimen, well tolerated, cheap and affordable, available, accessible, rapid acting with the potential to reduce transmission and limit the development of resistance (Adjuik et al., 2002, Grandesso, 2004).

A range of antimalarial treatments are available. The currently endorsed *Artemisinin based Combination Therapies (ACTs)* are *artesunate+sulfadoxine/pyrimethamine*, *artemether+lumefantrine* (Co-Artem®), *artesunate+amodiaquine* and *artesunate+mefloquine*. However, we will discuss *artesunate* (AS) and *amodiaquine* (AQ) for the purpose of this document.

Amodiaquine

It is a *4-aminiquinolone* antimalarial drug with anti-inflammatory and antipyretic properties belonging to the same class of drugs as *chloroquine* (Taylor, 2005). It is administered as a total dose of 25 to 35 mg base per Kg over three days. After administration it is metabolized in 8 hrs to desethylamodiaquine which is slowly eliminated with a half life of about 18 days (Gakuba and Van Den Ende, 2004). In 1990, the WHO removed its endorsement as an essential drug due to reported rare but serious toxic effects (Abacassamo et al., 2004) namely, hepatitis and agranulocytosis associated with the long term use as prophylaxis. However short term curative therapeutic use is well tolerated (Adjuik et al., 2002, Barennes et al., 2004) and it was reinstated in the drug list in April 2003 with recommended use in combination with *artemisinin* (Gakuba and Van Den Ende, 2004).

Risk profile

The side effect profile of the drug is similar to *chloroquine* and *sulfadoxine-pyrimethamine* (Abacassamo et al., 2004). Risk estimates are 1 in 2000 for *neutropenia* and 1 in 15,650 for *hepatitis*, the two most described serious complications of *amodiaquine* (Adjuik et al., 2002). Although minimal information is available about the teratogenic effects of *amodiaquine* since it is structurally and functionally similar to *chloroquine* which is associated with slight increase in fetal changes, teratogenecity with *amodiaquine* use can not be completely ruled out (Taylor, 2005). There is renewed interest for *amodiaquine* due to its efficacy, although variable, in areas with intense *chloroquine* resistance (Abacassamo et al., 2004, Adjuik et al., 2002). The *PfCRT* gene that confers resistance to *chloroquine* is also known to confer resistance to *amodiaquine* (Sowunmi et al., 2005). Little is known

about the real risks with large scale *amodiaquine* treatment and so large scale monitoring and routine surveillance data should be collected (Barennes et al., 2004).

Why Amodiaquine?

Advantages with the use of *amodiaquine* are that it is user friendly in children in terms of taste, causes lesser itching compared to *chloroquine* and is relatively the cheapest antimalarial drug after *chloroquine* (Barennes et al., 2004, Durrani et al., 2005). Besides, it is still effective in West and Central Africa although its efficacy has declined in East Africa (Olliaro et al., 2001).

Qinghaosu/Artemisinin

Artemisinin extracted from the leaves and the flowers of sweet wormwood (*Artemisia annua*) was discovered, tested and market by the Chinese who were using this as a herbal treatment for fever for over 20 centuries (Heemskerk et al., 2006, WHO, 1998). The active ingredient was isolated in 1971 by Chinese scientists. The drug line consists of two *lipophilic derivatives artemether* and *arteether*, a *hydrophilic derivative artesunate* and a *metabolite Dihydroartemisinin* (Heemskerk et al., 2006).

Artemisinin is poorly soluble in both water and oil and is only administered orally. It is administered at 4mg/Kg on first day and then 2 mg/kg once a day for 6 days. After administration the drug is metabolized to *Dihydroartemisinin* with a mean peak plasma concentration at 1-2 hours and mean elimination half life of 2-3 hours (Gakuba and Van Den Ende, 2004). Although not very commonly used by clinicians as monotherapy, it is available as a over the counter drug in many countries and this is a concern (Barennes et al., 2004). *Artemisinin* as monotherapy requires minimum regimen of 5 days, preferably of 7, due to the rapid elimination of the drug and due to the risk of recrudescence when used for lesser days (Barennes et al., 2004). Compliance is an issue due to a 7 day regimen. *Dihydroartemisinin*, (can also be administered as a oral drug) has greater *in vitro* antimalarial properties compared to *artemisinin* and this is explained by its presence the higher concentrations as compared to the parent drug (van Agtmael et al., 1999). The half life is very short < 6 hours which makes it less susceptible to resistance development (Heemskerk et al., 2006). *Arteether* and *artesunate* (AS) are water soluble and hence can be administered parenteraly (van Agtmael et al., 1999). *Artesunate* (AS) is the most widely used *artemisinin* compound. It is a *hemisuccinate derivative* of *Dihydroartemisinin,* which

is available as a rectal suppository as well (Gakuba and Van Den Ende, 2004). Availability in the form of suppository is an asset in peripheral malaria management when quick treatment initiation is the main determinant of the outcome (van Agtmael et al., 1999). *Artesunate* (AS) is administered as 4mg/Kg/day for three days.

Risk profile

Reproductive toxicity and *Neurotoxicity* are the two main safety concerns expressed with the use of *artemisinin* compounds. *Neurotoxicity* seen as a special pattern of *neuronopathy* in brain stem nuclei in dogs and rhesus monkey were not seen in rats even at a higher doses (WHO, 1998). The *"No Observed Adverse Effect Level (NOAEL)"* is between dose 6.25mg/Kg/day in dogs, 100mg/kg/day in monkeys and up to 175mg/Kg/day in rats (WHO, 1998). *Neurotoxicity* or any other *Serious Adverse Effect* (SAE) has not been reported in humans so far in any of the clinical studies that were done so far in about 10,000 patients, post marketing surveillance done in 4600 patients, and with the use of the drug in millions of patients in Asia (WHO, 1998). The bibliographic review of the 30 studies we conducted also did not find any serious adverse effects.

Higher doses of *artemisinin* also produced prolongation of QT interval, bone marrow depression and fetal resorption in laboratory animals (Tracy, 2002). However, at doses used in human it is less likely that there will occur serious toxic effects, however, the risk cannot be completely ruled out and close monitoring is required.

Reproductive toxicity seen as clear evidence of embryo death and morphological abnormalities in laboratory animals led the World Health Organization (WHO) recommending not using *artesunate* (AS) in the first trimester of pregnancy (Staedke et al., 2004, Gakuba and Van Den Ende, 2004).

The most common *Adverse Effects* (AE) reported with *artemisinin* use are *headache, nausea, abdominal pain, vomiting, diarrhoea*. Some cases of temporary suppression of *reticulocyte response* without *anaemia* and induction of *black water fever* have been reported but these were at the same rate as that of *quinine* (WHO, 1998). There are a few reports of bleeding disorders from Thailand following the use of *artemisinin* (WHO, 1998).

Risk of resistance

Laboratory tests have shown that strains resistant to *mefloquine* (MQ) are less susceptible to *artemisinin* (WHO, 1998). Apparent drug failure with use of *artemisinin* in falciparium

malaria was recently reported in West Africa (Barennes et al., 2004). Some reports of reduced susceptibility observed in China bordering Myanmar associated with weak health infrastructure, self medication and population migrations confirm that *artemisinin* also has a potential to develop resistance and utmost care should be taken to ensure its rational use (WHO, 1998). Repeated programmatic surveillance to detect genetic markers for resistance should be implemented since molecular findings suggest that the *artemisinin* based combinations are also vulnerable to selection of genetic markers (Martensson et al., 2005). The availability of *artemisinin* as a single drug monotherapy is a potential threat to the *Artemisinin based Combination Therapy (ACT)* strategy (Heemskerk et al., 2006).

III. Objectives

The main objectives of this study are:

Primary

Adaptation of a community based pharmacovigilance methodology in developing countries for the safety monitoring of antimalarial drugs

Secondary

Analysis of information obtained from 30 monitored studies conducted between 1999-2006 in 19 African countries for safety of *artesunate and amodiaquine* (AS+AQ) co-administration as treatment for uncomplicated falciparium malaria.

Proposal of a standardized methodology and a pictorial case report form to promote and facilitate reporting of unexpected events from peripheral areas through community facilitated reporting.

IV. Material and Methods

The study is based on a systemic review of articles, reports and studies obtained from published and unpublished sources reporting artesunate and amodiaquine co-administration therapy for the treatment of uncomplicated malaria from studies performed in Africa.

PubMed search was conducted using the following key words: amodiaquine, artesunate, malaria, safety, adverse drug effects, serious adverse drug effects, pharmacovigilance, drug safety, adverse effects for pharmacovigilance system.

The data set for safety analyses consisted of 30 clinical studies in the form of English and French reports / papers / publications from 1999-2006.

Artesunate + amodiaquine (AS+AQ) safety information obtained from the dataset was fed in Microsoft Excel for analyses.

A bibliographic review of articles was performed to support the preliminary findings from the studies to propose a community based pharmacovigilance system and formulate an Case Reporting Form (CRF). for the reporting of Adverse Effects (AE)

World Health Organization (WHO) reports and publications were used as further supporting reference documents.

V. Systemic Analysis of the Database

This section of the thesis is a part of the World Health Organization (WHO) report *"Artesunate and Amodiaquine for the treatment of uncomplicated falciparum malaria: an inventory of clinical studies and systematic review of safety and efficacy data" 2006-* P. Olliaro, M. Valliant, P. Mussano, R. Phalkey.

- ***Aims and Objectives***

The aim of this investigation is to inform better both policy and research pertinent issues of using *artesunate + amodiaquine* (AS+AQ) for treating uncomplicated falciparum malaria. By compiling an inventory, we intended to assess the safety of AS+AQ, and, for comparative trials, to conduct individual and aggregate comparative analyses of efficacy.

- ***Materials & Methods***

1. Search strategy & criteria applied

Published studies were identified through two, independent searches of PubMed and the Cochrane Registry using the key words "artesunate, amodiaquine, malaria, treatment". Unpublished studies were identified via personal contacts and examining WHO records. Consequently, investigators were contacted to provide raw data. Preset criteria were used to assess quality of studies and data. These were: (i) randomised trials, (ii) adequacy of data collection, (iii) blinded studies, (iv) adequate drug concealment (open trials), (v) adequate research and analytical methodology explained in the publications.

2. Data management and analyses

Data were extracted independently by two persons, compared and reconciled. These data were submitted to investigators to double check the information and provide additional data as needed. Data were entered and analysed using Microsoft™ Excel® and Revman®.The primary safety endpoint was the reporting of any adverse event (AE). We sought information on deaths and other adverse events.

The database and analyses were structured as follows: all studies identified are reported; then they are further divided into studies eligible to the assessment of (i) parasitological/clinical efficacy and safety and (ii) safety only (pharmacovigilance). Eligible comparative trials, a subset of (i), are reported. They will also become part of a Cochrane systematic review.

L'Abbé scatter plots

In the L'Abbé scatter plots[1], the proportions of cured patients with the experimental intervention (in this case AS+AQ) are plotted against the cure rate for the comparator drugs. Thus, each point on the graph represents one trial. We adapted these plots, so that the size of the bubble was proportional to the size of the study. If the efficacy of AS+AQ was better than the comparator drug, the bubble will lie in the upper part of the plot (between the Y axis and the line of equality) and *vice versa* (between X axis and line of equality). A bubble on the line of equality means the efficacies of AS+AQ and the comparator were the same.

L'Abbé plots allow one to visualize the absolute and relative efficacies of treatment regimens; the distribution of results also indicates the degree of agreement / disagreement (heterogeneity) among trials. We also modified the L'Abbé plots to represent cure rates and their 95%CIs for AS+AQ and the comparator drugs, which appear as a cross intersecting at the point estimate between the two results. The longer the 95%CIs lines, the smaller the study and the lower the confidence in the result.

3. Analyses of safety

Papers/reports were assessed for the quality and quantity of safety information, and these data were tabulated. Specifically we considered all adverse events, vomiting, serious adverse events, and laboratory assessment (haematology, blood chemistry).

For the assessment of safety in these studies, we derived the numbers of patients seen on Day 14, 28 or 42 from the papers or additional information provided, considering withdrawals, losses to follow-up, exclusions due to failure or lack of tolerance. Because safety data varied widely in terms of thoroughness of collection, these safety analyses

[1] L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Intern Med 1987 107:224-33

should be interpreted with caution; however, the same criteria were used for both AS+AQ and comparator drugs in comparative trials. We calculated the total, median and interquartile range of patient-days of follow-up.

For comparative trials, we used the L'Abbé plot to show the rates of patients reporting any adverse effects (AEs).

4. Combined efficacy and safety outcomes

For the combined assessment of efficacy and safety we plotted the Risk Differences (RD, with 95%CIs, calculated with Revman) between AS+AQ and each comparator arm for efficacy (Day 28 crude success rates) and safety (proportion of patients reporting any AE) for both individual studies and the studies combined. In this graph, the bottom right quadrant favours AS+AQ for both efficacy and safety.

- ***Description of the Database***

1. Types of Studies:

We identified 29 studies: 25 were comparative, 3 non-comparative, and one a pharmacovigilance study. For 20 studies, further details (beyond published data) were provided by investigators.

	detailed report available		
	No	Yes	Total
Published	8	10	18
submitted	1	3	4
Unpublished		7	7
Grand Total	9	20	29

Table 1: Type of studies

One published article reported results of a multicentre study from three countries that used a common protocol: each country has been counted as one study. Studies in different sites in the same country are counted as one country. Therefore, there were 31 country studies, of

which 27 comparative, 3 non-comparative and one pharmacovigilance study. Safety information was not available from Brasseur et al (Senegal) pharmacovigilance study.

2. Year of Completion of Studies:

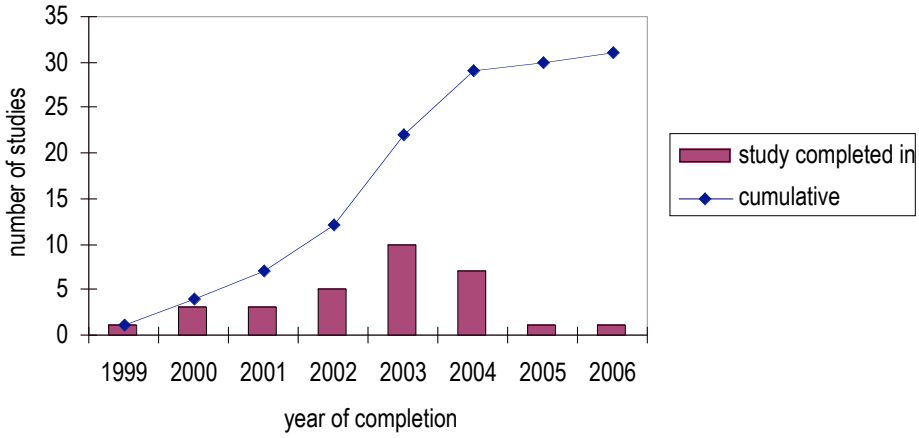


Figure 1: Year of completion of studies (by year and cumulative).

All studies were conducted between 1999-2006, with a peak around 2003.

3. Study participants

Protocols generally followed the 2003 WHO recommendations for assessing therapeutic efficacy. Entry criteria varied slightly between studies, usually in relation to the Day 0 parasite limits because of endemicity. All trials enrolled children and 5 also included adults: 2 comparative (Yeka et al, Uganda; Durrani et al, Afghanistan), 2 non comparative (Grandesso et al, Sierra Leone; Agnamey et al, Senegal) and the pharmacovigilance study. According to the protocols, age was <5 years in 18 studies (lowest age accepted varying from 4-12 months). Age was reported for 34 study arms in months or years as either means (+/- standard deviation) or medians (interquartile range) and cannot be summarised. Reported patients' ages matched the Materials & Methods section of the papers. Weight was reported for 17 treatment arms. Therefore, efficacy results in Africa are essentially based on data in children under 5 years of age. Safety data are largely related to a paediatric population (under 10s).

4. Treatment regimens

AS and AQ were given together as individually packaged products in 29 studies. Two studies used the co-blistered product Arsucam® (Mutabingwa et al, Tanzania, and some of the patients in Brasseur et al, Senegal). The target dose was 4 mg/kg/d for AS and 10 mg/kg/d for AQ for three days (total doses: AS 12 and AQ 30 mg/kg) in 26 efficacy studies as well as the pharmacovigilance study. Three studies used a lower dose of AQ (25 mg/kg) and one a lower dose of AS (8 mg/kg given as 4 mg/kg on day 1 and then 2 mg/kg/d on days 2 and 3: Barennes et al, Burkina-Faso).

The comparator drugs were:

- Single agents: amodiaquine(AQ), artesunate (AS), chloroquine (CQ), sulfadoxine/pyrimethamine (SP)
- Non-artemisinin based combinations (non-ACT): AQ+SP, CQ+SP
- ACTs: non-fixed AS+SP; fixed combinations artemether + lumefantrine (AM+LF, Coartem®), dihydroartemisinin + piperaquine (DH+PQ, Artekin®).

5. Analytical methods and reporting

Reporting of trials generally followed the Consort guidelines and used the WHO criteria for antimalarial drug efficacy. Analyses presented in this meta-analysis are per-protocol, consistent with the published data. PCR adjusted cure rates were reported by 18 studies but used different laboratory and reporting methods. The *P. falciparum* genes investigated were: (i) three (msp1, msp2 and glurp) in 8 studies, (ii) two (msp1 and msp2) in 10, and (iii) single msp2 in 5 studies. The way PCR corrected correction was done varied between studies e.g. how missing data and unresolved genotypes were counted; how new infections are considered.

6. Database structure

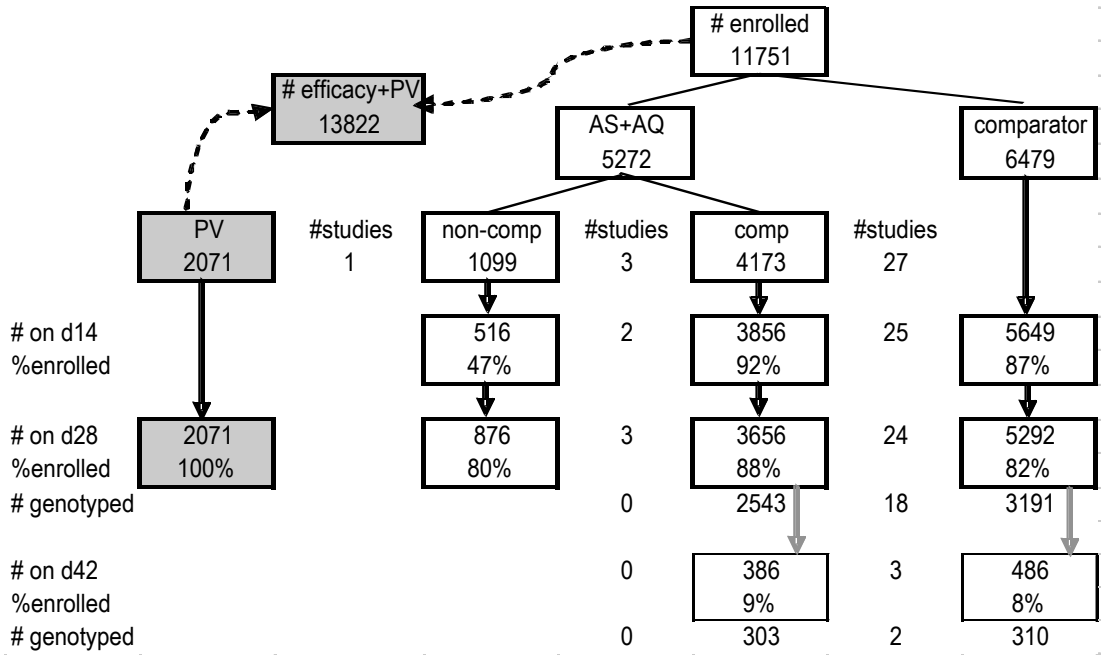


Figure 2: Overview and structure of the database.

These studies enrolled 13,822 patients. Of these, 2071 AS+AQ recipients were in the pharmacovigilance study, assessing only safety, and will be reported elsewhere. Efficacy analyses are based on a total of 11,751 patients, of whom 5,272 received AS+AQ (4,173 in comparative and 1,099 in non-comparative studies), and 6,479 a comparator drug.

7. Number of patients: by study and by country

Country of study	# of studies	# patients (Tot All trials)	# patients (Comparative trials)	# on AS+AQ
Afghanistan	1	268	268	79
Angola	2	324	324	166
Burkina-Faso	1	87	87	33
Burundi	1	295	295	153
Gabon	1	220	220	110
Ghana	1	168	168	54
Kenya	1	400	400	200
Mozambique	1	185	185	61
Nigeria	1	155	155	104
RDC	4	707	707	321
Rép de Guinée	1	220	220	110
Rep.Congo	1	298	298	101
Rwanda	2	1070	1070	410
Senegal	3	1294	321	1133
Sierra Leone	1	126	0	126
Sudan	2	430	430	214
Tanzania	1	1811	1811	515
Uganda	4	3286	3286	1175
Zanzibar	1	407	407	207
Grand Total	30	11751	10652	5272

Table 2: Patients contributing to the combined analyses of efficacy/safety by study and by country.

The majority of studies (27/30) follow patients for 28 days post-treatment and three studies for 42 days.

- ***Results***

1. Analysis of Safety

Assessment of safety information provided

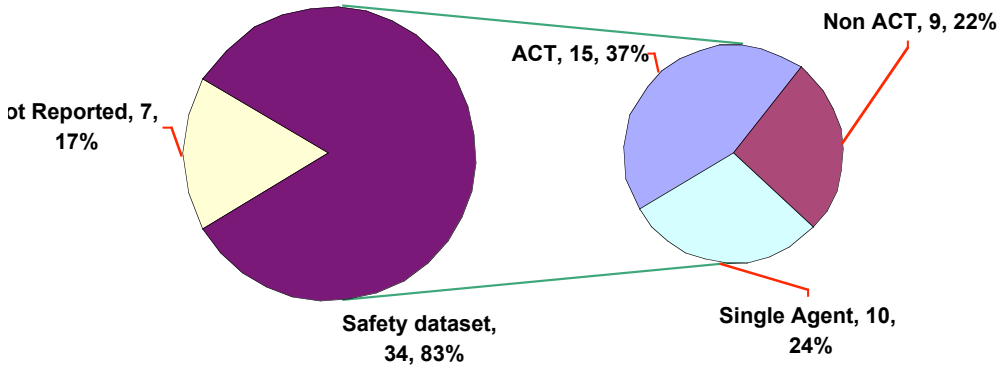


Figure 3: Reported safety in non AS+AQ arms of comparative trials.

Of the 30 studies, 24 (80%) provide safety information that could be consolidated and reported. In these studies, a total of 3,979 patients received AS+AQ, 126 in one non-comparative and 3853 in 23 comparative trials. The latter compared 15 ACT arms, 10 single agent and 9 non-ACT combination arms.

Patient attrition in the analyses of safety

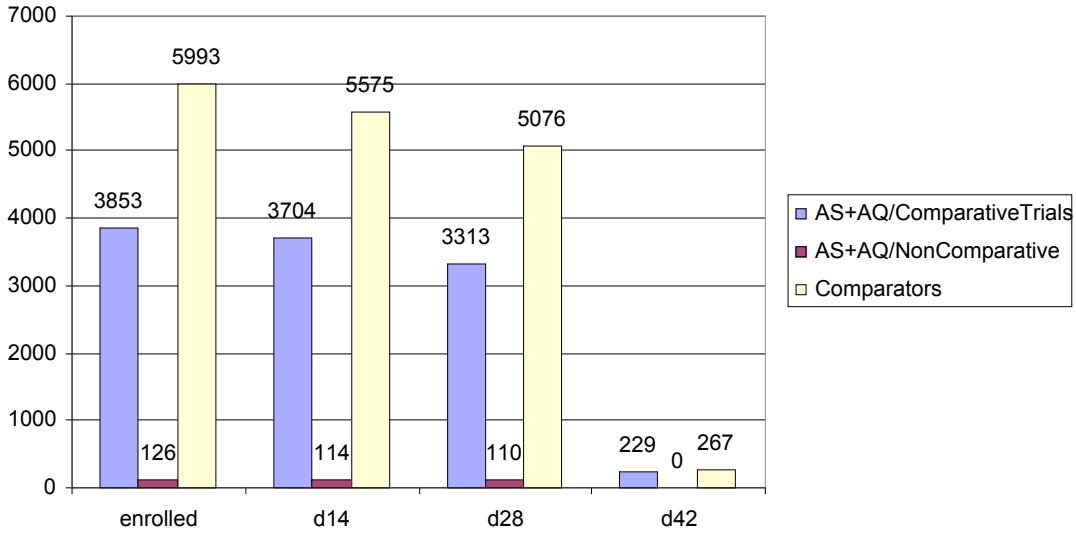


Figure 4: Patient attrition for the safety dataset.

Considering the 4173 patients who received AS+AQ in comparative trials and the 6479 on a comparator drug, 92% (3853 and 5993, respectively) enrolled studies reporting safety. The proportions of patients evaluable on day 28 are similar to those seen in the corresponding efficacy datasets.

These 24 trials followed AS+AQ treatments for a total of 131,836 person-days (361 person-years). In the 23 comparative trials, for AS+AQ the median (Q25-Q75) person-time of follow-up was 2884 (2135-4753) days, for a total of 104,564 person-days of follow-up. For the comparators, the median was 3976 (2436-5628) for a total of 144,578 person-days.

Quality of safety reporting

Safety information	**Number of studies**	**Authors**
Mentioned the numbers Do not specify the arm in which the AEs had occurred	2	Abacassamo et al. 2004 Durrani et al. 2005
Mentioned the numbers Do not discuss the types or individual frequencies separately	6	Kitz et al. 2005 Barennes et al. 2004 Bukirwa et al. 2006 Karema et al. 2006 Martensson et al. 2005 Bukirwa et al 2006
Report both the numbers of patients with AE and the number of AEs Do not report the frequency observed in each patients	3	Staedke et al. 2004 Karema et al. 2006 Yeka et al. 2005

Table 3: Quality of safety reporting.

In general, the reported safety data are sketchy and there was no standardized reporting or analytical patterns across the studies. Summarizing these data was difficult. For example, in Agnamey et al. 2005, study withdrawals due to AE irrespective of causality are classified as treatment failures, but details are not provided in the paper. In Koram et al. 2005, patients with SAE were withdrawn from the study, but numbers were not provided.

Safety as an outcome measure in the papers: Reference to safety is made in almost all the papers, but only 14 (47%) formally define outcome measures for safety, and only 9 clearly define Adverse Events (AEs) and Serious Adverse Events (SAEs). Although some of the

reports have mentioned the common adverse effects expected in the drugs used, only 5 papers have discussed the concerns with amodiaquine safety in particular and one paper mentioned the need for information dissemination to peripheral health care workers about the status of amodiaquine as a short term therapeutic drug post withdrawal following safety concerns.

Baseline exclusion criteria

Baseline exclusion criteria	**Number of studies**
Previous use of antimalarials in last 72 hours	9
History of vomiting in last 24 hours (baseline) - variably defined	10
Malnutrition	17
Known allergy to study drug	23
Convulsions	7
Anaemia	10
Severe paediatric anaemia (Hb<5g/dl)	11
Underlying concomitant illness	19
Hepatic/Renal Disease	2
Cardiac disease	3

Table 4: Baseline exclusion criteria.

There were several baseline exclusion criteria that were ethically justified for clinical studies but rendered the information obtained from such subjects less certain for application to real life field conditions. Some of these criteria are common in malaria patients; studies in such patients would provide additional and relevant safety information reflecting "real life" use.

Drug source and quality for artesunate and amodiaquine: The artesunate brand was given in 23/29 studies: 17 used Arsumax® from Sanofi Aventis, France; 3 used Plasmotrim® from Mepha, Switzerland; 2 used artesunate from Dafra Pharma, Belgium. 1 unspecified drug source from Nigeria. The amodiaquine brand was given in 21 studies: 14 used Camoquine® (+1 with local generic name Basoquine®), Pfizer, 3 used Flavoquine®, Marion Roussel, 1 from Sedapharm, 1 used Larimal, IPCA Pharmaceuticals, Nigeria; 1 used the IDA, Netherlands, product. Only 3 studies reported the batch number of drugs used in the clinical studies; no one provided information on expiry dates and storage conditions during the trial period.

2. Overall tolerability

Authors' assessment of tolerability: AS+AQ was reported as "safe" in 23 trials; 7 do not comment on the tolerability or safety of the drug. Except for vomiting, only one paper (Adjuik et al. 2002) reports the withdrawal of patients due to AEs other than vomiting.

Vomiting

Vomiting was the most discussed adverse event in all the studies. Only one study reports the number of patients (n=8) who were not enrolled because of persistent vomiting (Kitz 2005). Repeated vomiting (twice or more) after drug administration was specifically mentioned as a cause of study withdrawal in 26 studies.

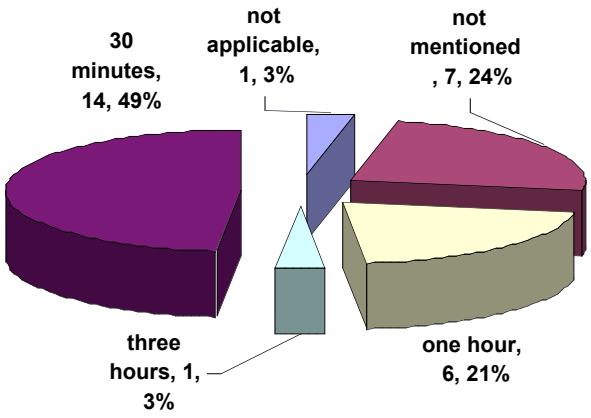


Figure 5: Time of observation after drug administration

Treatment was fully supervised (all doses) in 28 studies; in Abacassamo 2004 only the first dose was observed, while in Mutabingwa 2005 treatment was unsupervised. The time during which patients were kept under observation post-dosing was not the same for all trials. Time of observation was not mentioned in 7 studies and not applicable in Mutabingwa 2005 (unsupervised); 14 papers have reported observation time as 30 minutes and 6 as one hour. One study had a 3 hour observation period (Sowunmi 2005). For Brasseur 2006 information was not available.

Withdrawals due to vomiting

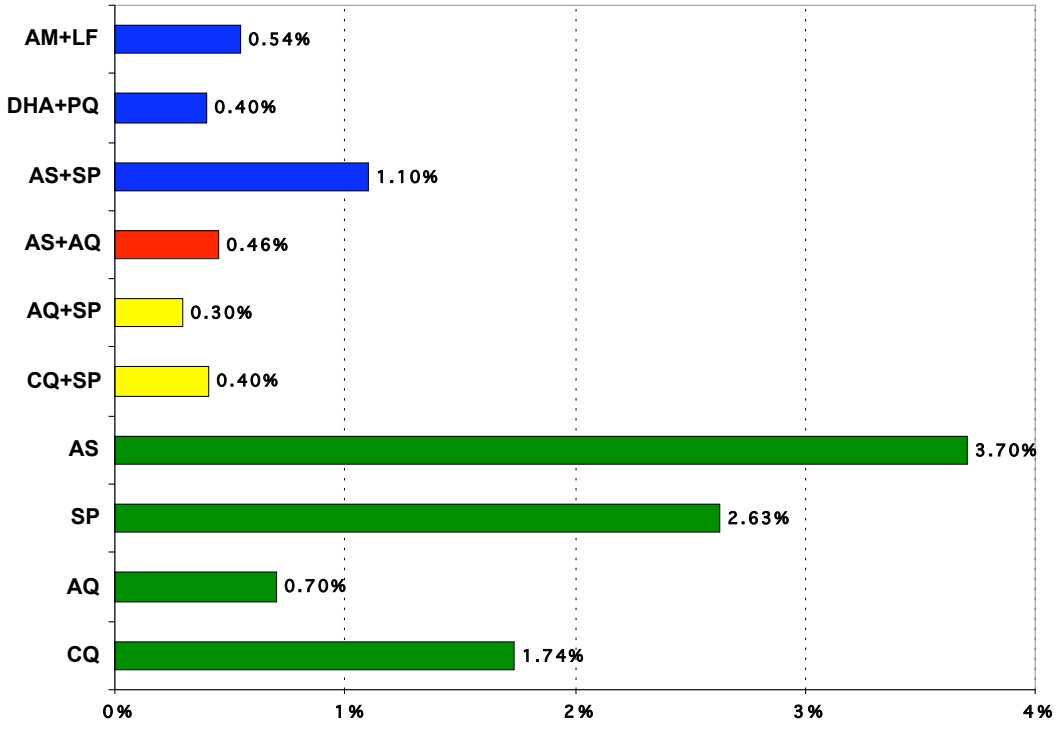


Figure 6: Vomiting after drug administration.

Vomiting lead to study withdrawal in 7 AS+AQ arms and 8 comparator arms. Overall, 19 patients treated with AS+AQ were withdrawn from study due to repeated vomiting out of a total of 463 exclusions (4%) for other reasons (e.g. failures, lost to follow-up, other AEs). By comparison, there were 14/683 (2%) study withdrawals due to vomiting of comparator drugs. Of note, not all studies clearly stated the number of exclusions due to vomiting; Abacassamo 2004 mentioned one case and Guthmann mentioned two cases of vomiting without specifying the study groups; some studies do not clearly distinguish vomiting on

Day 0 from other days. Patients withdrawn due to vomiting in all studies were 60 out of 10,652 (0.56%) with 19/4,173 (0.46%) in the AS+AQ arms and 41/6,479 (0.63%).

3. Serious adverse events

15 papers of the 24 (62.5%) reporting safety do not mention Serious Adverse Events (SAE). In the remaining 9 studies no SAE related to the study drugs occurred. The common SAEs discussed were meningitis and convulsions.

4. Laboratory Monitoring: Haemoglobin was the only laboratory investigation that was uniformly monitored in all the studies. The days of sampling differed (4 studies did not mention information about Haemoglobin monitoring.). 17 studies had no information about any additional tests.

Test	**No. of studies**	**Studies**
Haemoglobin	25	Brasseur no information, 4 not mentioned
PCV	4	Abacassamo 2004, Durrani 2005, Karema 2006, Rwagacondo 2004
Total WBC	5	Durrani et al. 2005, Karema et al. 2006 and Staedke et al. 2004, Martensson et al. 2005
Neutrophil Count	2	Martensson et al. 2005, Staedke et al. 2004
Platelets	1	Staedke et al. 2004
ASAT	8	Adjuik et al. 2002 (Kenya, Senegal, Gabon), Barennes et al. 2004, Durrani et al. 2005, Karema et al. 2006, Sowunmi et al. 2005, Agnamey et al. 2005
ALAT	9	Adjuik et al. 2002 (Kenya, Senegal, Gabon) Barennes et al. 2004, Durrani et al. 2005, Karema et al. 2006, Sowunmi et al. 2005, Agnamey et al. 2005, Staedke et al. 2004
Bilirubin	6	Adjuik et al. 2002 (Kenya Senegal, Gabon), Durrani et al. 2002 and Sowunmi et al. 2005
Creatinine	8	Adjuik et al. 2002 (Kenya, Senegal, Gabon), Barennes et al. 2004, Durrani et al. 2005, Sowunmi et al. 2005, Staedke et al. 2004, Agnamey et al. 2005 (results not reported)

Table 5: Laboratory monitoring.

5. Other Adverse Events

Other AEs listed in the studies were cutaneous (pruritus/itching, urticaria, rash), gastro-intestinal (abdominal pain, anorexia, diarrhoea, gastroenteritis), neurological (convulsions, headache, meningitis, vertigo, dizziness), respiratory (cough, pneumonia, asthma) haematological (anaemia, thrombocytopenia), general (fatigue, asthenia, weakness, dehydration, myalgia).

6. Comparative assessment of safety

We plotted the patient proportions reporting AS+AQ against that of the comparator arm for each comparison. The AE rates appear to be similar in AS+AQ treated and control patients.

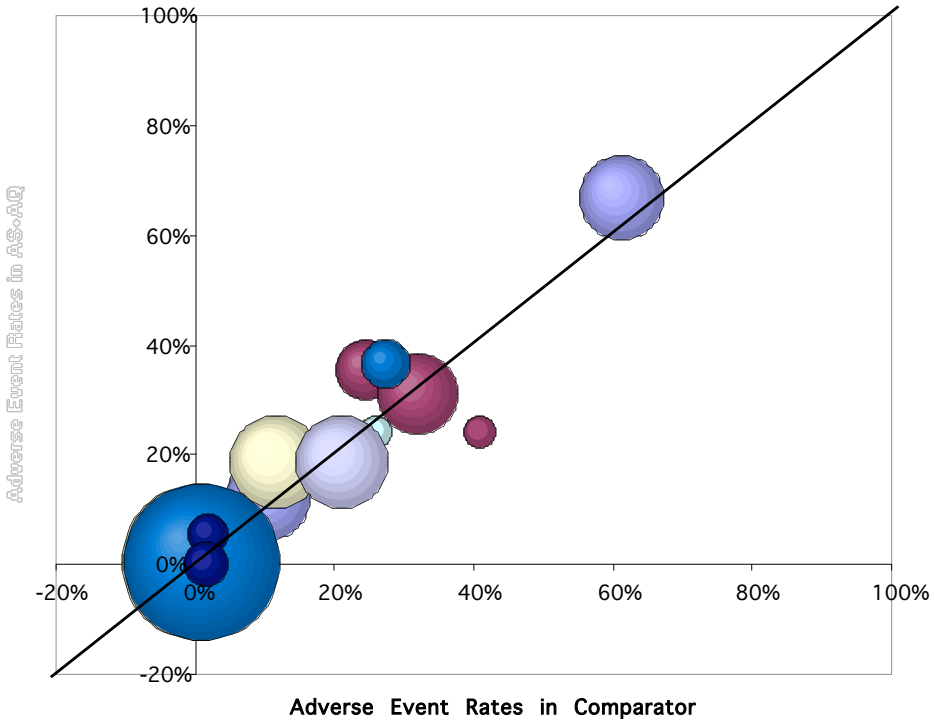


Figure 7: L'Abbé plot of adverse event rates in AS+AQ arms vs comparator arms

A log-scale plot is also presented to resolve studies clustering at lower frequencies:

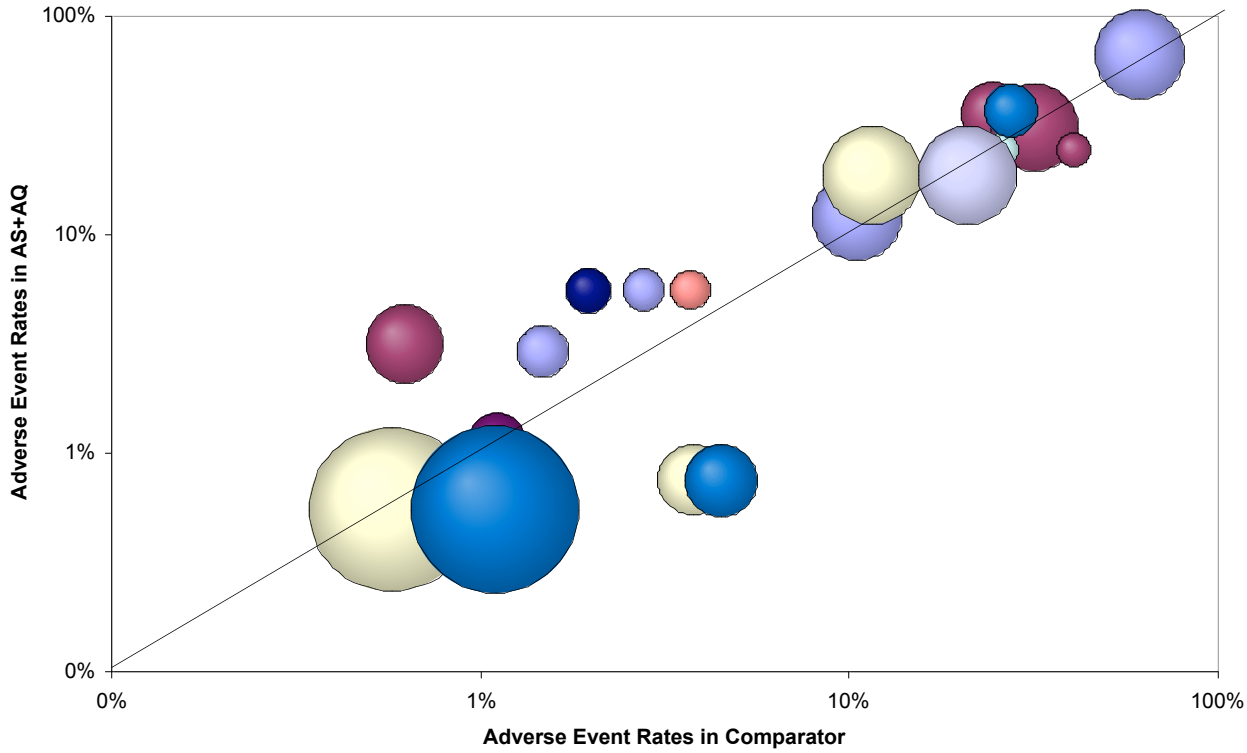


Figure 8: L'Abbé plot of adverse event rates in AS+AQ arms vs comparators arms (log scale).

7. Overall safety summary conclusions

We have identified and analysed a large database of studies of AS+AQ, predominantly conducted in African children with falciparum malaria and with 28 days of follow-up. Most of these studies are comparative and report standardized WHO efficacy outcomes, while safety reports are limited.

As these studies were done during 1999-2006, these analyses present an up to date situation of the performance of AS+AQ.

Overall, AS+AQ was significantly more effective than single agent treatment or combinations not including an artemisinin derivative; it was similar to AS+SP; it was inferior to AM+LF and DH+PQ when crude rates are considered, but not different after PCR correction.

Safety was not reported uniformly. Overall AS+AQ was "well tolerated" and vomiting, the most commonly reported event, occurred at comparable rates to other treatments.

8. Methodological issues with the conduct and reporting of study results

Although safety collection was weak in the majority of trials, this database has increased our knowledge of tolerability of AS and AQ. Overall this combination was well tolerated and comparable to its comparators. However, we believe that there should be a standardised approach to reporting safety data (similar to Consort) and there should be a raising of standards by scientific journals.

9. Implications for research

- The methodology of reporting and analysing antimalarial trials can be further refined. This is particularly true for PCR-corrected outcomes.
- Safety information is underreported and should be standardised both in general (along the lines of the Consort statement) and more specifically for antimalarial trials.
- For both research and policy, it is important to access and analyse systematically, in order for the resulting information to be disseminated readily. Not all studies done are publicly available and accessible.
- This initial database should be developed to become a tool to capture more information systematically as it become available and sustained. Some investments are made, both initially (to develop and test the best tool) and then to maintain it. Ideally this should be done by or under the auspices of WHO/GMP [2]. TDR can participate in the development phase in collaboration with CRP-Santé, Luxemburg (M.Vaillant) -which could also maintain it.
- reporting on efficacy & safety: It is high time to examine the optimal ways to report efficacy that maximizes sue of the data.

[2] Sibley CH, Ringwald P. A database of antimalarial drug resistance. Malar J. 2006 Jun 15;5(1):48

10. Implications for policies

- There are and there will be additional studies to capture and analyse. Systematic reviews of updated datasets are important (See above).
- By comparing the list of countries where these studies were done and the country policies, some discrepancies are apparent. Communication of research results and systematic reviews are key elements.
- The inventory is a good evidence for policy and the meta analysis useful in furthering our understanding about the combination. However, safety should be on an equal par with efficacy, many ACTs will be highly effective but safety and ease of use may tip the policy decision and this is an important concern.
- There is urgent need for local data about the performance of the combination in terms of both safety and efficacy due to the variations in baseline resistance patterns.

VI. Discussion and Recommendations

As seen from the database and also from the literature it is evident that clinical trials are excellent tools to quantify the efficacy profile of the drug, somehow it has several serious limitations in defining the safety profile of the drug which justifies the need for continued post marketing surveillance.

- ***Limitations of Clinical Trials***

(Talbot and Nilsson, 1998, Herdeiro et al., 2004, Martin et al., 2003, WHO, 2004, McMahon and MacDonald, 2000, Simon, 2002, Bavdekar and Karande, 2006, Mutabingwa et al., 2005, Atuah et al., 2004)

- It difficult to mimic real life settings in clinical trials
- Most often the drugs provided are free unlike real life settings
- The study population is not representative of standard population due to strict inclusion and exclusion criteria
- They provide limited information about safety in children, pregnant women and elderly. (18% of the population is elderly and they receive 45% of all prescriptions. Over the counter medicines are also very commonly used by this section of the population. Generally women constitute 50% of the population and 54% are in reproductive age groups (Atuah et al., 2004))
- Size of the study population is limited (In the preclinical phase the drug is administered to less than 5000 patients and this is not sufficient to detect rare adverse effects . 30,000 is the number of subjects needed to be sure to observe at least one case of an AE with an incidence of 1 per 10,000 and so surveillance in immediate post marketing phase is crucial (WHO, 2002a, Lang et al., 2006))
- No information of drug overdose can be obtained due to ethical reasons
- Duration of follow up is very short and insufficient to detect long term effects of the drug
- situations when drug used for unlicensed indications cannot be studied
- No information on interactions when used with other drugs (poly-pharmacy), alternate medicine or with food
- Effects when underlying co-morbid conditions such as diseases, malnutrition, Human Immunodeficiency Virus (HIV), anaemia etc. cannnot be studied
- Do not provide information about genetic variation in response to drugs

The above mentioned inherent shortcomings in the nature and methods of conducting clinical trials is further compounded by the inadequate and incomplete reporting of safety data in published information. A review of clinical trials reported that 80% of the studies failed to evaluate and report Adverse Drug Reactions (ADRs) in a proper way (Sjoqvist, 2000). As also evident in the database analyses, the main focus of most clinical trails is efficacy and very little attention is given to the recording and adequate reporting of drug safety. Safety information obtained from clinical trials can assist in estimating the safety profile of the drug, identifying the missing information and special concerns which can be useful to formulate the post marketing surveillance objectives. Hence object reporting is essential.

- ***"From the Cradle to the Grave Approach"***

Tolerability of the treatment can compromise implementation and success of the first line treatment even if it is highly efficacious (Karema et al., 2006). It is therefore necessary that the drug be followed up for safety information right from its initial inception through it entire therapeutic lifespan (Lang et al., 2006). Pre-marketing confirmed drug safety and efficacy can drastically vary in real life field use of the drug.

- ***Pharmacovigilance***

"Pharmacovigilance" previously referred to as *Adverse Drug Reaction Monitoring Schemes, Drug Surveillance Programs or as Drug Safety Monitoring* (Lawson, 1997), is defined as the science and activity relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicine related problems (WHO, 2006).

The concept of Adverse Drug Reactions (ADR) reporting emerged in 1963 following the thalidomide tragedy (1961). Pharmacovigilance was conceptualized at the 18th World Health Assembly WHA 18.42 which led to the formulation of the International Drug Monitoring Programme in 1970. As of 2006, there are 79 member countries of which 5 are African countries (Lang et al., 2006).

Pharmacovigilance is an umbrella term that describes processes for the development of operating systems to generate hypotheses in respect to unexpected or previously unobserved Adverse Drug Reactions (ADR) and then test each alert/signal generated there of (Lawson, 1997). It is often noted that the *Defined Daily Dose (DDD)* of the drugs is changed in actual

post marketing prescriptions. Studies done to investigate the patterns suggest that 60% changes are reductions, indicative of safety concerns (Atuah et al., 2004). Pharmacovigilance can be used to detect these changes and monitor off label prescriptions.

As in the past, pharmacovigilance concerns are no longer limited to conventional allopathic medicines and have now been extended to cover herbal products, traditional complimentary medications, blood products, biologicals, medical devices and vaccines (WHO, 2002b).

Developing country perspective (WHO, 2002a, Lang et al., 2006**)**

In most developing countries, the drugs are more often used irrationally right from the beginning and hence many treatments may be lost mainly due to the inadequate use that results in poor efficacy performance (Lang et al., 2006).

- most malaria patients are in peripheral regions away from the reach of formal health care
- These are usually young children and pregnant women
- Anaemia, malnourishment and now Human Immunodeficiency Virus (HIV) are important co-morbidities in these populations
- Special groups may be taking the drugs and experiencing AE even without the knowledge of anybody!
- Dose is an important factor for Adverse Drug Reactions (ADRs). Practical difficulties like absence of weighing scales to determine weights are common in rural areas.
- Absent robust drug policies in place, poor drug legislature, rudimentary/ absent pharmacovigilance systems
- Lack of resources and inadequate health care infrastructure
- Poor doctor :patient ratio
- Prescription of drugs by untrained personnel and high rate of self medication demands that the drugs be safe through all sections of the population particularly pregnant women.
- Over the counter availability of drugs, widespread circulation of counterfeit, substandard drugs
- Lack of information, high rates of illiteracy and poverty
- parallel systems of health care and lack of coordination between different systems of medicine

Integrating the pharmacovigilance systems in existing health care systems and public health care programmes such as the malaria control programmes could be a possible solution (Simooya, 2005). These partnerships will allow the sharing of resources, exchanging knowledge and experiences and avoid duplication of efforts thus saving on the scarce resources.

Need for an "individualized" approach (WHO, 2002a)

There are country specific problems and affects and although a standardized structure can be followed, adaptations to suit indigenous needs have to be incorporated. Direct import of successful interventions from another country do not necessarily work because the incidence, prevalence and disease patterns differ, the prescription patterns (particularly the indications, dose), drug availability, manufacturing practices , drug quality, drug distribution, health seeking behavior of the population, traditional complementary medications and above all the paying capacity of the patients are diverse and often unique to each country.It is therefore necessary to obtain baseline population data before formulation or application of any public health intervention preferably through pilot projects.

Pharmacovigilance focus issues

- Drug production: quality and good manufacturing practice, detect counterfeit and substandard drugs
- Drug distribution: access and availability, supply chain management
- Drug prescription patterns : indications, contraindications, dose and regimen, choice and compromise, detection of medication errors, prescriptions for unlicensed indications
- Drug adherence issues: patience compliance, feedback of treatment when failure
- Drug effects reporting: who, what, how, to whom
- Drug interactions: drug-drug, drug- food, drug- traditional medicines/alternate medicines, drug-concomitant disease
- Detection of Drug related mortality
- Detect use and abuse of medications
- Drug regulatory decisions: change drug labeling, change dose, restricted prescription, drug withdrawal, ban
- International: communication of safety information
- Donor policies: quality, date of expiry, dissemination issues

Key players in pharmacovigilance

(WHO, 2004, McNamee, 1996, Waller, 1998, WHO, 2002b)

Sustained close effective communication, collaboration, and regular flow of information, mutually supportive actions are the main features of the following partners:

Group component

1. Governments
2. Pharmaceutical Industry
3. Hospitals and academia
4. Medical/professional Pharmaceutical/Licensing and Drug Regulatory Associations
5. Poisons and Medicines information centres
6. NGOs /Research Groups
7. Media and communication agencies/Trade agencies/marketing agencies
8. World Health Organization and the Uppsala Monitoring Centre

Individual component:

Health care professionals

- Doctors/physicians/nurses/para medical staff

Patients/Consumers/end users

Figure 9: Key players in pharmacovigilance.

It is necessary that the community be involved to a greater extent right form inception stages in the formulation and implementation of pharmacovigilance as they are more aware of the feasibilities.

Basic functioning of pharmacovigilance system

Functions of the Pharmacovigilance system:(WHO, 2002b)

- Detection of Signals
- Assess signals for causality, frequency, distribution and identify risk groups
- Communicate safety information to regulators and decision makers

- Train professionals and public and propagate of rational, safe and cost effective medicines
- Assessment of benefit harm effectiveness and risk of medicines
- Timely detection and communication of safety concerns

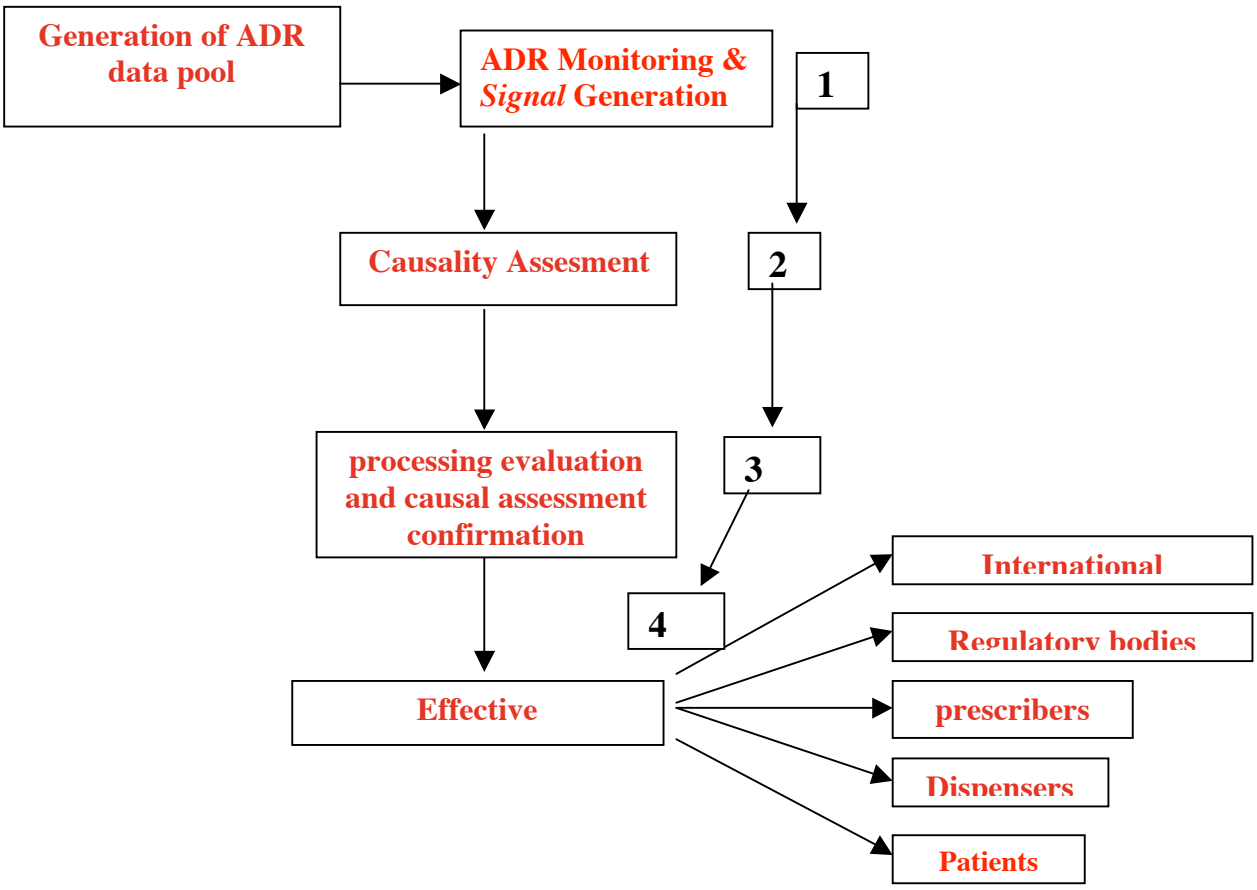


Figure 10: Structure and functioning of pharmacovigilance system.

1. ADR monitoring and *signal* generation

"A strong suspicion of previously unrecognized adverse reaction is termed as a signal" (Balkrishnan and Furberg, 2001, WHO) or it may also be defined as the "Reported information on a possible causal relationship between an adverse event and a drug, the relationship being known or incompletely documented previously" (WHO, 2002b). Usually more than one single report is required to generate a signal depending upon the seriousness of the report and the quality of information reported however even a "single" thorough report can qualify as a signal (Murphy and Roberts, 2005).

Pool resources for *signal* generation

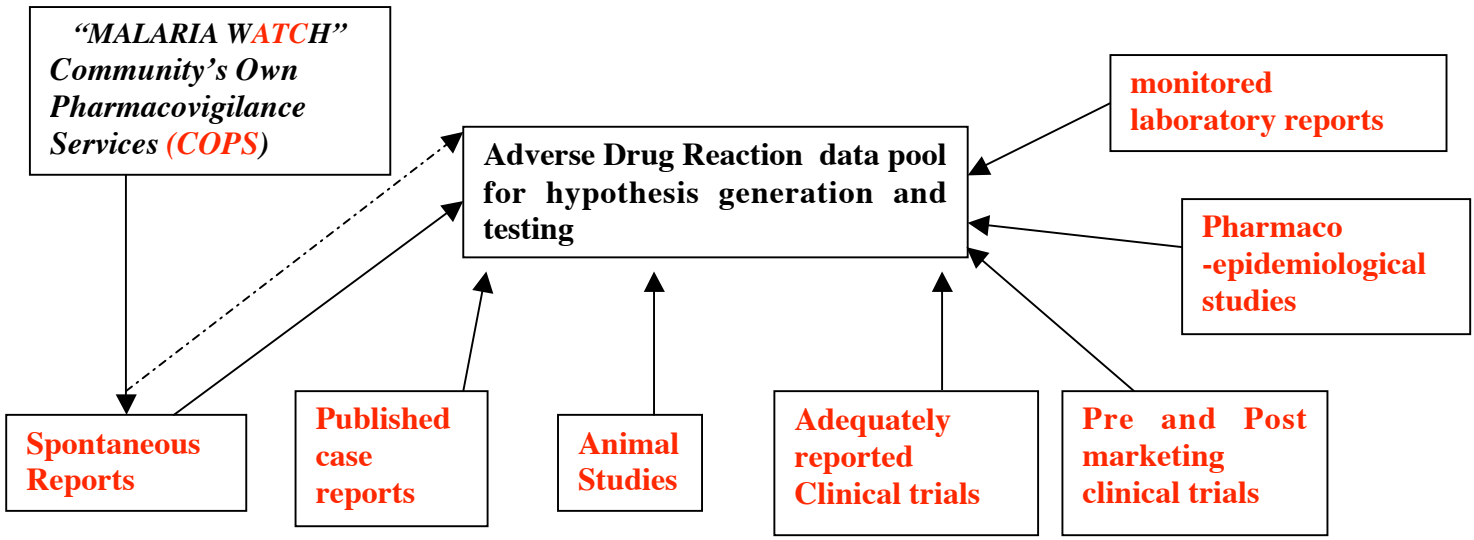


Figure 11: Pool resources for signal generation.

1a. Spontaneous reports (Talbot and Nilsson, 1998)

"Recording and reporting clinical observations of a suspected Adverse Drug Reaction (ADR) with a marketed drug is known as Spontaneous or Voluntary reporting" (Talbot and Nilsson, 1998). It is the basic and most common hypotheses generating tool for post marketing surveillance. The advantages of this system are, that it is available immediately post marketing, is a indefinite continuous process and covers all patients receiving the drug. however it is difficult to recognize previously unknown and uncommon ADRs. It does not confirm the hypothesis. But the main limitation remains gross under reporting (Lang et al., 2006). "Vigibase" the international Adverse Drug Reactions (ADRs) database maintained by the Uppsala Drug monitoring Center is currently holding more than 3.5 million case reports and is the largest Adverse Drug Reactions (ADRs) database available for online consultation to all the member countries. It uses the *Bayesian Confidence Propagation Neural Network* (BCPNN) to analyse the database. This method provides a quantitative measure of the strength of association of a drug/reaction combination (Olsson and Edwards, 2000).

Adverse Drug Reactions (ADRs)

There is no absolutely safe treatment (Simon, 2002). Drugs and other therapeutic medicinal

products can sometimes be dangerous and harmful even if they are very useful at other times, like a double edged sword (Hartigan-Go, 2002). Intelligence would recommend a wise use of a weapon with such immense potential. Although people are aware that drugs may have side effects, they usually believe that they are mild and rare enough that they will not happen to them, unless clearly warned (Waller et al., 2005).

Adverse effects terminology

Adverse Drug Reaction is defined as any noxious and unintended reaction that follows the administration of a medicinal product and that occurs at doses normally used in patients for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function (Simooya, 2005). "Adverse Event" is an untoward medical outcome attributed to the drug action and occurs when the patient is taking the drug but not necessary that there exists a causal relationship between drug use and the symptoms produced (Edwards and Aronson, 2000, Bavdekar and Karande, 2006).

Previously accepted terminology for reporting of Adverse Drug Reactions (ADRs) was the WHO's Adverse Reaction Terminology (WHO-ART), used along side the International Classification of Diseases terminology (ICD). Medical Terminology for drug regulatory authorities (MedDRA), is the new system accepted in USA, Japan and in the European Union. It includes term from WHO-ART, ICD9 and COSTART (Coding Symbols for a Thesaurus of Adverse Reactions Terms, which was used in the USA). International harmonization in the terms and classification used is extremely essential to achieve quick incorporation in national and international database.

Epidemiology of Adverse Drug Reactions (ADRs) and magnitude of the problem

Adverse Drug Reactions (ADRs) contribute significantly to the overall health expenditure with a few countries spending up to 15-20 % of their healthcare budget on drug related problems (Balkrishnan and Furberg, 2001, WHO, Hartigan-Go, 2002). In most countries and is one of the leading cause for hospital admissions (10-20%) and even mortality (amongst top 10 causes) (WHO, 2004). However due to variances in reporting they are not very apparently perceived. One in every 15 hospitalized patient in the US experiences a serious ADR (Balkrishnan and Furberg, 2001, Herdeiro et al., 2004). The European union reports more than 100,000 annual deaths attributable to Adverse Drug Reactions (ADRs) and over 2 million people experiencing other serious reactions (Herdeiro et al., 2004).

In the US, there is a 20% probability that in 25 years a drug acquired a [3]"black box" or was withdrawn. Drug labeling changes and withdrawals occurred in 50% of the drugs in the first 7 years and 2 yrs respectively. Hepatotoxicity is the single most frequent reported reason for drug withdrawal (Murphy and Roberts, 2005). The incidence of ADRs in developed countries with adequately functioning health systems are so significant and therefore with respect to developing countries it would be expected that they are at much higher for reasons discussed above. Thus ADRs are a serious problem in both the developed and the developing countries and require to be tackled with urgency.

ADR risk perception

Risk perception of Adverse Drug Reactions (ADRs) to a greater extent may influences the numbers reported. The perspectives of all parties involved in the processing of safety information varies greatly (Balkrishnan and Furberg, 2001). There is a major difference in the ADR risk perception between health and non health professionals as well which can severely compromise the selection of potential reporters (Bongard et al., 2002).

Percentage reported and identified reasons for under reporting:

51% of serious ADRs of drugs are not detected prior to their approval for marketing and so this demands greater support from the prescribers in assisting to detect these in the post marketing phase (Jarernsiripornkul et al., 2002). However, a common problem to all pharmacovigilance programmes is underreporting of Adverse Drug Reactions (ADRs) (Balkrishnan and Furberg, 2001). Even in Countries with high reporting rates only 10% of ADRs are actually reported (Herdeiro et al., 2004, Ferner et al., 2005, Morrison-Griffiths et al., 2003). ADR reporting is a part of good clinical practice and this is a grossly under-represented fact in medical and clinical professions (Hartigan-Go, 2002). Most clinicians consider pharmacovigilance as mere paperwork as against a part of clinical practice (Sjoqvist, 2000).

In a study conducted in the Netherlands, some of the reasons for not reporting ADRs were

[3] Black box warning is a warning issued by the US FDA which means that there is a reasonable evidence of an association of a serious hazard with the drug. A definite causal relationship to the drug does not have to be established. Placing the warning means that the adverse reaction may lead to death or serious injury. Usually the boxed warning is located at the beginning of the labeling so that it stands out and will be immediately seen by the prescribers, who can note the seriousness of the warning MURPHY, S, & ROBERTS, R. (2005) "Black box" 101: How the Food and Drug Administration evaluates, communicates, and manages drug benefit/risk. *J Allergy Clin Immunol,* 17**,** 34-39.

(Eland et al., 1999, Atuah et al., 2004):

- uncertain causal association
- too trivial to report
- too well known to report
- unaware of the existence and working of a national ADR reporting system
- did not know how to report ADR (lack of knowledge)
- too bureaucratic
- time constraints (35% thought reporting took too much time although simple procedure)
- concerned that report could be used in a legal case for damages by the patient

In general, reporting of Adverse Drug Reactions (ADRs) with older established drugs is fewer than the newer ones (Simon, 2002).

A theoretical model (Herdeiro et al., 2004) helps explaining the phenomenon of underreporting in a rather convincing way on the basis of intrinsic and extrinsic conditioning. It states that the information at disposal of the prescribers and their knowledge in respect to Adverse Drug Reactions (ADRs) moulds their attitude towards Adverse Drug Reactions (ADRs) reporting and this reflects in their reporting practices (*Knowledge-attitudes-practice)*. This in turn is influenced by the daily interaction of the prescriber with the patients, the administration and the pharmaceutical industry and the need to maintain harmonious relationship with all. This can be rightly explained by the *satisfaction of needs theory*. This results in *selective perceptions* of importance of adverse drug effects and its reporting and thus conscious /unconscious drug surveillance that is based more on demands than any other element (Tavassoli et al., 2005). A study conducted in the department of internal medicine in France identified that the *drug time* defined as the total time spent by the doctor to investigate drug intake and assessment of Adverse Drug Reactions (ADRs) thereof was very low compared to the total *visit time* of the patient. It will be useful therefore to conduct baseline surveys before the introduction of a pharmacovigilance system to have an insight into the reasons for underreporting so that adequate prophylactic measures can be taken.

Inculcating the culture of reporting

Safety monitoring should be an integrated aspect of good clinical practice (WHO, 2004). Accurate estimates for ADR are essential in weighing the risk and benefit of drug treatment

in post marketing use (Aronson et al., 2002)**.** Continuous and simultaneous verbal and visual reminders caused a five fold increase in the figures. Regular repeated interventions are required to stimulate the prescribers (McGettigan et al., 1997). It is reported that Doctors often fail to report ADRs to a required extent despite financial incentives or compulsory regulations (Herdeiro et al., 2004). It is important that all prescribers be adequately sensitized from time to time for the importance of ADR reporting.

Drug reactions from non conventional medicines when used individually and as parallel concomitant therapy

A study conducted in the Philippines reports that despite the unpopularity for traditional medications in western medical culture, people do resort to these treatments and the Adverse Effects (AE) from the use of these herbal medications are rarely reported. Partly because they are poorly understood, not formally recognized, sometimes perceived as a part of the healing effects and it will be less likely that the prescribers will come forth to report these (Hartigan-Go, 2002). People more likely to access alternate medicine are also less likely to report adverse effects experienced (Hartigan-Go, 2002). It is specially important to study the interactions between the concomitant use of traditional and herbal medications and the conventional medicines for important drug-drug and drug-substance interactions in the post marketing phase as these may significantly influence the safety and efficacy of the drug.

All in all it can be said that the most challenging issue in pharmacovigilance is the generation of comprehensive data pool which can assist in signal generation.

1b. Cohort studies (Talbot and Nilsson, 1998)

Comparative cohort studies to monitor the incidence of Adverse Drug Reactions (ADRs) are a potential tool for general hypothesis generating and testing. However this is ineffective for signal generation and carries *signal* vs *noise* problem.

1c. Post marketing randomized trials and epidemiological studies (Balkrishnan and Furberg, 2001, WHO, 2004, McNamee, 1996, Lang et al., 2006**)**

In the post marketing phase the focus shifts from safety and efficacy of the drug to the risk and benefit of prescription. Phase IV trials are helpful to detect and quantify the Adverse Drug Reactions (ADRs) which are not detectable with pre-marketing clinical trials so as to

identify the true risk profile of the drug. They help in monitoring of *still evolving* treatments in *real life situations* and investigate the efficacy of the drug in conditions where the drugs are taken unsupervised. It can be useful to watch for drug interactions and disease interactions with and other concomitant medical conditions. In the view of resistance issues, phase IV trials can assist in early detection thus making them an indispensable tool in safety monitoring post marketing. Ideally drug monitoring for the first 2 years post marketing can yield substantial information due to rapid increase in number of people using the drug.

1d. Electronic medical records

Electronic medical records (EMR) help improve Adverse Drug Reaction (ADR) detection, (Hannan, 1999). Data drive is a fundamental tool for continuous review of clinical data and identification of patterns, alerts so as to generate appropriate responses and also assist in rapid dissemination of information to a large geographic area (Allman et al., 2006). Datamining techniques, registries and sentinel reporting systems can also be potential signal generating tools.

Ie. Published case reports (Talbot and Nilsson, 1998)

In 1951 Leopold Meyler published the first book of 192 pages devoted to the description of unwanted drug effects in Dutch called *"Schadelijke Nevenwerkingen van Geneesmiddelen"* A year later, the English version *"Side Effects of Drugs"* was published by the then Elsevier Publishing company which then became the Meyler's *Side Effects of Drug* completed *by an annual up to date, Side Effects of Drugs, Annual (SEDA)* (Aronson et al., 2002). Published case reports are an established and time tested effective method to communicate Adverse Drug Reactions (ADRs) information however there is a potential delay in the occurrence and the reporting and not all reports can be published. Publication of safety information depends mainly on editor discretion and reporting exclusive drug safety information can be a challenge as very few journals are devoted entirely to Adverse Drug Reactions (ADRs) (Aronson et al., 2002). Internet sources and online journals can be of help in getting safety articles published (Balkrishnan and Furberg, 2001).

The most important aspect is not just the availability of these tools but the adequate utilization (Lumpkin, 2000).

The basic principle of pharmacovigilance is the detection, management and communication of drug risks to users and prescribers alike (Lumpkin, 2000). Drug risk detection includes

collection information pertaining to Adverse Drug Reactions (ADRs) of all new and old drugs on market and preferably all herbal and traditional pharmaceutical substances and presenting them in a format that is easy to comprehend, analyze and communicate both locally, nationally and
internationally. As seen in the discussions above it is evident that obtaining Adverse Drug Reaction reports is a challenge. Large efforts are needed from professionals and community members to collectively accumulate information and generate databases.

2. Causality assessment

There are a range of reasons and triggering factors that can lead to Adverse Drug Reactions (ADRs). Non causal associations are far more common than the causal associations in the field of Adverse Drug Reactions (ADRs) (Lawson, 1997). It is necessary therefore that adequate care is taken to rule out all possible confounders when investigation drug profiles. Large pre-recorded datasets can be ideal solutions to differentiate true drug related reactions and reactions due to other causes (Lawson, 1997).

Following are the reasons that can also give rise to Adverse Drug Reactions.

1. Errors in drug diagnosis and prescription
    - Adequate appropriate diagnosis
    - Assessing need
    - Selection of correct drug according to the indications and contraindications
    - Dose adjustment
    - Communication of regimen
2. Errors in dispensing, transcription errors
    - Reviewing the order
    - Processing the order
    - Dispensing the correct drug
3. Errors in patient administration and compliance
    - Right drug to the right patients
    - Adequate instructions for regimen
    - Ensuring that instructinons are followed
4. Pharmacological and physiological factors
    - Monitoring and documenting patient response
    - Identify AE and incorporate it as differential diagnosis

After the pioneering work of N.S Irey in 1974, about 20 methods for causality assessment of adverse drug events at an individual patient level have been proposed which roughly belong to three categories namely expert judgment, probabilistic approaches and algorithms(Arimone et al., 2005). Expert judgment or global introspection (WHO), all relevant available information is taken into account and an opinion expressed by an expert about causality. It is, in a way, similar to clinical diagnosis and lacks standardization. According to the global introspection method there are 6 levels of imputation: certain/definitive, probable, possible, unlikely, conditional and unclassifiable (Macedo et al., 2003). Almost all probabilistic approaches are based on *The Bayes' theorem*. In the absence of any relevant information it suggests a neutral estimation. Algorithms are simpler and assess successive criteria to arrive at a score or may use problem trees (Arimone et al., 2005). A new computerized method has been proposed based on the logistic function to model expert judgment and a scientific weighing using a multilinear regression and may make causality assessment easier (Arimone et al., 2005). In special situations biochemical markers and monitoring of laboratory reports may also assist in Adverse Drug Reaction(ADR) causality assessment (Talbot and Nilsson, 1998).

Identify AE and incorporate it as differential diagnosisTo confirm the suspected medicament and in assessing causality it is essential to probe that the drug prescribed was ordered, received and also the one taken by the patients at the correct dose (WHO, 2002a). Based on coroners reports one in 2000 deaths could be attributed to prescribing or administration errors (Hannan, 1999). More often herbal, traditional products and over the counter medications are not perceived as medicines and this makes it more important to probe the use of these products when investigating any Adverse Drug Reactions (ADRs).

3. Processing, evaluation and causal assessment confirmation

Blessing in Disguise:

The World Health Organization (WHO) now recommends that acute uncomplicated *Plasmodium falciparum* malaria should be treated with effective artemisinin-containing combination therapies (ACTs).[4] In response to changing conditions and emerging challenges with malaria treatment many African countries have changed their National Drug

[4] http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf

Policies and have initiated the use of artemisinin based combination therapies as first or second line treatments as per the WHO guidelines. Artesunate (AS) combined with amodiaquine (AQ) is currently one of the most widely used ACTs. As of April 2006 (data provided by WHO) 60 countries have adopted and 33 are implementing ACTs worldwide. In Africa, 15 countries have adopted AS+AQ as first line treatment (Burundi*, Cameroon, Côte d'Ivoire, Democratic Republic of Congo, Gabon*, Ghana*, Guinea, Liberia, Madagascar, Mali, Senegal*, Sao Tomé & Principe*, Sierra Leone*, Sudan (South)* and Zanzibar* - implemented by countries with *). Elsewhere, Indonesia has also adopted and implemented AS+AQ. However since many of these countries do not have adequate/robust national drug policies or pharmacovigilance systems in place the introduction of *Artemisinin based Combination Therapy* (ACT) at this time can be viewed as an excellent opportunity to formulate these systems where absent and strengthen the ones that are currently present (WHO, 2004). This simultaneous effort can assist building up of sustainable Infrastructure for future drug monitoring.

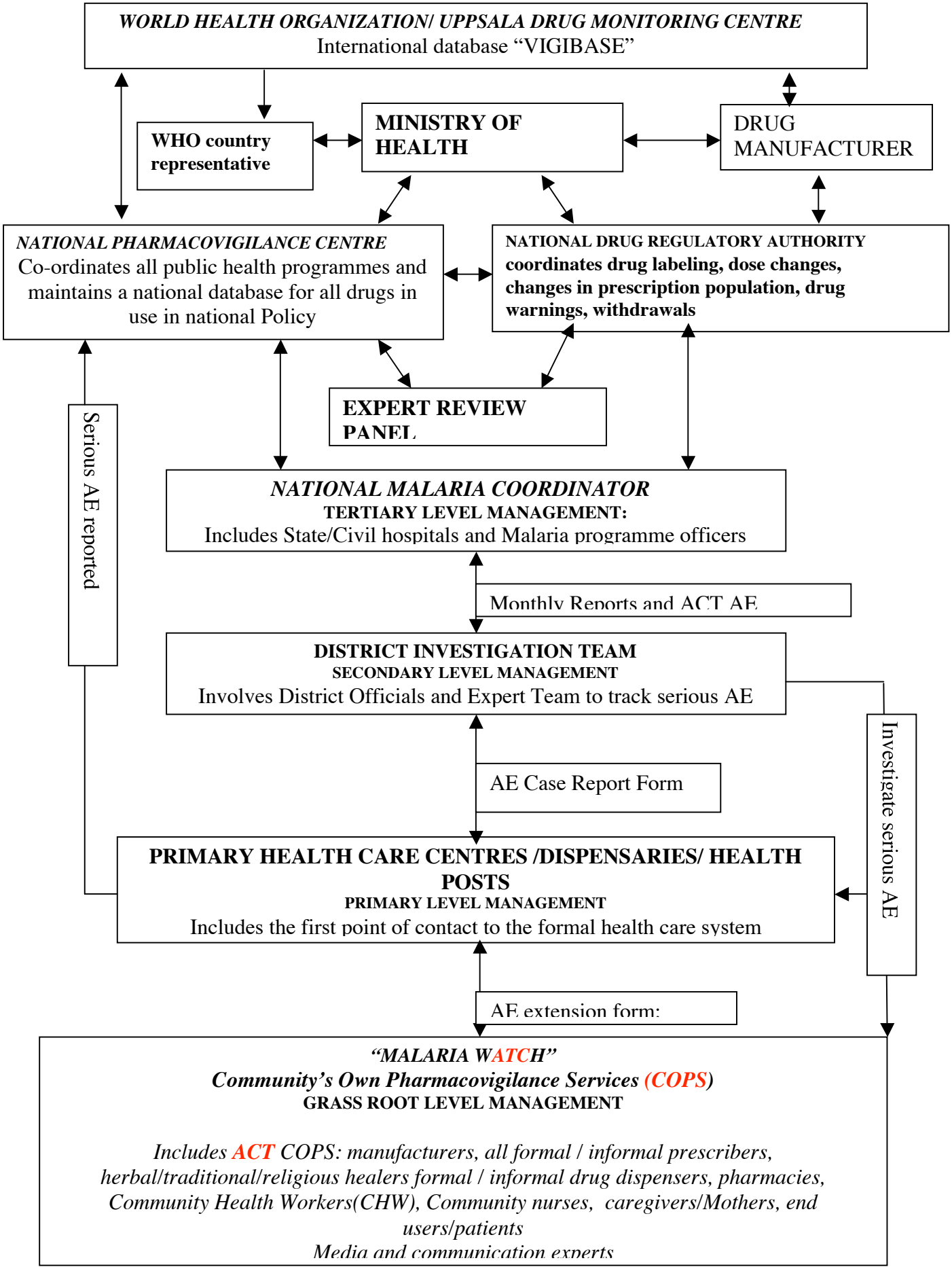


Figure 12: ACT Pharmacovigilance System

Facilitated referencing and assisted reporting: community involvement in signal detection

Community participation is the process by which communities influence decisions and resources that directly affect them (RBM, 2002). The basic principle of health promotion lies in individual education to achieve individual empowerment followed by effective social mobilization to eventually acquire successful community empowerment with greater awareness and informed decisions. In order to ensure total coverage of the population the most effective mechanism as proved in the past is to involve the "people" themselves (lectures, DTMPH-Berlin). Community based approaches compliment the formal health care sector and should be regulated, supervised and guided by the formal systems (RBM, 2002). Since a number of problems have been identified in the professional community reporting Adverse Drug Reactions (ADRs) adequately, an effective way to deal with large scale underreporting would be to target patients and potential future end users directly through community outreach projects. Community based health care initiatives are the basic systems that function as the lifelines, capable of reaching and working in the interest of the poor, isolated rural populations and these should be sufficiently utilized (RBM, 2002). In order to facilitate the reporting of adverse effects through community participation we propose a pictorial extension for the standard adverse effects form. This will assist in including the non literate part of the community in the pharmacovigilance efforts.

"Malaria WATCH" a holistic bottom to top approach

"Partnership is a collaborative relationship between entities to work toward shared objectives through a mutually agreed division of labour" (RBM, 2002). A consolidated effort should be made to involve and bring together all community based key persons and activists for active drug surveillance under the umbrella term "Malaria WATCH" "Community's Own Pharmacovigilance Services (COPS)". This will include pharmacists, community health workers, paramedical staff, midwives, traditional birth attendants, traditional healers, drug vendors, herbal prescribers, community nurses, religious healers and all other potential non-formal prescribers/sellers of antimalarial drugs irrespective of their educational background to form a community based referral system. All of them should be assigned status of "***ACT COPS***" and be registered with the first formal contact with the national health care system such as a peripheral health

post or a dispensary. It is a challenging job to arrive at a consensus for the training and supervision of such a diverse group for pharmacovigilance activities.

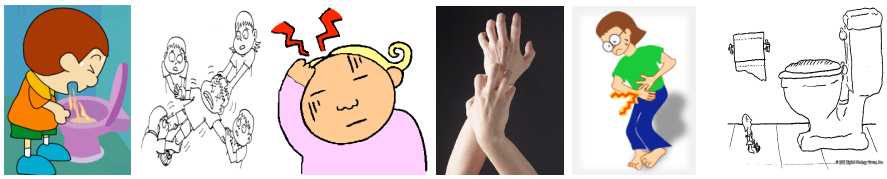
Proposed pictorial Adverse Effects (AE) Case Report Form (CRF) extension

Case report forms are the most crucial link in Adverse Drug Reaction reporting and documentation. In order to improve the reporting by informal health care sectors and personnel with educational constraints, visual representations of Adverse Effects (AE) forms would be helpful (Lang et al., 2006). We propose an additional component of the standard adverse drug reaction (ADR) Case Reporting Form (CRF). An annex that can be given to the patient for reporting or retained by the informal drug prescriber in order to assist in improving the reporting rate. This pictorial adverse effects (AE) report form will contain probable/possible and confirmed common adverse effects of amodiaquine and artesunate and will be attached as a perforated extension. It will also bear a sticky back so that when the patient comes back with this form it can be stuck on the back side of the formal adverse effects (AE) form and have the patient description on it. A formal health care worker like a community nurse, hospital nurse, general practitioner, specialist will be responsible to complete the standard adverse effects form on the basis of the information from the pictorial form.

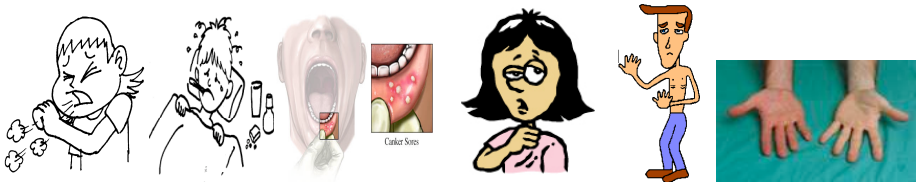
The Adverse Effects (AE) form should aimed to reach every consumer and efforts should be directed at effective system to monitor this. In the formal health care sector this can be achieved directly by the prescribing doctor/physician/specialist hand over the pictorial extension to the mother or the caregiver and ensures that it comes back to him at the end of the treatment. In the informal health care sector an effective mechanism of reaching all possible users is to provide it with the drug itself as an "*drug insert"* in the packaging. It is essential that the non formal health care community workers are trained in the use of the pictorial Adverse Effects form and its importance in facilitated reporting.

Adverse Effects (AE) Case Report Form (CRF) pictorial extension: to be detached and delivered to drug user in formal health care and a drug insert in field distribution

IF YOU OR YOUR PATIENT SUFFERS FROM ANY OF THE ABOVE SHOWN SYMPTOMS AFTER TAKING THE DRUGS PLEASE CONSULT THE NEAREST HEALTH POST OR DIRECT THE PATIENT TO BE TAKEN TO DOCTOR ALONG WITH THIS FORM.



VOMITING	CONVULSION	HEADACHE	ITCHING	STOMACH-PAIN	DIARROHEA



COUGH	FEVER	MOUTH-ULCER	SORE-THROAT	WEAKNESS	PALE SKIN

(Tick whatever applicable and make a note of the number of times or duration of time you felt the symptom and the time from first intake of medication)

Figure 13: Proposed 'AE CRF Pictorial extension' / 'Drug insert'.

"Community's Own Pharmacovigilance Services" (COPS)

Integrating manufacturers

Pharmaceutical companies can be actively involved by training them in implementation of good manufacturing practices. Monitoring of substandard drugs through standardized supply chain management of drugs to aid detection of counterfeit drugs can also be assisted by the manufacturers. They may be asked to report results of surveillance studies from the first two years of post marketing phase mandatorily to complete the registration procedures (Lang et al., 2006).

In order to increase the rate of Adverse Drug Reactions (ADR) reporting they can assist through their medical representatives in constant verbal reminders to professional prescribers for reporting ADRs. Pharmaceutical companies usually provide accessories like pens, mugs, stethoscopes to prescribers and these can be used to advertise visual reminders for reporting and also for highlighting 24hrs national hotline numbers for pharmacovigilance. Pharmaceutical companies can also be part or whole financers for the community efforts for drug safety monitoring.

Integrating prescribers: special focus on informal health care providers

One of the main challenges in developing countries is the integration of non-formal health care professionals. Initially, it is necessary that we identify persons who are actually prescribing the drugs outside of the formal health care system. 12-82% of malaria episodes in Africa are managed outside the formal health care sector primarily because of scattered populations living in remote areas. 40-60% of the drugs are dispensed in the private sector with unofficial sources like street sellers and market stalls accounting for upto 25% sales (RBM, 2002). In Africa 60-80% antimalarials are dispensed over the counter by minimally or untrained staff (Lang et al., 2006). It is necessary therefore to include these prescribers in pharmacovigilance activities. Formal recognition may work as an incentive for them and since they have strong local networks resistance to pharmacovigilance activities can be minimized (UNICEF. and WHO., 2006). They are often the more trusted health care dispensers in the society. They are culturally accepted and recognized by the community and hence play an important role in reaching the un-reached. Adequate training and awareness generation amongst them for the correct and rational use of *Artemisinin based Combination Therapy (ACTs)* is the most important issue however this can be a major challenge due to the variances in educational levels. It depends mainly on the type of

dispensing policy adopted by each country. If *Artemisinin Combination Therapy* (ACTs) are to be dispensed only through formal health care systems for various reasons like dose, resistance, compliance issues then informal prescribers can act as an important *referral system*. However adequate incentives have to be proposed to keep them in the system (UNICEF. and WHO., 2006). If they will dispense the drugs, now since the co-formulations are soon to be available, it will be necessary that they be trained with these drugs. They will dispense the drugs anyways and so it is worthwhile to include them in the system and work with them. They also need to be trained with the use of the pictorial Adverse Effects form to facilitate Adverse Drug Reactions (ADRs) reporting. Once they recognize their role and importance in the system it works as an automatic incentive(UNICEF. and WHO., 2006).

Integrating caregivers

This is a very broad term and in a way will include all people caring for the patient.

Mothers:

They are usually the first contact for the children and also the first ones to recognize *"signals"* from the child. Training mothers to detect Adverse Drug Reactions (ADRs) can be very useful in overall detection rates. In the community management of malaria, mothers play an important role and are trained to detect the signs and initiate treatment (UNICEF. and WHO., 2006). Reductions in mortality of up to 40% have been reported with these mother targeted interventions (RBM, 2002). Similarly training mothers to detect Adverse Drug Reactions (ADRs) can be crucial in detecting and confirming the causal associations between drug intake and symptoms. Clusters of households can be asked to elect a mother representative who will be trained in drug dose, administrations, compliance, determining causal association and recognizing Adverse Drug Reactions (ADRs). She in turn will pass on skills and knowledge to the cluster mothers and ensure that each suspected reaction is reported and investigated when required (UNICEF. and WHO., 2006). She can also be educated about the use of the pictorial AE form and can facilitate referral to health post in case of suspected reactions.

Similarly other family members or care givers can be eventually integrated in the cluster gradually.

Teachers:

These are the literate sections of the population and also well respected in the community. Besides having close contact with all parents, they also have some form of authoritative role in the society. They can be ideal people to educate and assist in awareness generation amongst the community members about the importance of reporting Adverse Drug Reactions (ADRs).Teachers, are usually engaged in the demographic or sentinel surveys be it electoral or population census and are familiar with the procedures of documentation. They can also be voluntary key persons in archiving of AE forms under supervision of the formal health care worker.

Community nurses an essential link between hospitals and communities:

Nursing staff are the largest part of health care system and serve as a crucial link between patients and doctors as well as health care settings and the community. They are the potential valuable source for effective pharmacovigilance if rightly tapped and utilized (Morrison-Griffiths et al., 2003). They can be trained in detecting, managing Adverse Drug Reactions (ADRs) as well as educating the society about the importance of reporting through mediated direct interactions through house to house visits. They can be responsible to transform information from the pictorial Adverse Effects (AE) form into the formal Adverse Effects (AE) forms.

Integrating patients

It is necessary that the end user be targeted with information with what potential risks exactly he is being exposed to (WHO, 2002b). It has been noted that patients do not report all symptoms they suspect to be ADRs to their General Practitioners (GP) and they in turn do not record all symptoms that may have been reported to them and hence “patient initiated surveillance” like the ones used in USA and Germany can contribute to increased ADR reporting. (Jarernsiripornkul et al., 2002). Patient reporting can be a very effective hypothesis generating tools and methods that will help patients to report need to be developed (Pirmohamed and Park, 2002) The pictorial Adverse Effect form can assist in visual reminder to the patients and motivate them to take an initiative to report the Adverse Drug Reactions (ADRs) experienced by them. The advantage with it remains that it can be used by the literate and the not-literate alike.

Non Governmental Organizations (NGOs)

Usually they have dedicated grass root level staff. They can be potential partners in pharmacovigilance activities since they have baseline understanding about the functioning of the community and have staff with a minimum defined education level. They can assist in facilitating referral to health care centres. Besides financing they can also lobby significantly in decision making processes since they are usually recognized by the governments and regulatory authorities. Integrating them would mean sharing of resources and avoiding duplication of work which is an important aspect in resource poor settings (RBM, 2002). International Humanitarian Aid agencies often provide a significant proportion of primary health care in most developing countries and they can be effective pharmacovigilance partners.

Awareness amongst other key persons

Other members of the society such as the village chiefs, religious leaders, shopkeepers, political figures, entertainment industry and media persons can play a vital role in generating awareness and educating the society for the importance of pharmacovigilance. They can be used to address the masses about the new drugs, the correct use and also give them insight into the responsibility of reporting unwanted drug reactions however mild they are. Influential persons can also assist in regulating the system and aid in decision making processes.

The community approach essentially should be decentralized in terms of power and finances (RBM, 2002). Participatory efforts and collective decision making processes are sustainable and bring a sense of control amongst the community, as seen from the *Bamoko* initiative which was implemented in Senegal in 1992 that accelerated the health primary health care through active community participation and recognizing them as essential partners. Using local networking instead of aiming at one big national structure to begin with can be a sustainable concrete feasible step (Bavdekar and Karande, 2006)

Thus, all the community players will act as facilitators for directing all patients and ADRs to the formal health care sector.

Primary level management of ADR forms

All the pictorial AE forms should reach the first contact point to the formal health centre like the *health post* or the *dispensary* which has a government appointed health staff.

What should be reported? (WHO, 2002a, Lang et al., 2006)

All suspected reactions with new drugs irrespective of seriousness and the serious and previously unknown reactions with established medications should be reported. Increased frequency of a particular reaction, any drug-drug, drug-food, drug-traditional therapeutic substance interactions, reactions with withdrawal of the drug should be reported at the earliest possible opportunity.

All technical formal Adverse Effects (AE) forms will be filled at the primary health care centre or the dispensary and causality will be assessed by the trained heath care staff. The peripheral staff should be provided with concrete guidelines for approximate causality assessment. Since most of the malaria cases are detected and treated at the peripheral level, this is the most important source of information. It will be fruitful to recognize valuable contributions by staff through citation on websites or in newsletter and also highlight *zero reporting* to build reporting culture and to motivate individuals at the peripheral level (Bavdekar and Karande, 2006). Another important aspect is facilitate infrastructure and logistical support like internet facilities at peripheral centres to improve program coverage and rapid communication (Bavdekar and Karande, 2006).

The forms should then be forwarded to the district hospital for archiving and if required investigating.

Secondary level management: District Investigation Team and data-mining

The District Investigation Team (DIT) should be a team of experts who will review the forms from the peripheral centres and will transform the data into electronic versions and prepare monthly reports. These monthly reports should be transferred to the national malaria control programme officer.

<u>After signal detection:</u>

Once a signal is detected the database is scanned for possibly additional cases reported , medical literature and the international agency reports. An effort is made to identify if any common trends, common risk factors, dose response relationships, consistency of association and specificity of association (Murphy and Roberts, 2005). Once confirmed the District Investigation Team (DIT) will be responsible for investigating all the signal reports and confirming causality.

Tertiary level management: malaria control programme officer

The malaria programme officer should be responsible for the archiving information and maintaining the database. The database should be reviewed quarterly for signal detection and from time to time as per the feed back from the district investigation Teams. The paper based data in the district health centres will serve as a backup for this large database.

National pharmacovigilance centre and the national drug regulatory authority

The quarterly reports from the national malaria officer will be reviewed and discussed by the national pharmacovigilance centre. The national level is better to detect *signals* as the number of patients and thus the number of ADRs are significant to draw conclusions.

This will be responsible to maintain databases of all drugs used in the national system and all national public health programmes. They should work in close coordination with the national drug regulatory authorities for decision making. The national drug regulatory authority will implement the action suggested by the Safety expert Review panel and communicate the decisions to the Ministry of Health and also the drug manufacturer.

Safety expert review panel

This should be an autonomous body which will be consulted for an opinion on the signals detected and the management of the risk. Ideally should consist of a clinical pharmacologist, a physician, internal medicine specialist, a specialist with regard to the drug in question for example a Paediatrician, Oncologist etc. and a pharmacist. These specialists will be crucial in deciding the fate of the drug and so carefully selected individuals with objective assessment skills should be employed. The expert review panel will advice the National Drug Regulatory Authority about changes in dose, treatment population, changes in drug labeling or regulatory action warnings and withdrawals.

The Ministry of Health will issue public health notices, dear doctor letters and also inform national and international community about drug status through press releases and through the Ministry of Information and broadcasting. They will also be responsible to convey the findings to the World Health Organization (WHO) country representative who will further it to the Uppsala drug monitoring Centre. All centres can report alarming or critical Adverse Drug Reactions (ADRs) to national centre to facilitate quick response generation.

The role of national drug policies

Besides ADRs other medicine related problems such as drug abuse, misuse, poisoning, therapeutic failures and medication errors also need to be detected and solved (WHO, 2002a).

All medicines have potential benefit and risk ratio, the challenge is to build an inverse proportionality between these measures and more importantly assess them from time to time throughout the lifespan of the drug. Some of the effort lies in the rational use of potent, quality, safe and efficacious drugs (WHO, 2004). A robust and consolidated national drug policy when regularly monitored and evaluated can play a crucial role in pharmacovigilance through legislative drug monitoring, provision of up to date Adverse Drug Reactions (ADRs) to prescribers as well and ensuring adequate functioning of pharmacovigilance through assessment of outcome indicators at a regular basis (WHO, 2004). However drug policy or its regulation is missing in around one third of WHO's member states (WHO, 2001). The WHO has made substantial efforts to harmonize drug regulation through efforts such as the International conference on Harmonization (ICH) and the South African Development Community (SADC) to arrive at an international consensus on quality, safety and efficacy standards of drugs (WHO., 2006).

Education and training

It is an essential component for effective pharmacovigilance. Education and information can contribute to effective monitoring of ADR reporting and can result in increased reporting (Hartigan-Go, 2002).The main principle should be to teach, train and enable to detect and manage ADRs at all levels of the community. Regular training in the form of workshops, courses and scientific meetings at regular intervals as seen in the French system proves to be effective (Balkrishnan and Furberg, 2001, WHO). It is necessary that all grass-root level training involves material that is self explanatory with pictorial depictions because of variances in the educational levels. At the formal health care level it should be mandatory that all staff undergoes refresher courses and Continuing Medical Education (CME) classes to be aware of the trends in pharmacovigilance. They should be trained to accept reporting as part of good clinical practice. There is marked variance in inter and intra country university studies and so suitable changes in undergraduate and postgraduate training curriculum is mandatory to achieve uniformity and also train students to scrutinize scientific material for relevant information (Herdeiro et al., 2004).

Standard operative procedures and manual thereof

It is necessary that all relevant procedures be described in detail in the standard operating manual. This document should contain all information regarding the system of pharmacovigilance, its functioning, identified level and functions. It should also have clearly defined roles and responsibilities and clearly mention the pathways of communication and mechanisms for feedback. This is very important in terms of maintaining the standardized working and avoid discrepancies of interpretation by individuals. It should describe flow charts for decisive actions to be taken in any unexpected situations and also mention the procedures for lab monitoring. Instructions on data maintenance, ADR forms, logistics, archiving and processing should be addressed efficiently.

4. Communication of safety information

The *Erice Declaration* drawn up at Sicily September 1997 for effective communications in pharmacovigilance calls upon all the key players from administrators to consumers to ensure highest professional and scientific standards in promoting safe use of medicines. Honesty and accountability has also been highlighted in communication of safety information. The aspects of the declaration is end user awareness about the facts and assumptions of the safety profiles of the products they use (WHO, 2002b).

Ideally communication should be

- informative
- accurate
- not: false, misleading or promotional
- should be based on human experience whenever possible
- should include following sections: Indications and use, Contraindications, warnings, Precautions and Adverse Drug Reactions (ADRs)

A simple and easy to read newsletter or an information bulletin can be helpful for providing feedback information to all partners involved. It can include a brief analysis of spontaneous reports but also general data from literature.

Drug labeling

A drug label is a legal document and is a "written, printed or graphic matter on the immediate container of the drug product or that which is accompanied with the product

(packing insert or product information)". It is the summary of the scientific information for the safe and effective use of the drug. The Summary Product Characteristics (SPC) may contain information and guidelines on monitoring of Adverse Drug Reactions (ADRs) (Ferner et al., 2005). This is the first and direct communication of safety information to the users and so utmost care should be taken to disseminate the right amount of warning without scaring the patients. It will be interesting to evaluate consumer attitude to these drug inserts and the impact on non-literate users.

The role of Media

Media has wider coverage as compared to medical journals and is a vital tool to reach the users and the prescribers alike. Transparency in drug information communication is an essential aspect of pharmacovigilance to ensure consumer empowerment and to enable them to take completely informed decisions (McNamee, 1996)**.** Media, when well balanced can be a vital link of communication (Waller et al., 2005). The knowledge, attitude and the approach used by journalists is also an important aspect (WHO, 2002b). It is extremely tricky to assess the time when information about a potential hazard under scrutiny be disseminated. Patients may be deprived of useful medications if the alert is early in time or is before confirmation of the hypothesis and may be exposed to unnecessary risks if the information comes too late (Talbot and Nilsson, 1998). In areas where there is low or absent awareness about new treatments and safety monitoring, often there is a misunderstanding that the people are being used as guinea pigs and media can play a crucial role on delivering the correct messages (Simooya, 2005).

It is important to note that absolute risks are usually perceived to be higher than relative risks and so care should be taken in communicating messages. Also it is essential to carry the message that readers/viewers are advised not stop taking the medicines without consulting their physicians even if adverse effects have come to light (Waller et al., 2005). Sometimes the balance between benefit and harm can be wrongly interpreted as commercial benefit Vs harm to patients. Communication mishaps are potential threats. It is also essential that the right message is received by the right population and more importantly by the target population. Before declaring the communication successful it must be ensured that the message was received completely , well understood and acted upon. (Balkrishnan and Furberg, 2001). For example the *thalidomide* tragedy, *thalidomide* was introduced in 1957 and withdrawn from market in most countries by1965 due to its teratogenic effects.

However due to its continued use in treating leprosy, 34 cases of *thalidomide embryopathy* were reported between 1969 and 1995 in leprosy endemic areas (WHO, 2004). Safety information communication should use simple language and standardized terminology and should bear in mind the socioeconomic, cultural and educational background of the targeted audience (Balkrishnan and Furberg, 2001, WHO, 2002b). In Philippines and the Australia videos and television programmes are used to generate ADR awareness and to boost reporting(WHO, 2002b). Other methods include newsletters, advertisements, electronic bulletins etc. Most importantly all information should be most objectively represented.

Suggested methods for outcome information dissemination (WHO, 2004):

- Targeted Education and Outreach: Dear Healthcare professional, Dear Doctor letters, Reminder systems: prompt, reminders, newsletters
- Performance Linked Access Systems linkages to laboratory testing or other documentation
- Media messages , patient information leaflets, Medicine Alerts

Herbal medications and traditional medicine

Herbal and traditional medicine are an important and preferred element in primary health care in the Asian, African and Central and South American continent mainly due to accessibility and affordability besides being an integral part of their belief system ((WHO, 2001). Complementary and traditional medicine is increasingly being accessed in Europe, Australia and North America for care in chronic diseases as parallel healthcare. Mutual cooperation, communication and support amongst the different medical systems is indispensable in holistic health care delivery and hence integration of all forms of health care systems is necessary when formulating a conventional drug and other medicinal products policy (WHO, 2001). Traditional medicine can be misunderstood to be completely safe due to the long tradition of use and the concept that natural is always safe. Recent reviews have proved these belief as false (Hartigan-Go, 2002).

Recognition and Integration of complementary and alternate medicine in mainstream healthcare:

The *WHO Traditional Medicinal Strategy 2002-2005* aims at integrating these parallel form in mainstream national health care policies and thus resolving some of the emerging challenges regarding the safety, efficacy, quality, access, rational use and monitoring of these form of healthcare products. *The legal status of Traditional Medicine and*

Complementary /Alternative Medicine summarizes the legal status of traditional medicines in 123 countries.

Changing needs and emerging challenges

(Balkrishnan and Furberg, 2001, WHO, 2001, WHO, 2004, WHO., 2006, WHO, 2002b)

Traditional pharmacovigilance systems focused on detection of serious life threatening Adverse drug effects, however, it is clear now that more attention need to be paid to the common mild symptomatic Adverse effects (Aronson et al., 2002).

As the advances in communication mechanisms and systems improve they can be a boon in effective communication of safety information. More often it emerges as a nuisance since the regulatory systems often lag behind. Some of the challenges that can be identified for the modern pharmacovigilance systems are as follows:

- overburdened health systems in developing countries mistakingly view pharmacovigilance as a added burden both financially and logistically, challenge to convince and self realization by the countries .
- direct To-consumer aggressive advertising
- increased willingness of patients to take new medical treatments
- limited scope of current global information dissemination systems
- speed at which pharmaceutical situation changes: increasing range and potency of medicines
- Globalization, consumerism
- free trade and communication across national and international borders
- increased use of internet , illegal sale of medicines over internet
- non prescription medicines becoming increasingly available for general use
- doctor and health professional to patients ratio in the developing countries is a major challenge in implementing safety monitoring through formal health care.
- increasing pressure for higher standards of performance
- irrational and unsafe drug donation practices
- increased manufacturing of counterfeit and substandard drugs and smooth seepage into drug markets
- increasing use of herbal and traditional medicines as a threat to drug-drug interactions and poly-pharmacy issues

All of the above factors contribute to the changes in the way people access medicinal products and vital information about the use.

VII. Conclusion

The artemisinin combination therapy artesunate and amodiaquine has proved to be safe so far and no serious adverse effects have been reported. No drug resistance or reduced efficacy has been identified either. However before the large scale deployment of the drug for use in Africa in view of the expected coformulation there are certain mandatory prophylactic steps that need to be taken to ensure its rational use and to protect it from resistance . An essential step will be a functional pharmacovigilance system to effectively monitor the drug throughout its therapeutic lifespan for both efficacy and more importantly safety.

- Efficacy and safety are two indispensable drug profiles that unless thoroughly investigated and described can lead to major policy related implications. Efficacy is more or less considered more impressive parameter and important indicator as compared to the safety for drug performance.

- Clinical studies and experimental settings are criticized by safety investigators for their inherent shortcomings of short follow up period, strict inclusion criteria, study population different from target population, and in a way best case scenarios with laboratory conditions optimized for best drug performance. As seen from the above information these inherent shortcomings are further complicated by the lack of clear safety information reporting from the studies performed.

- This brings to our notice the probable lack of sufficient safety reporting guidelines for clinical data. Ideally we desire simple, comprehensible, objective accessible safety information as a basis for policy decisions. There is lack of any other tool besides clinical trials, currently, that can make safety data available in early stages of new drug use. The necessity to have efficacy and safety reported in a standardized pattern should be advocated with immediate effect in order to shorten the time duration of unexpected Adverse Effects detection, its immediate communication and effective management where required.

- Science and experience demand that a drug be monitored throughout its lifespan for its safety as the equations may change over time. Lack of comprehensive safety data

in the pre-marketing phase due to inherent shortcomings of clinical trials, post marketing surveillance is of utmost importance. Spontaneous reporting of Adverse Drug Reactions (ADRs) is the mainstay of drug safety monitoring in post marketing phases, however there is gross underreporting of Adverse Drug Reactions (ADRs) by the formal health care providers and prescribers.

- There are many complex issues with developing countries that make drug monitoring greatest challenge of disease management. Absence of robust national drug policies if just one of the several factors.

- One possibility to improve the situation may be to involve the community in monitoring of Adverse Drug Reactions (ADRs) and appropriate sensitization of the community based resource persons in Pharmacovigilance.

- Main challenge in including people from all walks of life in safety drug monitoring is their varied educational backgrounds. Possible solution is the use of facilitated referencing to the formal health care centres and use of pictorial Adverse Drug Reaction case reporting forms.

- As the African countries prepare the launch of the new co-formulation, it can be an excellent opportunity to build sustainable pharmacovigilance systems to be extended to other drugs for example anti-retrovirals in the near future.

Drug safety problems will occur despite adequate precautions being taken and things well done (Waller et al., 2005). All in all , this draws our attention to the lack of comprehensive information available in the study reports and highlights the immediate and urgent need for a efficient and functional safety reporting system post clinical studies. Additionally also, an effective post marketing vigilance system for population based safety monitoring of the new drugs introduced.

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IX. Annexes

Annex I: Definitions/ Glossary:

Drug/Medicine:

Any substance used in a pharmaceutical product used in or on the human body for prevention, diagnosis or treatment of disease, or for the modification of physiological function. The term medicinal product or drug is used in a wider sense to include the whole formulated and registered product, including the presentation and packaging, and the accompanying information.

Side Effects:

Any unintended effect of a pharmaceutical product occurring at doses normally used by a patient which is related to the pharmacologic properties of the drug.

Adverse Drug Reaction/Adverse Reaction:

A response to a medicine which is noxious, unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function.

Unexpected Adverse Reaction:

An adverse reaction the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the drug.

Adverse Event or experience:

Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.

A serious Adverse Event:

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires or prolongs patient hospitalization, results in persistent disability/incapacity, or is a congenital anomaly/birth defect (Internatinal Conference on Hramonization)

Signal:

Reported information on a possible causal relationship between an adverse even and a drug, the relationship being unknown or incompletely documented previously. Usually more than one single report is required to generate a signal depending on the seriousness of the event and the quality of the information.

Bayesian confidence propogation neural network (BCPNN): A computer programme that uses logic to determine the disproportionality of relationships between any of the items in the database including complexes of items compared with the background of the remaining selected items. Changes in the disproportionality can be monitored, as new data are added or different patters of items are selected. This method provides a quantitative measure of the strength of association of a drug/reaction combination

Benefit:

An estimated gain for an individual or a population.

Effectiveness/Risk:

The balance between the rate of effectiveness of a medicine versus the harm. It is a quantitative assessment of the merit of a medicine used in routine clinical practice. It is more useful than efficacy or hazard predictions from premarketing studies that is limited to selected subjects evaluations.

Benefit/Harm:

Benefit and harm are positive and negative subjective qualitative experinecs of individual patients.

Risk Evaluation:

It is a complex process of determining the significance or value of the identified hazards and estimated risks to those concerned with or affected by the process.

Risk Management:

The making of decisions concerning risks, or action to reduce the consequences of probability of occurance

Counterfeit medicine:

A medicine that is deliberately and fraudently mislabeled with respect to identity and /or concent and /or source.

Pharmacoepidemiology:

The study of the use and effects of drugs in large numbers of people.

Annex II: Examples of successful Post marketing surveillance in Developed countries (Balkrishnan and Furberg, 2001, WHO)

France:

Decentralized interactive approach includes regulatory authorities physicians and health care professionals report cases to 31 regional centers.

New Zealand:

The Intensive medicines monitoring program (IMMP), organized in 1977 relies on observational cohort studies including patients with the prescribed drug. Data established from pharmacies throughout the country. This system prevents the masking of ADR by separating drug events into reactions and incidents.

Advantages are pro-active, cost efficient, limited resource, ability to successfully obtain data from first cohort receiving a new drug.

UK:

Prescription Event Monitoring (PEM) monitors the entire population centrally through an electronic prescription system . For all new drugs the Drug Safety Research Unit (DSRU) identifies prescriptions, patient details and prescriber details through the electronic system. It uses the green forms to obtain data from GPs, but the response rates are low.

Yellow Card Scheme is the national system in UK where doctors, dentists and more recently hospital pharmacists are encouraged to report ADRs. Pharmaceutical companies also collect such reports(Talbot and Nilsson, 1998).

Sweden:

Mandatory reporting for physicians since 1975 supported by epidemiological studies since 1982. unique features are that it utilizes mandatory reporting, case control studies and also clinical trial data and conducts economic evaluations of drug safety.

USA:

Adverse Event Reporting system (AERS), consists of computerized database that combines the voluntary AE reports submitted by health professionals to Medwatch and the mandatory reports submitted by the pharmaceutical companies (Murphy and Roberts, 2005). Its online since 1997. and has advanced data mining techniques such as Bayesian and visualization tools combined with the traditional spontaneous reporting. (Balkrishnan and Furberg, 2001, WHO).

MEDWATCH is a program with 160 partners and administered by the FDA for rapid dissemination of drug safety information on the Internet and email notification to health professionals, institutions, public and the partners (Murphy and Roberts, 2005). Includes voluntary reporting by public and health care professionals and mandatory reporting by the pharmaceutical industry.

Annex III: **List of documents used for database analyses**

Type of publisher	No.	Authors	year
Tropical Medicine and International Health	7	Abacassamo et al. Barennes et al. Durrani et al. Ndayiragije et al. Rwagacondo et al. Sowunmi et al. Agnamey et al.	2004 2004 2005 2004 2004 2005 2005
The Lancet	3+2	Adjuik et al. (Kenya, Gabon, Senegal) Mutabingwa et al. Staedke et al.	2002 2005 2004
MSF Report	7	Bonnet et al. Bonnet et al. Couhet et al. Grandesso et al. Kitz et al. Swarthout et al. Van den Broek	2004 2006 2004 2006 2005 2006 2005
PLOS Clinical Trials	2	Bukirwa et al. Yeka et al.	2006 2005
Royal Society of Tropical Medicine and Hygiene	2	Guthmann et al. Hamour et al. + report	2005 2005
Acta Tropica 95	1	Koram et al.	2005
Clinical Infectious Diseases	1	Martensson et al.	2005
Malaria Journal	1	Van den Broek + report	2006
unpublished	3	Guthmann et al. Karema et al. Grandesso et al.	2006 2006 2006
TOTAL	29	+ 1 Senegal study= 30	

Table 6: Types of Documents used.

Addition of one study from Senegal by Brasseur et al. and the pharmacovigilance study by Brasseur et al. together makes the database of 31 studies that were analysed. Adjuik et al. was a study conducted in Kenya, Gabon and Senegal and these account for separate studies.

Annexe IV: Standard Adverse Effects Case Report Form

Confidential information unless serious enough and requires investigations:

Patient information:

1. Identity
2. identifiable address and telephone contact if possible
3. Age: Sex: date of birth:
4. If female pregnant ☒ ☒
5. Date of last Menstrual Period:

Reporter information:

1. identity
2. address and telephone contact
3. training, occupation, speciality details
4. in case of non formal healthcare reporter, details of both should be included.

Event information:

1. Description of event
2. date of event
3. time passed after first dose, last dose
4. any significant laboratory abnormalities noted
5. background medical history of the patient
6. frequency of outcome

Drug/substance Information:

1. name, brand name, contents
2. date of manufacturing/expiry
3. batch number and source if known
4. date of therapy first and last
5. indication for use
6. event absent when drug stopped
7. event reduced with reduced dose
8. re-challenge: event back when tretment reinstated
9. concomitant drugs used and their details, herbal traditional medications, long term therapies with any other drugs, food history, unusual activities.

Adverse Drug Reaction Case Reporting Form: Id No.:

Patient Details: **Δ :** **Microscopy: ☑ ☒**

Complete Name:		other names			
date of Birth:	approx age:	yrs	Sex: ☐F ☑M	Weight(Kg):	Height(m/Ft):
If F Pregnant? ☑ ☒ ☒ot Known			Date of last Menstrual Period:		
Address(Traceble):				Phone:	

Description of Event:

Date of onset:	Date of first Dose:	Date of event end:	Frequency:
Description:			
Laboratory tests conducted: (attach copy of results if abnormal)			
Event management:		Drug treatments:	
Result: ☐Recovered Completely ☐Recovered with sequalae ☐Recovering ☐Other:			
Outcome: ☐Death ☐Life Threatening ☐Hospitalization/ Prolonged stay ☐Permanent Disability ☐Congenital Anomaly ☐Other(give details)			

Medications Taken: List suspected drug first, include all herbal, traditional drug details, Long term therapy if any:

Name of drug	Batch/Source	Date of manufacture	date of expiry	Indication for use	dose & No. taken	Date Started	Date stopped	Prescribed self/Other

Previous allergies: same drug/ Other
Other relevant medical history/food changes:
Concomitant Illness:
Long term medications:

Reporter Details:

Name:	Signature:	date:
Professional qualification:	Designation:	
Institute/ Hospital Address:		
Telephone: Fax:	E-mail:	

Annex V

Questions for causality assessment:

What is the nature of the reaction?

Is there a reasonable time relationship between the initiation of treatment and the occurrence of symptoms?

Is it a known reaction mentioned on the drug insert?

Did the reaction abate once the treatment was stopped?

Re challenge: If there was a history of similar incident in the patient in the past when the drug was used and if the treatment was reinstituted did the same reaction occur?

Is there any other possible explanation of the event?

X. Declaration of Original Work

This thesis is the result of independent investigation. Where my work is indebted to the work of others, I have made appropriate acknowledgements.

I declare that this study has not already been accepted for any other degree nor is it currently being submitted in candidature for any other degree.

Ms Revati Phalkey

Date: 24th July 2006

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