

Malaria and HIV interactions
and their implications for public
health policy

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Malaria and HIV interactions and their implications for public health policy



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Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
ANC	antenatal clinic
ART	antiretroviral treatment
ARV	antiretroviral
BCC	behavioural change communication
CQ	chloroquine
HIV	human immunodeficiency virus
IEC	information, education and communication
IPT	intermittent preventive treatment
ITN	insecticide treated net
IUGR	intrauterine growth retardation
MTCT	mother-to-child transmission
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
<i>P. falciparum</i>	<i>Plasmodium falciparum</i>
PI	protease inhibitor
PLWA	people living with HIV/AIDS
RDT	rapid diagnostic test
SP	sulfadoxine-pyrimethamine
STI	sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS

Key epidemiological terms

Stable malaria	Malaria transmitted by abundant anthropophilic long-lived vectors. Transmission is intense and continuous, though seasonal variations may occur. Immunity develops early in life. Young children and pregnant women are the population groups at greatest risk for malaria morbidity and mortality.
Unstable malaria	The risk of malaria is less predictable and not continuous. The disease burden is similar in all age groups though usually higher in children than in adults, unless exposure is linked to occupation. Extremely unstable malaria corresponds to epidemic malaria.
Clinical malaria	Acute disease caused by malaria parasites with fever or anaemia as one of the main symptoms. Clinical malaria may be classified as uncomplicated or severe.
Low-level HIV epidemic	Although HIV infection may have existed for many years, it has never spread to significant levels in any sub-population. HIV prevalence among pregnant women is below 1% and has not consistently exceeded 5% in any defined sub-population (such as injecting drug users sex workers and men who have sex with men).
Concentrated HIV epidemic	HIV has spread rapidly in a defined subpopulation, but is not well established in the general population. HIV prevalence is consistently over 5% in at least one defined subpopulation but the HIV prevalence among pregnant women is below 1%.
Generalized HIV epidemic	HIV is firmly established in the general population, reflected by an HIV prevalence consistently over one percent among pregnant women.
HIV-1 and HIV-2	There are two HIV types: HIV-1 and HIV-2. HIV-1 accounts for nearly all cases except a minority of strains that originate in West Africa. Compared with HIV-1, HIV-2 is less transmissible, is associated with a lower plasma viral load, and is used to refer to HIV-1.

Executive summary

Malaria and HIV are among the two most important global health problems of our time. Together, they cause more than 4 million deaths a year. Malaria accounts for more than a million deaths each year, of which over 80% occur in tropical Africa, where malaria is the leading cause of mortality in children under five years of age. Aside from young children, pregnant women are among the most affected by the disease. Depending on malaria transmission intensity, the main complications of malaria during pregnancy include maternal death, severe anaemia, and adverse birth outcomes such as low birth weight. Constituting 10% of the overall disease burden, malaria places a substantial strain on health services and costs Africa about US\$ 12 billion in lost production each year.

Sub-Saharan Africa is also home to an estimated 25 million adults and children living with HIV/AIDS. In 2003 in Africa, HIV claimed the lives of some 2.2 million people and over 600 000 children were newly infected with the virus. HIV increasingly accounts for a large proportion of mortality among children under five years in heavily affected countries. By 2002, the virus was responsible for almost 10% of all child deaths in the region. By taking its greatest toll on people in the prime of their working and parenting lives, HIV hinders sustainable development in Africa.

Treatment of HIV/AIDS with highly effective combination antiretroviral therapy is now being scaled up in most high-burden countries in line with the WHO 3 by 5 initiative, which sets a global target of 3 million people in need of therapy living in resource-limited countries on ART by the end of 2005. Treatment is now an integral component of all HIV/AIDS programmes and will help accelerate and reinvigorate prevention efforts. The new focus on care and treatment provided by 3 by 5 is a further impetus to consider the main preventable and treatable causes of morbidity and mortality in HIV-infected adults and children globally.

Malaria and HIV/AIDS are both diseases of poverty and causes of poverty and they share determinants of vulnerability. Given the wide geographical overlap in occurrence and the resulting co-infection, the interaction between the two diseases clearly has major public health implications. WHO convened a technical consultation in Geneva from 23 to 25 June 2004 with researchers, policy-makers and programme managers to review evidence on interactions between malaria and HIV and the implications of such interactions on prevention and control of both diseases. The technical consultation included presentations of working papers, group and plenary discussions as well as recommendations that form the basis of this report.

Epidemiology of interactions between malaria and HIV

The major burden of malaria and HIV occur in sub-Saharan Africa, South-East Asia, Latin America and the Caribbean. However, the prevalence of malaria and HIV as well as the extent of geographical overlap varies widely within each region. Even in countries with a high prevalence of both infections, there may be differences in disease distribution at a local level.

The impact of the interaction of malaria and HIV is most apparent in areas with generalized HIV epidemics and stable malaria. Sub-Saharan Africa carries a high burden of both diseases, thus co-infection is common in many areas. In the most severely affected countries (i.e. Central African Republic, Malawi, Mozambique, Zambia and Zimbabwe), more than 90% of the population is exposed to malaria, and HIV prevalence in adults is above 10%. In contrast, southern Africa, which has a relatively low burden of malaria is the worst HIV-affected sub-region. Frequent malaria epidemics in southern Africa may, however, increase the risk of dual infection.

In Latin America and the Caribbean some overlap of malaria and HIV occurs in the general population in Belize, El Salvador, Guatemala, Honduras, Guyana, and Brazil. South-East Asian countries such as Myanmar and Thailand have a generalized HIV epidemic but malaria distribution is heterogeneous in this region. Considering that an estimated 1 billion people in South-East Asia are exposed to unstable malaria even small overlaps of malaria and HIV in these settings may have a large public health impact.

Executive summary

In areas with a low malaria and HIV burden, certain population groups such as migrant workers and injecting drug users are at high risk for both diseases, and they facilitate transmission of HIV from high-risk groups to the general population. Transmission of both malaria and HIV can result from improper blood-transfusion practices and unsafe injections.

In HIV-infected individuals, a malaria case definition based on fever alone can result in a febrile illness due to a wide range of ordinary, virulent and opportunistic infections being misdiagnosed and treated as malaria. This may lead to inappropriate care of HIV-infected adults with severe febrile illnesses due to causes other than malaria. With the use of more costly antimalarial drugs, it has become necessary to consider the widespread introduction of parasitological diagnosis, particularly in areas with a high HIV prevalence. The low specificity of a fever-based malaria case definition could diminish the validity of malaria case fatality data.

Evidence of interactions between malaria and HIV

Evidence of interactions between malaria and HIV in non-pregnant adults is accumulating. In areas with stable malaria, HIV increases the risk of malaria infection and clinical malaria in adults, especially in those with advanced immunosuppression. In settings with unstable malaria, HIV-infected adults are at increased risk of complicated and severe malaria and death. Reports also suggest that antimalarial treatment failure may be more common in HIV-infected adults with low CD4-cell counts compared to those not infected with HIV. Additional research is needed to investigate the impact of malaria on the natural history of HIV, potential therapeutic implications, and interactions at a cellular and molecular level.

Acute malaria episodes cause a temporary increase in viral replication of HIV and hence plasma viral load. However, there is no evidence that malaria has a substantial effect on clinical progression of HIV, HIV transmission or response to antiretroviral treatment in areas where malaria and HIV overlap.

Few studies have examined the interaction of malaria and HIV in children. In areas of stable malaria, HIV-infected children may be at increased risk of clinical malaria compared to children not infected with HIV. Advanced immunosuppression in HIV-infected children results in more episodes of clinical malaria and higher parasite densities compared with HIV-infected children whose immune status is less compromised. In areas of unstable malaria HIV-infected children may be at increased risk of severe disease and death. However, no conclusions can be made to date without further specific data on co-infection with malaria and HIV.

The effects of interactions between malaria and HIV are particularly deleterious to maternal and infant health. HIV infection impairs the ability of pregnant women to control *P. falciparum* infection. They are more likely to develop clinical and placental malaria, more often have detectable malaria parasitaemia and have higher malaria parasite densities.

It is estimated that in 2003 in sub-Saharan Africa at least 440 000 women had malaria infection during pregnancy attributable to HIV. Most women in their first or second pregnancy are at higher risk of severe or complicated malaria than during subsequent pregnancies. HIV alters this typical pattern by shifting the burden from mainly women in their first or second pregnancy to all pregnant women. Compared to women with either malaria or HIV infection, co-infected pregnant women are at increased risk of anaemia, preterm birth and intrauterine growth retardation. As a result, a considerable proportion of children born to women with dual malaria and HIV infection have low birth weight and are more likely to die during infancy. Whether infection with malaria increases the risk of mother-to-child transmission of HIV is unclear, as studies examining this relationship have inconsistent findings.

The presence of HIV results in a poorer response to both prophylaxis and treatment of malaria during pregnancy. Furthermore, there is a risk of adverse drug reactions if sulfadoxine-pyrimethamine for the prevention of malaria in pregnant women and cotrimoxazole for opportunistic infection prophylaxis are taken together, as both are sulfa-containing drugs.

Interactions between antimalarials and antiretroviral medicines

Pharmacokinetic interactions of ARVs with antimalarials involve mostly non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) which are included in first- or second-line therapy for HIV. The potential for interaction resulting in excessive toxicity suggests that lumefantrine should be used with caution in patients receiving protease inhibitors (PIs) and halofantrine is contraindicated. The effect in patients receiving NNRTIs is unknown.

Widespread cotrimoxazole use could accelerate the development of resistance in malaria parasites to sulfadoxine-pyrimethamine, the first-line drug for the treatment of uncomplicated malaria and the prevention of malaria in pregnant women in many parts of Africa. While more research to investigate pharmacokinetic interactions is required, emphasis should be placed on close monitoring and pharmacovigilance in the treatment of malaria and HIV.

Implications for health systems and service delivery

Providing integrated health services in areas heavily affected by malaria and HIV is crucial for reducing the burden of the two diseases. The introduction of new medicines and diagnostics by malaria and HIV programmes at the same time, offers opportunities for joint planning, training and service delivery.

Consideration of research needs

In light of the epidemiological overlap and global importance of the two diseases, there is an urgent need for more research on a wide range of unanswered questions. Only with sufficient evidence can appropriate public-health policy be devised on integrating the prevention, care, treatment and support activities for malaria and HIV. The consultation has considered the key research issues that should guide further research in this area.

Conclusion

This technical consultation was the first meeting of international experts assessing the impact of interactions between malaria and HIV on the health of people affected by both diseases. The meeting was a major step in identifying implications of such interactions for research, public health policy and health service delivery. The challenge is to combine activities to control malaria and HIV at various levels of the health system, tailor responses to community needs, and optimize the use of scarce resources for integrated service delivery. There are many opportunities for synergism, in particular at a time of growing political and financial commitment to reduce the burden of HIV/AIDS, tuberculosis and malaria.

Executive summary

Key recommendations

- ▶ HIV-infected people—including pregnant women—living in areas of stable and unstable malaria are particularly vulnerable to malaria. Their protection against malaria by insecticide-treated nets or other locally suitable preventive measures is a high priority.
- ▶ Reproductive health services need to be strengthened to ensure the delivery of the WHO-recommended antenatal care schedule of four visits (focused antenatal care), which includes a minimum package of interventions for the prevention of both malaria and HIV.
- ▶ HIV-infected pregnant women in areas with stable malaria should—according to the stage of HIV-infection—receive either intermittent preventive treatment with at least three doses of sulfadoxine-pyrimethamine or daily cotrimoxazole prophylaxis. Malarial illness in HIV-infected pregnant women who receive cotrimoxazole prophylaxis should be managed with antimalarial medicines that do not contain sulfonamides or sulfones.
- ▶ The UNAIDS and WHO interim recommendation on opportunistic infection prophylaxis with cotrimoxazole needs to be revised and updated in 2005.
- ▶ In areas with stable malaria and high HIV prevalence, there should be a high suspicion of HIV among patients with repeated episodes of fever, and the treatment of fever as malaria alone (in particular among patients other than young children) is inadequate; in addition to providing malaria treatment, health providers should offer HIV testing and counselling.
- ▶ A fever-based malaria case definition may result in febrile illnesses caused by opportunistic infections being misdiagnosed as malaria, leading to over-treatment of malaria. However, prompt antimalarial treatment is vital to prevent progression to severe malaria and death, particularly in young children. As improvements in health systems occur, confirmatory testing for malaria should increasingly become available in malaria-endemic areas.
- ▶ In countries with generalized HIV epidemics, routine monitoring of antimalarial drug efficacy or effectiveness should include assessing the effect of HIV on antimalarial treatment outcome.
- ▶ Integration of services for prevention and control of malaria and HIV is vital for reducing the burden of both diseases; programmes need to collaborate to plan the most efficient use of existing limited resources for service delivery. Integration of services is particularly important within the framework of reproductive and child health services.
- ▶ The evidence base is inadequate in several important areas and further operational research, observational studies and clinical trials are urgently needed.
- ▶ All future treatment trials of new antimalarial treatment strategies or drugs should identify the HIV status of all trial participants and evaluate the potential impact of HIV-related immunosuppression on response to antimalarial therapy.

Introduction

Malaria and HIV—among the most important health problems of our time—overlap extensively, co-infecting large numbers of people. Together, they cause more than 4 million deaths each year. In sub-Saharan Africa an estimated 25 million children and adults are living with HIV, which in 2003 claimed the lives of 2.2 million people in this region. By comparison, there are an estimated 240–300 million episodes of malaria in Africa each year, resulting in almost 900 000 deaths. Over 80% of malaria deaths in the world occur in Africa, mostly in children under five years of age. Compared to HIV, malaria is responsible for a larger number of deaths in young children, accounting for approximately 20% of all deaths among children in Africa. However, HIV is an ever-increasing cause of child mortality in sub-Saharan Africa. By 2002, it represented close to 10% of all child deaths in the region.

Both malaria and HIV have potentially severe effects on pregnant women and on the outcome of pregnancy. The symptoms and complications of malaria during pregnancy differ with the intensity of malaria transmission and thus with the level of immunity acquired by the pregnant woman. For pregnant women living in areas of unstable malaria, the risk of developing severe malaria is 2-3 times higher than that for non-pregnant women living in the same area. In areas of stable malaria, most adult women have developed some immunity and the principal impact of malaria infection in these pregnant women is malaria-related anaemia, which increases the risk of low birth weight infants.

HIV is the leading cause of adult morbidity and mortality, and has become one of the major causes of maternal mortality in many settings heavily affected by the HIV epidemic. It has an impact on obstetrical causes of maternal mortality by increasing the risk of pregnancy complications such as anaemia, post-partum haemorrhage and puerperal sepsis. Furthermore, in the absence of interventions about a third of infants born to HIV-infected women will become infected with the virus.

In areas of stable transmission, malaria accounts for up to 40% of public health expenditure, up to half of all hospital admissions and as much as one third of outpatient visits. It is estimated that malaria costs Africa about US\$ 12 billion in lost production each year. Similarly, HIV—by affecting people in the prime of their working and parenting lives—is hindering sustainable development in Africa. The World Bank has calculated that HIV costs 24 African countries 0.5%-1.2% of per capita growth each year.

Malaria and HIV are both diseases of poverty and causes of poverty and they share determinants of vulnerability to infection. Many of the circumstances that give rise to such vulnerability are present in sub-Saharan Africa. Thus, it is not surprising that malaria and HIV overlap geographically in many countries in this region given the presence of vulnerable populations and low levels of access to information, education, health care services, and means of treatment and prevention. In the most severely affected countries (such as the Central African Republic, Malawi, Mozambique, Zambia and Zimbabwe) more than 90% of the population is exposed to malaria and HIV prevalence among adults between 15-49 years of age is above 10%. In contrast, in South-East Asia and South America the two diseases coincide in specific high-risk groups such as migrant workers and injecting drug users.

Co-infection with malaria and HIV is common where the two diseases coexist in general populations or in specific high-risk groups. Given this extensive overlap with resulting high levels of co-infection, interactions between the two diseases have major implications for the treatment, care and prevention of both.

In light of the epidemiological overlap and increasing evidence of interactions between malaria and HIV, the Roll Back Malaria and HIV/AIDS Departments convened a technical consultation to:

- ▮ review the evidence, supplemented by expert opinion where evidence was lacking or inconclusive, on interactions between malaria and HIV;
- ▮ examine what the implications of each disease are for the treatment, care and prevention of the other; and
- ▮ identify and prioritize research needs.

The technical consultation included presentations of working papers as well as group and plenary discussions resulting in recommendations. The working papers and proceedings of the meeting form the basis of this report.

Summary of presentations

The meeting was opened by Fatoumata Nafotraoré, Director of the Roll Back Malaria Department, on behalf of Jack Chow, Assistant Director-General of the HIV/AIDS, Tuberculosis and Malaria Cluster, WHO. She pointed out that a relative lack of data may make it difficult to quantify some aspects of the interaction between malaria and HIV. In her address, she emphasized that aside from reviewing evidence on interactions between malaria and HIV and providing expert opinion where evidence is lacking or inconclusive, the technical consultation must consider what the implications of these interactions are for current policies concerning the treatment, care and prevention of both diseases. In addition, factors affecting the integration of malaria and HIV activities at the health service level must be taken into account in order to improve the effectiveness of such services.

Antoine Kaboré and Sornchai Looaresuwan were elected as chairperson and co-chairperson respectively, Annette Reinisch and Marie-Thérèse Abena Obama as rapporteurs. The meeting included presentations on the following topics:

1. Epidemiological considerations of interactions between malaria and HIV, *James Whitworth and Kirsten Hewitt*
2. Interactions in children and non-pregnant adults, *Neil French*
3. Interactions in pregnant women and infants, *Feiko ter Kuile*
4. Interactions between antimalarials and antiretrovirals, *Saye Khoo*
5. Health systems and service delivery considerations, *Thierry Mertens and Juliana Yartey*.

1. Epidemiological considerations of interactions between malaria and HIV

Malaria and HIV are two of the most important infectious diseases in the tropics, and any interaction between the two diseases is expected to have far-reaching public health implications, in particular in countries with constrained resources.

Although the major burden of malaria and HIV occurs in the same regions (sub-Saharan Africa, South-East Asia, Latin America and the Caribbean), the prevalence of malaria and HIV varies widely within each region as does the extent of geographical overlap. Even in countries with a high prevalence of both infections, there may be differences in disease distribution at a local level. For example, in many heavily affected countries, malaria mostly affects young children in rural areas, while HIV infection occurs more commonly in sexually active adults in urban areas. In India, HIV prevalence is highest in the southern regions while the highest malaria incidence rates are in the north-east of the country. However, there is clearly a geographical overlap in some Indian cities affected by urban malaria and in some communities in north-eastern states (and elsewhere in parts of rural South-East Asia) where intravenous drug use is widespread.

Effects of the interrelationship between malaria and HIV are most pronounced in areas with concomitant generalized HIV epidemics and stable malaria. As sub-Saharan Africa carries a disproportionate burden of both diseases, co-infection is common in many areas. In the most severely affected countries, (the Central African Republic, Malawi, Mozambique, Zambia and Zimbabwe) more than 90% of the population is exposed to malaria, and HIV prevalence in adults between 15-49 years of age is above 10%. In contrast, southern Africa has a relatively low burden of malaria but is the world's worst HIV-affected region. More than 20% of adults in South Africa and Namibia are living with HIV and in Botswana and Swaziland adult infection rates have exceeded 35% (1). However, malaria epidemics in southern Africa such as in Kwazulu-Natal (2), may result in significant overlap of the two diseases in affected areas (see also Box 1).

Box 1. The burden of co-infection with malaria and HIV in areas of high HIV prevalence

An estimated 2-fold risk of clinical malaria in HIV-infected individuals could increase the burden on clinical services in areas where HIV is prevalent.

The population-attributable fraction of adult malaria due to HIV in sub-Saharan Africa with an HIV prevalence of 8% among adults is about 4% for parasitaemia and 5% for clinical malaria. In a region with an HIV prevalence of 30%, such as parts of southern Africa, the population-attributable fraction could reach 20% for parasitaemia and 35% for clinical malaria.

Source: Whitworth J et al. (3)

Surveillance data from Latin America, the Caribbean and South-East Asia are limited, making it difficult to characterize the coexisting distribution of malaria and HIV. Available data from countries in Latin America and the Caribbean indicates that some overlap of malaria and HIV occurs in the general population in Belize, El Salvador, Guatemala, Honduras, Guyana and, to a limited extent, in Brazil. Although there is a generalized HIV epidemic in South-East Asian countries such as Myanmar and Thailand, malaria distribution is heterogeneous in this region. However, considering that an estimated 1 billion people in South-East Asia are exposed to unstable malaria, small overlaps of malaria and HIV in these settings may have a large public health impact (4).

It is important to note that even in areas with a low malaria and HIV burden, there are certain population groups at high risk for both diseases. Studies in Brazil and Guyana reported that an epidemiological overlap occurs among migrant workers such as gold miners (5, 6). Similarly, in regions with a high number of migrant workers, such as in border regions of Cambodia, Thailand and Viet Nam, HIV-infected people may also be exposed to malaria infection. In Brazil, north-east India and South-East Asia injecting drug users may be at increased risk of co-infection (5,7). These high-risk populations may act as bridging groups, facilitating transmission of HIV from high-risk groups to the general population. This potentially leads to co-infection in areas with malaria.

Transmission of both malaria and HIV can result from improper blood-transfusion practices and unsafe injections (8,9). In some settings, policies to minimize the risk of

HIV transmission through transfusion exist but are not implemented. In areas with improper blood-transfusion practices, malaria may indirectly increase the risk of HIV transmission, as severe malaria-associated anaemia often leads to blood transfusions, particularly in children. For example, in the Democratic Republic of Congo, malaria accounts for almost 90% of blood transfusions administered to children (10). It is estimated that each year between 5300 and 8500 children in areas of stable malaria in Africa acquire HIV infection from blood transfusions given for severe malaria (11).

In areas with a generalized HIV epidemic much controversy surrounds the use of a malaria case definition based on fever alone. The clinical presentation of malaria does not vary according to HIV status and can be difficult to distinguish from other causes of febrile illness in persons with HIV infection. In people living with HIV, febrile illnesses caused by a wide range of ordinary, virulent and opportunistic infections (particularly in children) may therefore be misdiagnosed as malaria. Therefore, HIV infection lowers the specificity of a fever-based malaria case definition. In other words, the higher the prevalence of HIV in a population, the lower the probability that a person with fever has malaria. In areas with a generalized HIV epidemic, this may result in over diagnosis of malaria and overuse of antimalarials. Aside from potentially compromising the care of the HIV-infected individuals, this could raise treatment costs. The increasing use of more costly antimalarial medicines is one more reason to consider the widespread introduction of microscopic techniques or malaria rapid diagnostic tests, particularly in areas with a high HIV prevalence.

The low specificity of a fever-based malaria case definition makes it difficult to investigate interactions between malaria and HIV. Moreover, overestimating the number of malaria cases using a fever-based case definition could diminish the validity of malaria case fatality data. Valid surveillance data are a vital component of programme planning and advocacy. Recent efforts to improve the methods used to estimate the burden of malaria may clarify the potential contribution of HIV to estimates of malaria mortality.

Summary of presentations

SUMMARY OF EVIDENCE

Epidemiological considerations of malaria and HIV interactions

- ▶ Malaria and HIV are two of the most important infectious diseases in the tropics, and any interaction between the two diseases is expected to have far-reaching public health implications.
- ▶ Malaria and HIV are widespread among the poorest populations in sub-Saharan Africa, and co-infection is common in many settings. However, some areas of southern Africa with the highest HIV prevalence have little malaria. In South-East Asia and Latin America, it is difficult to characterize the extent of malaria and HIV overlap, but so far it is likely to be focal. [local?]
- ▶ Risk groups include communities living in areas with generalized HIV epidemics and stable malaria. However, due to a lower immunity to malaria, those in settings of unstable malaria could be most affected from the interaction of malaria and HIV.
- ▶ Even within low risk areas, certain sub-groups of the population are at higher levels of risk and include temporary workers or injecting drug users. These high-risk populations may act as bridging groups, facilitating transmission of HIV from high-risk groups to the general population. This fuels HIV transmission among the general population, potentially leading to co-infection in areas with malaria transmission.
- ▶ As an important cause of anaemia, malaria frequently leads to blood transfusions, which is a potential risk factor for HIV infection.
- ▶ HIV prevalence decreases the specificity of malaria case-definitions based on fever. In areas with a generalized HIV epidemic, this may result in over diagnosis and over treatment of malaria. Aside from potentially compromising the care of the HIV-infected individuals, this could increase treatment costs.
- ▶ Overestimating the number of malaria cases using a fever-based case definition may diminish the validity of malaria case fatality data. This needs further investigation.

2. Interactions in children and non-pregnant adults

This section considers the effect of HIV on the clinical presentation and outcome of malaria in children and non-pregnant adults. Despite the epidemiological overlap and global importance of the two diseases, there are few studies of sufficient quality. Uncertainty exists about the impact of malaria on the natural history of HIV, potential therapeutic implications, interactions between HIV and malaria in children and interactions at a cellular and molecular level.

Earlier studies on the interactions of malaria and HIV in pregnant women have been well designed and showed convincing results. However, the small number of earlier

reports on the interaction of malaria and HIV in children and non-pregnant adults were not able to show consistent links between the two infections. These studies were either small, cross-sectional, or suffered selection bias (12). Hospital- and clinic-based studies that conducted a cross-sectional assessment of sick individuals were biased in their identification of study patients (13-15). The lack of information on therapy prior to attendance and of consideration of variations in immunosuppression found at different stages of HIV infection are likely to have an impact on the interpretation of the results. Similarly, a prospective study from Kinshasa involving adults and children did not separate the results by age group (16). There will be major differences between adults and children and the nature of the malaria/HIV interaction, which will depend on the state of antimalarial immune responses.

More recent research provides better evidence on the interactions between malaria and HIV in non-pregnant adults and children. Nevertheless, the interaction between these two diseases is of such great potential that further studies investigating the many unanswered questions are urgently needed.

The effect of HIV on malaria in adults

The underlying epidemiology of malaria transmission in part predicts the clinical consequences of the interaction between malaria and HIV. A cohort study from rural Uganda—an area with stable malaria—indicates that HIV-infected adults have higher levels of asymptomatic parasitaemia compared to those without HIV infection (3). Data from this same cohort have shown a greater prevalence of parasitaemia episodes in HIV-infected individuals, which increases with falling CD4-cell count. In addition, HIV-infected adults are more likely to develop clinical malaria, and this risk becomes more pronounced with advancing immunosuppression (3, 17-19), such that at CD4 counts below 200 cells/mL (AIDS) individuals suffer more than twice the rate of malarial fever as those with CD4 counts above 500 cells/mL (early HIV disease) (17).

There is no clear evidence of an increase in the rates of severe or complicated malaria in HIV-infected adults. An observational cohort study in Entebbe, Uganda did not report cases of cerebral or complicated malaria or deaths clearly attributable to malaria (17). This finding is consistent with data from the large cohort of HIV-infected adults in a rural location in south-west Uganda (3). In contrast, two small case-series studies of severe malaria from Burundi (20) and Zambia (21) (also areas of stable malaria) both suggest that HIV-infected adults have a higher malaria case-fatality rate. A cohort study in Côte d'Ivoire that examined cotrimoxazole prophylaxis in HIV-infected adults did not detect deaths attributable to malaria. However, failure to provide antimalarial treatment in cases of acute unexplained fever was independently associated with death (22). The explanation for this finding is uncertain; speculations about the cause include unrecognized malaria, a beneficial effect of antimalarial treatment independent of its anti-plasmodial properties or a by-chance finding.

In areas with epidemic or low malaria transmission, HIV-infected adults are as likely to be exposed and then to develop clinical malaria as those not infected. There is, however, evidence of increased severity and complications of malaria in HIV-infected individuals in regions of unstable malaria. Three smaller studies from Zimbabwe (23), South Africa (24) and India (25), and a large cohort study from Kwazulu Natal, South Africa (2), all reported increased severe disease with underlying HIV infection. The frequency of severe and complicated malaria increases with the progression of HIV-related immunosuppression (24). However, there is insufficient evidence available to quantify the extent to which this excess morbidity and mortality is a consequence of severe and complicated malaria or other HIV-related illnesses. Despite the constraints of the clinic-based study in Kwazulu Natal death was observed seven times more frequently among the hospitalized HIV-infected individuals with malaria than the HIV-uninfected with malaria (2). HIV-infected individuals will have a greater in-patient mortality irrespective of cause but this is of the order of twice the mortality of the HIV-uninfected. Thus, the interaction of malaria and HIV is likely to be causal in the reported deaths in Kwazulu-Natal. The other studies did not clearly address issues of co-morbidity.

Both reports from South Africa reported details of the clinical presentation of severe disease. Renal failure and disseminated intravascular coagulation were more frequent in the HIV-infected individuals. Coma, jaundice and severe anaemia may also be HIV-associated. Male sex was an independent predisposing factor for severe disease, an unexplained result that may relate to healthseeking behaviour rather than a difference in host-pathogen interaction.

There are no reports describing clinically important interactions of non-falciparum malaria with HIV-infection.

Summary of presentations

The effect of malaria on HIV

Malaria is an important cause of disease in HIV-infected adults wherever the two infections coexist. Some authorities have postulated that much of the improved survival seen in HIV-infected adults and children with use of daily cotrimoxazole prophylaxis is due to a reduction in malaria infection (26). In cotrimoxazole prophylaxis studies performed in malaria endemic regions, malaria is consistently reduced (26, 27), (J. Whitworth, unpublished observations, 2000-2001). A recent study in South Africa reported a survival benefit in a rural HIV-infected population where malaria is not a significant cause of morbidity (28), thus the benefits of cotrimoxazole cannot be specifically attributed to malaria protection.

Increases in HIV transcription by HIV-associated co-infections have been described for a number of conditions, and this is also the case with malarial fever. Studies from Uganda (29) and Malawi (30) have demonstrated that a transient increase in HIV plasma viral load occurs during a malarial fever episode. However, the convalescent viral loads were similar to levels prior to the disease event, suggesting that these events do not modify the individual viral load significantly. Whether repeat episodes of malaria and other opportunistic infections (which also transiently increase viral load during the acute episode) reduce overall survival times remains to be established. A report on the median survival time with HIV noted that this outcome is similar in Uganda to that in the United States of America and Europe prior to the use of antiretroviral therapy (31). Thus the limited data on the natural history of HIV disease from Africa do not provide the evidence that malaria has a substantial effect on clinical progression of HIV in areas where malaria and HIV overlap. It is also unlikely that this transient rise in plasma viral load has a major impact on HIV transmission or response to antiretroviral treatment. At the peak of the transient viral load increase, most adults are probably sick with malaria and unlikely to engage in much sexual activity.

Response to antimalarial therapy

Emerging evidence indicates that antimalarial drugs may be less efficacious in people living with HIV. A small study in Ethiopia found that HIV-infected adults had an increased parasite and fever clearance time following artemisinin treatment for uncomplicated malaria (32) consistent with the view that the host immune response to parasites is important in determining response to therapy. Furthermore, a low CD4-cell count may predict a poorer response to antimalarial treatment. In a randomized controlled trial in Zambia, HIV-infected adults with CD4 counts less than 300 cells/ml who received antimalarial drugs for uncomplicated malaria had significantly higher rates of parasitological treatment failure to both sulfadoxine-pyrimethamine and artemether-lumefantrine (D. Hamer, unpublished observations, 2004). However, these are preliminary findings and the results in relation to different CD4 cell strata need to be carefully assessed. Similar findings in relation to SP have been reported from Kisumu in Kenya (33). Additional research is required to investigate the implications of these findings for treatment of malaria among people living with HIV to determine whether a reduced response to antimalarial treatment among HIV-infected people increases the malaria case fatality rate, and the potential implications for control of malaria transmission.

Despite the importance of the issue, there are no data on antimalarial effectiveness in children with HIV infection. The meeting noted with concern that current trials evaluating artemisinin-based combination therapy and other treatment developments, especially in sub-Saharan Africa, were still being undertaken without identifying HIV status of the participants and thus they were not able to examine the potential effect of HIV on reducing clinical effectiveness. It was strongly urged that all future trials routinely evaluate HIV status and analyse all results according to HIV status.

Malaria and HIV interactions in children

As in adults, earlier cross sectional studies in children have been inconclusive (14, 34-36). The observation of sick hospital patients who were recruited in a cross-sectional manner (14, 33) or incomplete HIV testing strategies not addressing the problems of HIV diagnosis in young children (14, 35, 36) are likely explanations for the inconsistent results.

However, two cohort studies from Kinshasa—an area of stable malaria—assessed the relationship of malarial fever and HIV rather than merely the presence of parasitaemia. The first study reported an increased rate of clinical malaria in HIV-infected children compared to children not infected with HIV (16). Nevertheless, no data on parasite densities were reported for better differentiation between parasite carriage and disease. The second study showed that HIV-infected children with advanced immunosuppression have more episodes of clinical malaria and higher parasite densities compared with HIV-infected children without advanced immunosuppression (10). The main shortcomings of this study are the poor specificity of the malaria case definition, the lack of reported parasitaemia data and the limited follow-up time in the HIV-infected group.

A study in rural Kwazulu-Natal, an area of unstable malaria, reported that HIV-infected children are more likely to experience severe disease particularly as a consequence of coma. Although the study included only small numbers of children, there was a tendency to increased mortality in the HIV-infected (see also Box 2) (37).

More research is urgently required. Without it, the public health significance of malaria and HIV interactions in children will remain uncertain.

Box 2. The impact of malaria and HIV on under-five mortality in Africa

After decreases during the 1970s and the 1980s, all-cause under-five mortality levelled off in African countries during the 1990s. Some countries (Kenya, Senegal, Uganda, the United Republic of Tanzania, Zambia and Zimbabwe) have even shown a resurgence in under-five mortality (38). The following data suggest that both malaria and HIV contributed to the halt of the decline in under-five mortality in Africa during the 1990s.

A recent review of mortality data from demographic surveillance sites in rural Africa found that malaria-attributable mortality in children under five years of age in East Africa increased between the 1980s and the 1990s (39). Since non-malaria mortality fell in these sites, the proportion of deaths due to malaria in children under five years of age increased from 18% to 37%. In West Africa, the malaria mortality rate was stable but non-malaria mortality fell, so that the proportional mortality due to malaria increased from 18% to 23%. These increases are probably related to the spread of parasite resistance against chloroquine, the most widely available antimalarial drug in Africa.

A review of HIV data from 39 sub-Saharan African countries estimated that HIV infection caused 7.7% of under-5 deaths in 1999, against 2% in 1990 (40). The countries with highest paediatric HIV mortality were Botswana, Namibia, Swaziland, Zambia, and Zimbabwe. If HIV prevalence increased further in these countries, so might paediatric HIV mortality also increase further, although the contribution of HIV to under-5 mortality is always limited because at least two thirds of infants born to HIV-infected mothers do not get HIV-infected.

Malaria is especially important in West, Central and East Africa, while the burden of HIV is greatest in Southern Africa. Limited data from areas of unstable malaria suggests that dual infection with malaria and HIV has an impact on morbidity and that there is a tendency to increased mortality in HIV infected children (37). However, no conclusions can be made to date without further specific data on co-infection; more research is needed.

Summary of presentations

SUMMARY OF EVIDENCE

Interactions in children and non-pregnant adults

Non-pregnant adults

- In areas of stable malaria
 - ▶ HIV increases the risk of asymptomatic malaria, clinical malaria and case fatality. The risk of clinical malaria increases with advancing HIV-related immunosuppression.
 - ▶ HIV infection may compromise malaria treatment; the risk increases with advancing HIV-related immunosuppression.
- In areas of unstable malaria
 - ▶ HIV increases the risk of complicated and severe malaria and death.
- **Malaria** contributes to transient rise in viral load among HIV-infected adults.

Children

- In areas of stable malaria
 - ▶ HIV infection leads to increased rates of malaria fever
 - ▶ Malaria and parasite density are higher in children with advanced immunosuppression.
- In areas of unstable/epidemic malaria
 - ▶ HIV-infected children are more likely to experience severe disease and coma.

Further studies investigating the impact of malaria on the natural history of HIV, potential therapeutic implications, interactions between HIV and malaria in children and interactions at a cellular and molecular level, are needed.

3. Interactions in pregnancy

Pregnant women have specific risks of complications from both malaria and HIV infection. This section provides an overview of the clinical effects and epidemiological characteristics of malaria and HIV co-infection in pregnant women. Many women in this region are exposed to both infections; in 11 of the 43 sub-Saharan African countries with malaria at least 10% of pregnant women attending antenatal clinics are HIV infected (Box 3).

Box 3. Sub-Saharan African countries with malaria where HIV prevalence among pregnant women attending ANC* is at least 10%

- | | |
|----------------------------|----------------|
| ▶ Botswana | ▶ Rwanda |
| ▶ Burundi | ▶ South Africa |
| ▶ Central African Republic | ▶ Swaziland |
| ▶ Ethiopia | ▶ Uganda |
| ▶ Malawi | ▶ Zambia |
| ▶ Mozambique | |

*Young pregnant women (15-24 years of age) attending antenatal clinics in capital city

Source: Whitworth J et al. (3)

The symptoms and complications of malaria during pregnancy differ with the intensity of malaria transmission and thus with the level of pre-existing immunity already acquired by the pregnant woman. Each year in malaria endemic areas of tropical Africa an estimated 25 million women become pregnant. In these areas, most adult women have developed sufficient immunity such that, even during pregnancy, *P. falciparum* infection does not usually result in fever or other clinical symptoms. However, particularly during their first or second pregnancy, women are highly vulnerable to the adverse consequences of malaria: maternal anaemia, placental malaria and low birth weight infants due to preterm delivery and intrauterine growth retardation (IUGR). For pregnant women in areas of unstable malaria, the risk of developing severe malaria is 2-3 times higher than for non-pregnant women. In addition, in these areas, malaria may result in low birth weight infants, spontaneous abortion or neonatal death.

The health of women in malaria-endemic areas is further affected by HIV. Women in Africa are being infected at an earlier age than men and at present in sub-Saharan Africa there are, on average, 13 HIV-positive women for every 10 HIV-positive men. HIV has become one of the major causes of maternal mortality in many resource-constrained settings (41, 42). It has an impact on obstetrical causes of maternal mortality by increasing the risk of pregnancy complications such as anaemia, post-partum haemorrhage and puerperal sepsis. Furthermore, in the absence of interventions about a third of infants born to HIV-infected women will become infected with the virus.

The effect of HIV on malaria during pregnancy

A meta-analysis of studies on co-infection in pregnancy (43) demonstrates that HIV infection impairs the ability of pregnant women to control *P. falciparum* infection (see also Box 4). They are more likely to develop clinical and placental malaria, more often have detectable malaria parasitaemia and have higher malaria parasite densities.

Most women in their first or second pregnancy are at higher risk of severe or complicated malaria than during subsequent pregnancies. However, this protective effect is diminished in HIV-infected women who, irrespective of the number of pregnancies, remain susceptible to the negative consequences of malaria infection. Hence, in the presence of HIV infection, the malaria-associated risks in pregnant

women who have had two or more pregnancies are comparable to the malaria-associated risks during the first or second pregnancy in women without HIV infection.

Anaemia can result from infection with malaria or HIV and during pregnancy contributes to higher levels of maternal morbidity and mortality as well as low birth weight infants. Studies from western Kenya (44, 45) and Malawi (Rogerson et al., unpublished data, 1998-2000) describe a synergistic interaction between malaria and HIV such that pregnant women with dual infection are at a significantly greater risk of anaemia than women with malaria or HIV infection alone. The increased risk of anaemia that occurs in co-infected pregnant women may be due to the higher parasite densities and longer duration of malaria infection that occurs in HIV-infected pregnant women.

Studies on cellular and humoral responses to malaria suggest that the increased susceptibility of HIV-infected pregnant women to malaria is due to modifications in systemic and placental immunologic parameters (43).

Box 4. Estimating the magnitude of the impact of HIV on the burden of malaria during pregnancy

The impact of HIV on the burden of malaria during pregnancy can be estimated using data on the prevalence of HIV among pregnant women, and on the HIV-associated increased risk of malaria during pregnancy.

In areas with stable malaria in Africa, approximately 25 million pregnant women are exposed each year to the disease. Of these women, at least 10.5 million develop malaria in the second or third trimester. It can be estimated that in 2003, the proportion of malaria infections during pregnancy attributable to HIV was 4.2% (range 3.8%-4.6%), based on an HIV prevalence among pregnant women in sub-Saharan Africa of 7.5% (range 6.9%-8.3%) in 2003. Using this data, it can be calculated that in 2003 the HIV epidemic resulted in an additional 440 000 (range 399 000-483 000) malaria cases during pregnancy in Africa.

Source: Adapted from Ter Kuile F et al. (43)

Summary of presentations

The effect of malaria on HIV in pregnant women

Several studies have reported a transient increase in HIV plasma viral load that is in part reversible with successful antimalarial treatment in pregnant women with malaria (46-49). There also appears to be an association between placental parasite density and placental viral load. A study in Malawi found that women with placental malaria had a 2-fold increase in placental viral load. These increases were independent of maternal CD4-cell count and most marked in women with a high placental parasite density (48).

Research investigating the impact of malaria infection on the risk of mother-to-child transmission (MTCT) of HIV has reported conflicting results. Therefore, it is not known whether malaria infection increases the risk of MTCT. In a study from Uganda, placental malaria was associated with an increased risk of MTCT (50). However, no association between placental malaria and risk of MTCT was detected in Mombasa, Kenya (46). In contrast to these findings, data from Kisumu, Kenya indicates that placental malaria reduces the risk of MTCT (49). Although some of these studies have adjusted for CD4-cell count and plasma viral load of pregnant women, others provide insufficient details on the biological status of women. Differences between the studies in maternal immunological status, plasma viral load, HIV subtype or mode of delivery may account for the inconsistent findings. These conflicting results may also reflect the complex relationship between maternal immune responses to malaria which, depending on the immune response, may either have a protective effect or increase the risk of MTCT. The direction of effect may depend on the degree of HIV-related immunosuppression and on the severity of malaria and thus the degree of placental monocyte infiltrates and pro-inflammatory cytokine and chemokine responses (43).

Impact of co-infection with malaria and HIV on pregnancy outcome

Compared to women with either malaria or HIV infection, women who are co-infected have a higher risk of preterm birth and intrauterine growth retardation and are therefore more likely to have low birth weight infants. Reports suggest that there is no consistent effect of maternal HIV on congenital malaria (51-53) or on the relationship between maternal and infant malaria (35, 54). In addition, whether dual exposure to both placental malaria and HIV increases the risk of infant mortality compared with infants born to HIV-infected women without placental infection is not clear; data from studies in Malawi (55) and two subsequent studies from southern

Malawi (56) and western Kenya (52) have reported conflicting results.

Maternal HIV infection induces pathological changes in the placenta that potentially could interfere with the mother-to-fetal transfer of antibodies. However, the mechanism of this process and whether a decreased transfer of antibodies to some malaria antigens has an impact on increased susceptibility to malaria in infants is not known.

Considerations for treatment, care and prevention of malaria and HIV in pregnant women

Data from a study in Malawi that compared different chloroquine prophylaxis regimens suggest that the presence of HIV results in a poorer response to both prophylaxis and treatment of malaria during pregnancy (51). In western Kenya, the usual IPT schedule of two doses of sulfadoxine-pyrimethamine (SP) for the prevention of malaria among pregnant women was sub-optimal among HIV-infected women in their first and second pregnancies. At least three doses of sulfadoxine-pyrimethamine may be required to achieve impact in HIV-infected women (57).

UNAIDS and WHO recommend opportunistic infection prophylaxis with cotrimoxazole (sulfamethoxazole-trimethoprim) for certain groups of HIV-infected individuals, including children and pregnant women after the first trimester (58). It is possible that the risk of an adverse drug reaction is increased if sulfadoxine-pyrimethamine for IPT and cotrimoxazole are taken together, as both are sulfonamide-containing drugs. As the interim recommendations on opportunistic infection prophylaxis inadequately considered the overlap of both prophylactic regimens they will be revised and updated in early 2005.

Although cotrimoxazole has been shown to decrease malaria morbidity in the general HIV-infected population, it is unknown whether it is effective in preventing malaria in pregnant women.

The prevention of malaria with insecticide-treated nets (ITN) plays a central role in malaria control strategies. A study in the Gambia demonstrated that ITN reduces the prevalence of malaria infection among pregnant women and the number of premature births (59). In a highly malarious area in Kenya, pregnant women using ITN gave birth to 25% fewer babies who were premature or small for gestational age than women who did not sleep under ITN (60).

SUMMARY OF EVIDENCE

Interactions in pregnancy

The effect of HIV on malaria

- ▶ HIV-infected pregnant women are at increased risk of
 - malaria parasitaemia in general, in the placenta, and at the time of delivery
 - higher malaria parasite densities
 - clinical malaria.
- ▶ HIV shifts the burden of malaria from women in their first and second pregnancy to all pregnant women.
- ▶ HIV impairs prophylaxis and treatment of malaria among pregnant women: at least three doses of IPT with SP are required to achieve efficacy in areas with high HIV-prevalence.

The effect of malaria on HIV

- ▶ Malaria contributes to increased HIV replication, which is greatest among women with highest parasite density, irrespective of the degree of immunosuppression.
- ▶ Research on the impact of malaria during pregnancy on the risk of mother-to-child transmission of HIV has given conflicting results.

The effect of co-infection on pregnancy outcome

- ▶ Infection with both malaria and HIV, in particular in individuals with low CD4-cell count, contributes to increased risks of
 - anaemia
 - low birth weight
 - preterm birth
 - intrauterine growth retardation (IUGR).
- ▶ It is not clear whether dual exposure to both placental malaria and HIV increases the risk of infant mortality compared with infants born to HIV-infected women without
- ▶ It is not known whether maternal HIV infection results in increased susceptibility to malaria in infants.

Considerations for the prevention of malaria and opportunistic infections

- ▶ There is a potential risk of increased adverse drug reactions if opportunistic infection prophylaxis with cotrimoxazole and malaria prevention with sulfadoxine-pyrimethamine are taken together.

4. Interactions between antimalarials and medicines used for treatment and care of people living with HIV

Interactions between antimalarial medicines and ARVs

Several different classes of antiretroviral drugs (ARVs) exist. The WHO recommended first-line ARV regimens consist of a five-drug formulary, with a triple-combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTIs). Most ARV treatment guidelines do not consider PIs as part of first-line regimens, but they are included in second-line therapy and available in many private clinics.

Since HIV PIs are potent inhibitors of cytochrome P₄₅₀ enzymes (a major pathway for drug metabolism), and NNRTIs

are inducers and/or inhibitors of these enzymes, pharmacokinetic interactions with anti-malarials mostly involve PIs and NNRTIs. In patients receiving PIs (or the NNRTI delavirdine), halofantrine is contraindicated because of excessive risk of toxicity. It is also possible that interactions with artemether and/or lumefantrine can occur. The very potent cytochrome P₄₅₀ enzyme inhibitor ketoconazole has been shown to have a modest effect on lumefantrine and artemether exposure (approximately 2-fold increase), which was not associated with an increase in side effects (61). However, the magnitude and clinical significance of these potential interactions needs further research. For patients receiving other NNRTIs (nevirapine or efavirenz) lower concentrations of both antimalarials may lead to increased risk of treatment failure. A potential interaction between quinine and NNRTI or PI drugs also needs to be investigated (Annex Table 1).

Summary of presentations

Inter-individual variability of plasma concentrations has been observed for PIs and NNRTIs (62). Differences in drug adherence, drug absorption, body weight and gender may account for this variation. Studies from the Netherlands (63) and United Kingdom (Liverpool Therapeutic Drug Monitoring Service, unpublished observations, January 2004) have observed that women have significantly higher plasma levels of nevirapine and efavirenz (NNRTI drugs) than men and may be at increased risk of toxic plasma concentrations. Certain ethnic groups may also be at higher risk of toxicity due to genetic factors (64-67). However, the effect of these variables on the pharmacokinetics of ARV drugs and on interactions with other drugs, including antimalarials, is not clear.

Some studies have described moderate antiretroviral properties of antimalarial drugs. In vitro, chloroquine suppresses HIV replication and in HIV-infected cells it was shown to have an additive effect with zidovudine (a NRTI drug) and—according to more recent reports—synergy with numerous PIs in T-cell lines (68, 69). However, the clinical significance of these findings is unknown and the antiretroviral effects of chloroquine are modest when compared with triple-combination antiretroviral drugs.

Low adherence, poor-quality drugs and drug resistance decrease the effectiveness of both antiretroviral and antimalarial drugs and may further hamper treatment outcome. There is potential for integrated strategies to overcoming these challenges that could benefit malaria and HIV treatment.

Interactions between antimalarials and other medicines used in the care of people living with HIV

The use of cotrimoxazole (sulfamethoxazole-trimethoprim) for prophylaxis of opportunistic infections in HIV-infected adults and children may have implications for treatment of malaria. Furthermore, severe allergic reactions to sulfa-containing medicines have been reported in prophylactic settings, and this risk may increase with more frequent use of cotrimoxazole or sulfadoxine-pyrimethamine. Widespread cotrimoxazole use could also accelerate the development of resistance in malaria parasites to sulfadoxine-pyrimethamine (although, due to extensive parasite resistance to SP, it is unlikely that this drug remains first-line treatment for malaria for much longer). Cotrimoxazole could select for mutations in the enzymes that are inhibited by the sulphonamide and pyrimethamine components of sulfadoxine-pyrimethamine. This potential impact emphasizes the importance of drug resistance monitoring, in particular in communities where prophylaxis with cotrimoxazole is common.

Overlapping drug-associated syndromes and toxicities may complicate the clinical presentation of malaria and HIV co-infection, and may include fever, rash, anaemia, agranulocytosis or pancytopenia, Stevens-Johnson's syndrome or toxic epidermal necrolysis, lactic acidosis, hepatitis and renal failure (Annex Table 2). Given the multiple potential causes of these syndromes, determining the causative factors in individual cases may be difficult.

SUMMARY OF EVIDENCE

Pharmacodynamic and pharmacokinetic interactions between antimalarials and antiretrovirals

- ▶ Pharmacokinetic interactions involve mostly PIs and NNRTIs; thus in patients receiving PIs (or the NNRTI delavirdine) halofantrine should not be given because of excessive risk of toxicity; other NNRTIs should be used with caution. A potential interaction between quinine and NNRTI or PI drugs also needs to be investigated.
- ▶ Chloroquine was shown to have in-vitro antiretroviral properties; the clinical effect of chloroquine in HIV-infected adults is currently being examined.
- ▶ Research on the impact of malaria during pregnancy on the risk of mother-to-child transmission of HIV has given conflicting results.
- ▶ Cotrimoxazole has an antimalarial effect and could accelerate the development of resistance to sulfadoxine-pyrimethamine. Therefore, monitoring drug resistance, in particular in communities where prophylaxis with cotrimoxazole is common, is important.
- ▶ More research is urgently required; close monitoring and pharmacovigilance needs to be emphasized in the treatment of malaria and HIV.

5. Health systems and service delivery considerations

The financial and human resource constraints of health systems in countries most affected by malaria and HIV, and the shared determinants of vulnerability for both diseases, indicate the need for integration of preventive and curative services for malaria and HIV and strengthening the health systems that deliver these services. Opportunities for collaborative and complementary malaria and HIV prevention and control measures are presented in this section.

HIV control programmes have introduced new elements of counselling, chronic diseases care and management to be provided by an infrastructure that was originally planned at a time when HIV/AIDS was unknown, or not recognized as a major problem. At the same time, malaria control programmes are introducing new diagnostic tools and new medicines. These new elements of care in impoverished settings call for innovative thinking on health systems and service delivery in affected areas.

Maternal and child health services are the most accessible health services in many communities. In these settings ANC clinics serve as the main entry point for prevention and care

services for pregnant women and their children. But they also serve as a good link to other health services for families and communities. In sub-Saharan Africa, antenatal care utilization is relatively high. Hence, reproductive health services, and antenatal care services in particular, could serve as the pivotal entry point for simultaneous delivery of interventions for the prevention and control of malaria and HIV in pregnant women and their neonates with linkages to the community, child health, HIV counselling and testing, treatment, care and support services, family planning and other services for tuberculosis and sexually transmitted infections.

Delivery of malaria and HIV interventions within existing health services may permit effective utilization of human resources and address serious resource constraints. The challenge is to ensure coherence at each level of the health system, and to maximize the use of available resources for integrated service delivery.

Partnerships and collaboration among maternal and child health, malaria, HIV and other programmes are a prerequisite for joint planning and implementation of effective integrated services.

SUMMARY

Health systems and service delivery considerations

- ▶ New elements of prevention, diagnosis, treatment and care in both programmes call for renewed thinking on health systems organization and service delivery, as well as infrastructure and human resources development and planning in affected areas.
- ▶ Reproductive health services, and in particular antenatal care services, could serve as the pivotal entry point for the delivery of interventions for the prevention and control of malaria and HIV in pregnant women and their children.
- ▶ An integrated package of interventions could be provided to clients at service delivery points for tuberculosis, sexually transmitted infections and family planning; combining services with existing social and health programmes may permit the most effective utilization of human resources and address serious resource constraints.
- ▶ Effective implementation and widespread utilization of malaria and HIV interventions will require strong health systems, including essential maternal, child and other adult health services and a functioning referral system.
- ▶ Partnerships and collaboration among relevant programmes are a prerequisite for planning and implementation of integrated services.

Recommendations

A. Policy and programmatic implications of interactions between malaria and HIV

Working group discussions were held to identify normative gaps and other priorities for WHO and partners and to discuss policy implications of interactions between malaria and HIV. The findings of working group discussions were presented to the plenary for further discussion and refining. This section presents the recommendations adopted by the technical consultation meeting.

1. Recommendations for prevention, treatment and care in children and non-pregnant adults

Depending on the malaria transmission setting, HIV-infected individuals are at increased risk of asymptomatic parasitaemia, clinical malaria or severe and complicated malaria. Therefore, they have an even greater need for malaria prevention and effective treatment than individuals not infected with HIV. Though the whole population should benefit from malaria prevention in endemic areas, access to ITN or other locally appropriate prevention measures for groups at particular risk, including HIV-infected people is considered a high priority.

A fever-based malaria case definition may result in febrile illnesses caused by opportunistic infections being misdiagnosed as malaria, leading to over-treatment of malaria. However, prompt antimalarial treatment is vital to prevent progression to severe malaria and death, particularly in young children. In the absence of an alternative to the fever-based malaria case definition applicable in a wide range of resource-constrained settings (community- and home-based management of fever), the technical consultation concluded that current recommendations for the use of effective treatment of malaria at the onset of fever symptoms remain unchanged. As improvements in health systems occur, confirmatory testing for malaria should increasingly become available in malaria-endemic areas, and would clearly be of use in such clinical situations.

In settings with stable malaria and high HIV prevalence, there should be a high suspicion of HIV among individuals with repeated episodes of fever, and the treatment of fever as malaria alone (in particular, among patients other than young children) is potentially detrimental. Therefore, in addition to providing malaria treatment, health providers at the periphery of health services should offer HIV testing and counselling.

Infection with HIV reduces the effectiveness of anti-malarial treatment. Therefore, in countries with generalized HIV epidemics, routine monitoring of antimalarial drug effectiveness should include the assessment of the effect of HIV on antimalarial treatment outcome. The surveillance of resistance to commonly used sulfa-containing

drugs (i.e. sulfadoxine-pyrimethamine for the prophylaxis and treatment of malaria and cotrimoxazole for prophylaxis of opportunistic infections) should be incorporated into already existing surveillance activities. Where needed, the capacity for pharmacovigilance needs to be strengthened and additional systems established. As additional evidence emerges on the efficacy of drugs, prescribing knowledge must be updated accordingly and widely disseminated.

2. Recommendations for prevention, treatment and care of malaria and HIV in pregnancy

Reproductive health services play a key role in the delivery of treatment, care and prevention to pregnant women and their infants. With respect to HIV, reproductive health services are a critical place to offer routine provider-initiated HIV testing and counselling and to follow this up with prevention of MTCT interventions according to national policy for those who test positive, coupled with entry to ART programmes for those sick and in need of immediate therapy. These services, therefore, need to be strengthened to ensure the delivery of the WHO-recommended antenatal care schedule of four visits (focused antenatal care), which includes a minimum package of interventions for the prevention of both malaria and HIV. In addition, all pregnant women living in malaria endemic areas—irrespective of HIV status—should be provided with ITN.

Based on evidence that IPT with two doses of sulfadoxine-pyrimethamine is less efficacious in HIV-infected pregnant women in their first and second pregnancies, the technical consultation agreed that the current WHO recommendation on the use of IPT needs to be revised. At least three doses of sulfadoxine-pyrimethamine should be given for the prevention of malaria in HIV-infected pregnant women, unless the woman receives cotrimoxazole prophylaxis.

The technical consultation evaluated the potential implications of widespread use of cotrimoxazole on the development of resistance in malaria parasites to sulfadoxine-pyrimethamine and the beneficial effect of cotrimoxazole on reducing HIV-related morbidity. There was consensus that the current UNAIDS/WHO recommendations on the prophylaxis of opportunistic infections with cotrimoxazole in people living with HIV need to be revised and updated. In the meantime, pregnant HIV-infected women should

not receive IPT with sulfadoxine-pyrimethamine in addition to cotrimoxazole prophylaxis (see above recommendation). Clinical malaria in these women should be treated with antimalarial drugs other than sulfa-containing drugs.

3. Implications for health systems and service delivery

Interactions between malaria and HIV necessitate collaboration between malaria and HIV programmes. The extent of these interactions among at-risk populations also provides justification and opportunities for joint programming with other service delivery programmes focusing on reproductive and child health, tuberculosis and sexually transmitted infections. In particular, integrating services for prevention, treatment and care for malaria and HIV within the framework of maternal and child health services, is vital for reducing the burden of both diseases.

Collective action needs to be mobilized to control malaria and HIV. Such effort should include establishing mechanisms for collaboration and joint programming at various levels. Collaborative programming should take into consideration strategies that have been developed for improving drug quality and adherence to antimalarial and antiretroviral treatment, including establishing drug resistance surveillance programmes. The use of rapid diagnostic testing and other methods for malaria diagnosis should be assured in the context of HIV.

Malaria and HIV programmes should contribute to strengthening health systems and capacity for equitable service delivery, to address the needs of poorer communities that are most at risk of these diseases. Improving human resources will be key to this effort since human resources constraints have become critical in areas with a high burden of malaria and HIV infections. Strategies should include:

- ▶ harmonization of policies and plans for human resources development and capacity-building;
- ▶ addressing migration of health professionals;
- ▶ harmonization of management of the major commodities (i.e. ITNs, antimalarial medicines, ARVs, diagnostics) for both diseases at national and local levels; and
- ▶ strengthening existing institutions, management structures and health information systems.

Recommendations

Opportunities for strengthening health systems exist through increasing availability of resources for malaria and HIV through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

Mechanisms for delivering interventions for malaria and HIV outside of health facilities need to be explored in areas with weak health-care infrastructure. The provision of antimalarial treatment at the community level and as close to the household as possible as well as efforts of the 3 by 5 initiative to decentralize the provision of ART and other HIV-related services are necessary for increasing the accessibility and coverage of services. Experiences with home-based treatment of malaria could inform the establishment of similar community-based, HIV-related activities. Furthermore, community-based agents and people living with HIV/AIDS (PLWA) could play a key role in delivering integrated services for malaria and HIV at the community level. Their potential support to ITN distribution may have particular importance in increasing coverage with ITN among HIV-infected individuals as well as in reinforcing preventive and supportive behaviours.

The technical consultation recommended core activities for integrating interventions for the prevention and control of malaria and HIV at the different levels of the delivery system. They are summarized in Table 1.

Table 1

Core activities for integrating prevention and care services for malaria and HIV

Level of intervention	Activities	
<p>Primary level health care</p>	Prevention	
	HIV	Malaria
<p>District-level health care</p>	Prevention	
	<ul style="list-style-type: none"> – IEC/BCC – Voluntary counselling and testing – Prevention of MTCT – Distribution of products – Prophylaxis of opportunistic infections with isoniazid and cotrimoxazole 	<ul style="list-style-type: none"> – IEC/BCC – IPT – Distribution & re-treatment of ITNs – Integrated vector management
	Care	
<p>Control programme level</p>	<ul style="list-style-type: none"> – Antenatal care (including IPT and prevention of MTCT of HIV) – Delivery with skilled birth attendant in an enabling environment – Clinical diagnosis for both diseases; introduction of confirmatory testing for malaria and HIV – Treatment of malaria and HIV-related opportunistic infections – Referral to appropriate treatment care and support services – IEC/BCC – HIV testing and counselling – Prevention of severe anaemia – Laboratory services for HIV, malaria and anaemia. 	
	<ul style="list-style-type: none"> – Diagnosis – Management of opportunistic infections – ART 	<ul style="list-style-type: none"> – Confirmatory diagnosis (microscopy/RDT) – Case management of febrile pregnant women – Case management of severe malaria – Case management of referred cases
	<ul style="list-style-type: none"> – Coordination of planning by the various programmes for service delivery – Streamlining of policies, strategies, guidelines and capacity-building – Participation in the human resources development agenda – Quality assurance for diagnosis and treatment – Optimizing the management of medicines with a short shelf life, especially anti-retrovirals and artemisinin-based combination treatment for malaria 	

Recommendations

B. Future research needs

During the presentations and group discussions, a number of research issues were identified. The summary for the different areas is given below in Table 2.

Table 2

Overview of research questions pertaining to malaria and HIV interactions

Research area	Issues
Epidemiology	<ul style="list-style-type: none"> ▶ Interactions of malaria and HIV, including the effect on antimalarial immunity stratified by transmission setting ▶ Effect of HIV on malaria transmissibility ▶ Interaction between non-falciparum species and HIV ▶ Development of detailed maps to identify risk areas for co-infection ▶ Identification of levels of antimalarial medicine use in sub-Saharan Africa, linked with HIV status ▶ Evaluation of potential contribution of HIV to overestimates of under-five mortality in Africa attributable to malaria
Prevention of malaria in pregnant women	<ul style="list-style-type: none"> ▶ Monitoring of efficacy of currently recommended schedule of at least 3 doses of IPT with SP ▶ Evaluation of the safety and efficacy of potential alternative medicines to replace SP for prevention of malaria in pregnant women, stratified by <ul style="list-style-type: none"> – HIV infection status – different ARVs being used
Cotrimoxazole (role in prevention and treatment of malaria)	<ul style="list-style-type: none"> ▶ Comparison of the efficacy of daily cotrimoxazole for pregnant women with symptomatic HIV infection with the efficacy of IPT with SP, with regard to the reduction of: <ul style="list-style-type: none"> – placental parasitaemia at delivery – maternal anaemia – LBW ▶ Antimalarial effectiveness of cotrimoxazole ▶ Role of cotrimoxazole in the treatment of breakthrough infections
Treatment/Clinical implications of interactions	<ul style="list-style-type: none"> ▶ Improvements in malaria case definition and diagnosis, where HIV is prevalent ▶ Identification of more efficacious drugs or regimens using existing drugs for treatment of malaria in HIV-infected pregnant women, adults and children ▶ Impact of different CD4 cell levels on the efficacy of antimalarial treatment ▶ Role of prevention and treatment of anaemia in dual-infected pregnant women ▶ Impact of HIV infection <ul style="list-style-type: none"> – on resistance to antimalarials – at an individual level, on further increase of failure rate of therapy ▶ Clinical effect of malaria-induced transient increases in viral load on HIV prognosis

Research area	Issues
MTCT of HIV	<ul style="list-style-type: none"> ▶ Evaluation of the impact of malaria on MTCT of HIV, taking into consideration <ul style="list-style-type: none"> – biological status of the mother (i.e. CD4 cell count and variations in HIV sub-type) – type of delivery of babies
Children	<ul style="list-style-type: none"> ▶ More detailed evaluation of interactions between malaria and HIV ▶ Impact of HIV on antimalarial efficacy (including severe and complicated malaria)
Drug interactions	<ul style="list-style-type: none"> ▶ Evaluation of the impact of cotrimoxazole prophylaxis on resistance to antifolates (because of high and frequent dosing of sulphamide and cotrimoxazole) ▶ Evaluation of interaction between antimalarials and ARVs (e.g. quinine, artemether, lumefantrine and PIs or NNRTIs) in different settings including assessment of potential implications for the treatment of malaria ▶ Impact of inter-individual variability (i.e. gender, age and body weight) and ethnic differences on <ul style="list-style-type: none"> – plasma concentrations of ARVs – drug penetration of ARVs – interaction between antimalarials and ARVs
Operational research	<ul style="list-style-type: none"> ▶ Implementation of integrated services including <ul style="list-style-type: none"> – HIV-related care and treatment – malaria case management – delivery of commodities, e.g. delivery of ITN through ARV programmes ▶ Evaluation of the capacity of community-based agents to deliver extended packages ▶ Development of IEC/BCC packages with consistent messages on interactions between malaria and HIV for antenatal care and other related services
Quality of research conduct	<ul style="list-style-type: none"> ▶ Consistency of high-quality standards for conduct of research; e.g. observational studies and randomized trials on questions that pertain to policy implications

Conclusion

This technical consultation was the first meeting of international experts that assessed the interactions between malaria and HIV and the consequences of such interactions for the health of people affected by both diseases.

The technical consultation has emphasized the vital importance of providing integrated health services in areas heavily affected by malaria and HIV for reducing the burden of the two diseases. On the basis of the evidence presented and the findings of this meeting, many opportunities for collaborative cross-programme activities and research exist. HIV prevention, care, treatment and support activities must incorporate interventions relating to malaria prevention and control. Similarly, malaria control programmes must consider the prevention of HIV and the care and treatment needs of HIV-infected children and adults. Reproductive health services play a key role in the delivery of care to pregnant women and their infants who are at greatest risk for the adverse consequences of infection with malaria and HIV.

Also outside the context of reproductive health, integration of services pertaining to the prevention and care of malaria and HIV is likely to provide advantages over delivering malaria and HIV interventions separately. However, considering the current constraints to delivering quality health services, further discussion on future collaborative work in integrated health services is essential.

Providing antimalarial treatment at the community level and as close to the household as possible as well as efforts of the 3 by 5 initiative to decentralize the provision of ART and other HIV-related services are necessary for increasing the acceptability and coverage of services. Experiences with home-based treatment of malaria may be used to inform the setting up of similar home-based HIV-related activities. Furthermore, community-based agents and PLWA could play a key role in the delivery of integrated services for malaria and HIV.

It is anticipated that one of the positive consequences of the 3 by 5 initiative and related activities will be an improved laboratory capacity, spearheaded by the needs for HIV diagnosis and monitoring of antiretroviral treatment (ART) but which will benefit all disease control programmes. Prompt antimalarial treatment is crucial in particular in young children, but where possible, malaria diagnostic testing should be used in HIV-infected febrile children and adults. Access to valid and reliable diagnostic services is especially important for HIV-infected individuals receiving ART.

The challenge in delivering integrated services is to combine activities for malaria and HIV at various levels of the health system, tailor responses to the need of communities, and optimize the use of scarce resources. There are many opportunities for synergism, in particular at a time of growing political and financial commitment to reduce the burden of HIV/AIDS, tuberculosis and malaria.

Nevertheless, this meeting has emphasized the urgent need for more research on a number of unanswered questions. Only with sufficient evidence can appropriate public health policy be devised on integrating the prevention, care, treatment and support activities for malaria and HIV.

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Annex

Table 1
Overview of potential drug interactions

Drug group	Quinine	CQ	SP	Pro	Dap	MQ	AQ	ASU	LUM	HAL	ATQ
Protease Inhibitors											
Saquinavir	■	◆	◆	◆	◆	◆	—	—	●	●	◆
Ritonavir	■	■	■	■	◆	◆	—	—	●	●	■
Indinavir	■	◆	◆	◆	◆	◆	—	—	●	●	◆
Nelfinavir	■	◆	◆	◆	◆	◆	—	—	●	●	◆
Amprenavir	■	◆	◆	◆	◆	◆	—	—	●	●	◆
Lopinavir	■	◆	◆	◆	◆	◆	—	—	●	●	■
Atazanavir	■	◆	◆	◆	◆	◆	—	—	●	●	◆
NNRTIs											
Nevirapine	■	◆	◆	◆	◆	◆	—	—	■	■	◆
Efavirenz	■	◆	◆	◆	◆	◆	—	—	■	■	◆
Delavirdine	■	◆	◆	◆	◆	◆	—	—	●	●	◆
NRTIs											
Zidovudine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Lamivudine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Didanosine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Stavudine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Abacavir	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Zalcitabine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Emtricitabine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Tenofovir	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

Key:

CQ - chloroquine, SP- sulfadoxine-pyrimethamine, Pro- proguanil, Dap - dapsone, MQ - mefloquine,

AQ - amodiaquine, ASU- artesunate, LUM - lumefantrine, HAL - halofantrine, ATQ - atovaquone

— There are no clear data, actual or theoretical, to indicate whether an interaction will occur

◆ No clinically significant interaction, or interaction unlikely based on knowledge of drug metabolism

■ Potential interaction that may require close monitoring, alteration of drug dosage or timing of administration

● Interaction likely, do not use or use with caution

Source: adapted from www.hiv-druginteractions.org

Annex

Table 2

Overlapping drug-associated syndromes and toxicity that potentially complicate the clinical presentation of malaria and HIV co-infection

Syndrome	Causes
Fever	Malaria, opportunistic infections, HIV itself , drug hypersensitivity such as that encountered with abacavir or nevirapine
Anaemia	Common finding in HIV-infected patients in Africa, and may be HIV-related, or else caused by drugs (zidovudine, dapsone, cotrimoxazole), haemolysis (e.g. in G6PD deficient patients) or malaria infection
Agranulocytosis or pancytopenia	Amodiaquine, dapsone, cotrimoxazole, zidovudine or else HIV or other infection
Rash	Most antimalarials and anti-HIV drugs
Stevens-Johnson's Syndrome/Toxic Epidermal Necrolysis	Nevirapine, abacavir and rarely sulfadoxine-pyrimethamine (1:20,000)
Lactic acidosis	NRTIs, malaria
Hepatitis	Amodiaquine, NNRTIs, PIs, NRTIs, background chronic hepatitis B
Renal failure	Malaria nephritis, HIV nephropathy, microsporidiosis, sulphonamides (at <i>Pneumocystis carinii</i> pneumonia treatment doses), indinavir, tenofovir

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