President's Malaria Initiative

Technical Guidance on the Prevention and Control of Malaria in Africa

Introduction: Although malaria is a preventable and treatable disease, it is estimated to cause between 300 and 500 million illnesses and is responsible for killing between one and two million people each year. More than 90% of these illnesses and deaths occur in sub-Saharan Africa where malaria transmission is most intense. In most of sub-Saharan Africa, children under five years of age and pregnant women are the most vulnerable to infection, as they have little or reduced protective immunity. In other regions of the world, particularly Latin America, and most of Asia, levels of transmission are much lower and malaria tends to affect people of all ages, causing severe morbidity, but less commonly resulting in deaths.

In June 2005, President Bush announced a new $1.2 billion initiative, the President's Malaria Initiative (PMI) to reduce malaria-related mortality by 50% in up to 15 sub-Saharan African countries through a rapid scale up of a package of proven malaria prevention and treatment measures: artemisinin-based combination therapy (ACT); insecticide-treated mosquito nets **(**ITNs), intermittent preventive treatment in pregnancy (IPTp), and indoor residual spraying (IRS).

To meet the challenge of reducing the global malaria burden, PMI supports strategies that:

- prevent malaria infection and illness through the use of ITNs and IRS;
- promote effective treatment of malarial illnesses;
- protect pregnant women from malaria through a combination of IPTp and ITNs;
- prevent or contain malaria epidemics; and
- address the needs of populations in complex humanitarian emergencies.

In this "Technical Guidance on the Prevention and Control of Malaria in Africa" answers are given to frequently asked technical questions about how best to prevent malaria infection, to treat malarial illness and to protect women during pregnancy. Bibliographical references and web linkages for additional information are provided. While each Question and Answer is organized around a specific area of intervention (treatment, prevention, etc.), it is important for malaria control programs to support a comprehensive package of preventive and curative services. This "package" approach is key to realizing the full potential of these interventions and to reducing the burden of malaria.

Options for Preventing Malaria

The most effective way to prevent malaria is through the selective and safe use of measures that reduce contacts between mosquitoes and human beings. There are two primary options for reducing the risk of malaria transmission: indoor residual spraying (IRS) and insecticide-treated nets (ITNs). The President's Malaria Initiative supports the use of both IRS and ITNs. The choice of which intervention to use should be driven by local conditions and needs.

Q. How do IRS and ITNs work?

A. IRS is the organized, timely spraying of an insecticide on the inside walls of houses. It is designed to interrupt malaria transmission by killing adult female mosquitoes when they enter houses and rest on the walls after feeding, but before they can transmit the infection to another person. IRS has been used for decades, and has helped to greatly reduce or eliminate malaria from many areas of the world, particularly where the mosquito vectors are indoor-resting and where malaria is seasonally transmitted. In tropical Africa, the best data for IRS are from the Garki Project in the Nigerian savanna during the 1970's, where 25-30% reductions in infant mortality rates were documented in sprayed villages when compared to unsprayed villages. More recently, a large-scale multi-country project in the Republic of South Africa, Swaziland, and Mozambique and another on Bioko Island, Equatorial Guinea have demonstrated the feasibility and impact of IRS on malaria in sub-Saharan Africa.

Bednets treated with an appropriate insecticide (insecticide-treated bednets; ITNs), or manufactured with a wash-resistant insecticide preparation (long-lasting insecticide-treated nets; LLINs) have been shown to be highly effective in reducing malaria transmission. In addition, the netting acts as an additional protective barrier. Consistently sleeping under an ITN has been shown to decrease severe malaria by 45%, reduce premature births by 42% and reduce all-cause child mortality by 17%–63%. When coverage rates reach 80% or more in a community, even those residents not sleeping under an ITN obtain a protective benefit. This "mass effect" or "community effect," as it is called, suggests that a major result of the use of ITNs in an area of intense malaria transmission may be to reduce the overall mosquito population in addition to reducing human-vector contact at the individual level.

Q. When is IRS a better option for malaria prevention?

A. Historically, IRS has been most frequently used in areas with unstable malaria (i.e., where transmission varies considerably from one season or one year to the next), for epidemic-prone malaria (especially in Southern Africa and in the Horn of Africa), in urban areas when local transmission of malaria is well documented, and in refugee camps. In each of these settings, IRS has the advantage in that it can produce rapid and reliable short-term impact.

Indoor residual spraying has significant operational and management demands which require careful planning and preparation for effective implementation. In countries with little or no recent experience with IRS, it is desirable to begin the planning process at least 6-8 months prior to the beginning of the rainy season or the anticipated start of spray operations. Expert advice is extremely valuable during this planning process.

There has been less experience with the use of IRS in sub-Saharan African countries with year-round, moderate- to high-level transmission. Recent successes with IRS programs in Southern Africa and in Equatorial Guinea indicate the potential value of this control measure. This area merits further study, and PMI will be supporting and thoroughly evaluating IRS campaigns in several moderate- to high-transmission areas during the coming years. As part of these efforts, comprehensive evaluations of the impact and cost-effectiveness of IRS will be carried out. It will also be important to understand how best to use IRS and ITNs in combination, including measuring the added benefit of IRS when used together with ITNs in settings with varied transmission intensity and population densities. More information on the use of IRS can be found under "Vector Control" on the Roll Back Malaria website (www.rbm.who.int/).

Evidence concerning the cost-effectiveness of IRS in relation to that of ITNs has been mixed. In some cases IRS appears to be more cost-effective than ITNs; in other cases the reverse was found. USAID has commissioned a team of technical experts to evaluate the relative cost-effectiveness of IRS and ITNs, and to identify the most important factors which make a difference in particular settings. The findings from the study will be available later in 2006. Some general observations can be drawn, however, from existing information. When the infrastructure requirements for delivery of ITNs and IRS and the frequency with which insecticides need to be reapplied are factored in, the cost for delivery of ITNs and two rounds of IRS in urban and periurban settings are almost equivalent---about $3-6 per person covered per year. As one moves to more rural and infrastructure-poor areas, where the risk of malaria is often the highest, the costs for IRS would be expected to rise relative to the cost for an LLIN, which has a higher initial cost but does not require return visits during the lifetime of the net (estimated at 3-4 years).

Q What are ITNs and LLINs?

A. The use of bednets treated with some of the same insecticides (insecticide-treated nets or ITNs) used for IRS has been shown in trials across Africa to be a highly effective option for protecting households from malaria. The most commonly used insecticides are the synthetic pyrethroids, such as deltamethrin and lambdacyhalothrin. Traditional ITNs need to be retreated with insecticides after they have been washed several times.

Long-lasting insecticide-treated nets (LLINs) are nets manufactured with a wash-resistant insecticide. These nets maintain their insecticidal properties during multiple washes and do not require retreatment with insecticides. To-date, WHO has approved two long-lasting products," Vestegaard Frandsen's *PermaNet*®, and Sumitomo's *Olyset*

Net®. While these products employ different technical processes, each has been certified as being capable of maintaining the full protective effects of an insecticide treated net through a minimum of 20 washes. By comparison, the traditional process of dipping nets in insecticide has an effective life of only about three washes. This difference translates into LLINs providing full protection from malaria infection for the effective lifetime of the net (3-4 years), while a traditional ITN will require re-treatment at least every six months. Recent data suggests that after washing, the insecticidal activity of the Olyset Net may need to be regenerated by placing it in a plastic bag in the sun for one hour. One disadvantage of the LLINs is that they are at least 50 to 100% more expensive than traditional ITNs. Over the coming year, with USAID assistance, at least two new LLINs will be introduced to the market, which are expected to be less expensive and have even longer life-spans.

Q. When are ITNs a better option?

A. ITNs have been shown to be highly deployable in rural Africa using, community groups, public sector infrastructure, including mass immunization campaigns, and the existing commercial sector. Maintaining reliable supply chains can be a challenge and ensuring compliance with the care and use of the nets can also be a problem requiring effective promotion activities, but well-designed programs are having good success in many countries.

The cost for delivering ITNs through a combination of commercial, non-governmental organization (NGO), and community groups remains fairly steady at $4-6 per person, depending on how the costs of delivery are distributed. The availability of LLINs has made this control option more cost-attractive by eliminating the costs associated with retreating nets with insecticides ($1 or more per net per year). The overall effectiveness of traditional ITNs is limited by the generally poor rates of net retreatment in most programs.

Q. What insecticides are used for IRS?

A. The WHO Pesticide Evaluation Scheme (WHOPES) lists the following insecticides as approved for use in IRS:
http://whqlibdoc.who.int/hq/2003/WHO_CDS_WHOPES_2002.5_Rev.1.pdf

1. alphacypermethrin (P)
2. bendiocarb (C)
3. bifenthrin (P)
4. cyfluthrin (P)
5. DDT (OC)
6. deltamethrin (P)
7. etofenprox (P)
8. fenitrothion (OP)
9. lambda-cyhalothrin (P)

10. malathion (OP)
11. pirimiphos-methyl (OP)
12. propoxur (C)

These insecticides are listed in alphabetical order and consist of pyrethroids (P), carbamates (C), organophosphates (OP) and an organochlorine (OC). The choice of which insecticide to use in a particular setting should be made with expert consultation during the planning period for spraying. The document referenced above contains general guidelines for selection which need to be considered in light of local information concerning the mosquito vector species, its biting and resting habits, wall surfaces/housing construction, insecticide resistance levels in vector species, logistic capacity, and local environmental regulations.

Q. Are there prohibitions against the US Government procuring insecticides?

A. The US Government can and does procure insecticides for its health programs. Activities to support purchase or use of insecticides require an environmental risk assessment. This is a mandatory legal requirement because insecticides are toxins and if inappropriately used, can create serious health problems, such as poisoning, cancer, birth defects or fertility loss, and can damage the environment on which the local people rely for essential food supplies. These risks can be minimized in properly planned, organized, and managed vector control programs. The purpose of the environmental review process is to ensure that this planning takes place and that risks are properly managed.

The required environmental assessment procedures are described in Title 22 of the Code of Federal Regulations, Part 216 (22 CFR 216). In brief, this assessment consists of an evaluation of which pesticide(s) may be procured or used (including ones procured by US Government partners) based on scientific selection of the safest and most efficacious pesticide(s) according to U.S. Environmental Protection Agency registration data. The assessment includes a plan for safe use to reduce to a minimum any risks to humans or the environment and includes a fully-funded mechanism for ongoing monitoring and compliance throughout the life of the project. The environmental assessment must be approved by a USAID Bureau Environmental Officer before any USAID funds can be obligated for the activity. A copy of the text of 22 CFR 216 is available to the public at: http://www.usaid.gov/our_work/environment/compliance/regulations.html. USAID Bureau Environmental Officers or Regional Environmental Advisors can provide details and examples of these procedures.

Insecticide-treated nets: Insecticides for use in ITN programs have been thoroughly evaluated in a Programmatic Environmental Assessment (PEA) prepared by USAID's Africa Bureau in 2001. Thanks to this PEA, the level of effort required for an environmental assessment for an ITN activity has been greatly reduced. ITN programs in Africa with insecticide treatment and re-treatment activities should prepare their environmental assessments as amendments to the existing PEA. This amendment, or Supplemental Environmental Assessment (SEA) as it is called, will only have to deal

with country- and site-specific aspects of the ITN use.

Long-lasting ITNs (which do not require insecticide re-treatment) also require compliance with 22 CFR 216. Although the Africa ITN PEA may be expanded in the future to cover LLINs, it does not at present. Consequently, the environmental documentation for LLIN distribution programs (i.e., an Initial Environmental Evaluation or IEE) covering the pesticide-specific procedures described in 22 CFR 216.3b must be detailed in a document known as a Pesticide Evaluation Report and Safe Use Action Plan (PERSUAP).

Indoor residual spraying: A PEA for IRS activities is in final stages of preparation. Until that document is approved, IRS programs will require an Initial Environmental Examination (IEE), a brief overview of the proposed activity to judge what further assessment is required. Normally for an IRS activity, the IEE will result in a requirement for a Pesticide Evaluation Report and Safe Use Action Plan (PERSUAP) or an environmental assessment, depending on the EPA registration status of the pesticides being proposed. Once the PEA has been finalized, (estimated in September 2006) only the IEE and a simplified SEA for country and site-specific application will be required. The preparation of the SEA should ideally be combined with the preparation of a logistic needs assessment for IRS during the planning period. USAID has a central contract which can provide experienced consultants to prepare the SEA or PERSUAP. The cost of such an assessment will usually run in the range of $30,000-50,000.

Q. What about the purchase and use of DDT?

A. DDT is one of several insecticides that can be used for IRS, as shown in the list above. Each insecticide has its advantages and disadvantages for a particular setting. DDT is normally considered to have an advantage on rough wall surfaces, such as mud or un-plastered cinderblock. In most situations, it has a longer-lasting insecticidal effect, generally considered to be about six months, but it has been documented to last up to 12 months in South Africa. The duration of an insecticide's effective action requires testing in the local climate and on local surfaces. DDT is also less expensive than most other insecticides on a kilogram per kilogram basis.

Under the terms of the Persistent Organic Pollutants (POPs) Treaty, malaria control is the only remaining approved use for DDT. The US Government can procure and/or use DDT for IRS when an activity is designed and funded to ensure its proper handling and use. As with any of the insecticides discussed above, procurement or use of DDT in a US Government-supported activity will require completion of the appropriate 22 CFR 216 Environmental Assessment and a SEA.

Q. Where can I learn more about USAID's environmental procedures and find out who can help me?

A. USAID maintains an environmental compliance section on its public website to make information readily available anywhere in the world. This section includes the text of 22 CFR 216, a who's who of environmental experts in the Agency who can provide advice, and guidelines and examples on how to undertake this work. The main page address is: http://www.usaid.gov/our_work/environment/compliance

Q. Where can I learn more about IRS?

A. An excellent source of information on appropriate insecticides for IRS (including DDT), operational issues such as formulation, dosage and safety, vector ecology and behavior, and social factors, such as community mobilization/support for spraying, is contained in the WHO document *"Insecticides for IRS"* by Drs. Najera and Zaim (WHO/CDC/WHOPES/2001.3). A recent WHO technical report of an expert committee in 2004, "*Malaria Vector Control and Personal Protection,"* has just been released with further discussion of relevant issues (http://www.who.int/malaria/docs/WHO-TRS-936s.pdf). A summary of the evidence on effectiveness of ITNs and IRS is contained in "Indoor Residual Spraying and Insecticide-Treated Nets" by Christian Lengeler and Brian Sharp (Reducing Malaria's Burden, Global Health Council, 2003).

Q. What is PMI's policy on the provision of "free" ITNs?

A. PMI supports an approach to the distribution of ITNs that is aimed at ensuring both equity and sustainability. Tactically, this means working with ministries of health, commercial partners, NGOs, and donor agencies to create sustainable public health impact through increased availability, affordability, and demand for ITNs, particularly among those populations that are most vulnerable to malaria---children under five, pregnant women, and people living with HIV/AIDS. PMI's investments are in line with the Roll Back Malaria (RBM) "*Strategic Framework for Scaling up with ITNs"* (http://www.who.int/malaria/cmc_upload/0/000/015/845/itn_programmes.pdf) Poverty must not be a barrier to ITN availability. PMI strongly supports the provision of free ITNs targeted to vulnerable groups, particularly those living in rural areas where the risk of malaria is highest and poverty greatest. At the same time, PMI supports efforts to increase demand for and access to ITNs, so that those who can afford to pay will be able to purchase them and public sector funds can be spent on those most in need. This includes working with host governments to reduce or eliminate taxes and tariffs on ITNs and insecticides.

Q. What are the best approaches for providing "targeted" ITNs?

A. There is no single "best" approach for providing ITNs to vulnerable populations and it would be unwise to limit PMI's strategy to just one approach. Subsidies for ITNs can range from 100% (i.e., free nets) to no more than a small reduction in cost. They can also take many forms including a direct reduction in the cost to the public or a voucher system in which a free voucher can be redeemed for an ITN at a reduced price.

Several "models" for delivery of targeted ITNs have been developed. The choice of model should be guided by local conditions and circumstances. Among the most successful of these are:

- ITNs distributed free during large-scale integrated immunization or health campaigns;
- ITNs distributed free during routine visits to antenatal clinics, immunization days, and other contacts with the health system;
- ITNs sold at a subsidized price to qualifying beneficiaries at government health clinics as part of regular service delivery;
- ITNs sold at a subsidized price through community-based groups; and
- Coupons/vouchers delivered through the health system to qualifying beneficiaries, providing a discount on commercially-available ITNs.

These approaches and their variations are appropriate in different country contexts and are presented here in order of their pertinence to increasingly mature commercial market conditions. For instance, in areas where the commercial sector is inactive, incapable, or unwilling to handle the logistics of delivering ITNs, it would be more effective to use the public sector or NGOs to provide ITN services. Conversely, in areas where retail shops are active and have a demonstrated capacity to handle the logistics and financing of ITNs, they may be better suited for delivery of ITNs to be redeemed by coupons or vouchers. Each of these approaches has its advantages and disadvantages in relation to coverage and equity, effect on other ITN programs, effect on the health system, risk of fraud/leakage, opportunities for behavior change, and exit strategies. The choice of approach(es) should be guided by local conditions and circumstances.

Q. Where can I get more information on how best to deliver ITNs via targeted subsidies?

A. A detailed discussion on "best practices" for targeted subsidies is discussed in an RBM document: "*Targeted Subsidy Strategies for National Scale ITNs: Principles and Approaches*, and *Malaria Vector Control and Personal Protection*," which can be accessed on the RBM website www.rbm.who.int/.

Q. What is the current status of LLIN availability?

A. As recently as early 2006, there have been significant supply shortages and long lead times ranging from 6-9 months for the procurement of WHOPES-approved LLINs. This situation has been alleviated as both Sumitomo and Vestergaard Frandsen have increased

production capacity in response to demand. In addition, A to Z Tanzania also produces WHOPES-qualified Olyset nets and has expanded production capacity. Current lead times for procurements are estimated at 3-6 months.

Q. Are there any other "new ITN technologies" on the horizon?

A. The interest in ITNs and LLINs is expanding and a number of new nets are in development and being evaluated. One useful new product that has recently been released is K-O Tab 123, a "long-lasting net re-treatment." which employs a new technology that mixes insecticide with chemical "binders." The traditional "dipping" of nets with this product is intended to transform them into longer-lasting nets. Early evaluations of this long-lasting net re-treatment have shown some variation in the duration of the insecticidal effect of the nets, but it is clear that they last longer than a net that has been traditionally retreated. A multi-center study is underway to resolve this issue. The WHO Pesticide Evaluation Scheme (WHOPES) has not yet certified the K-O Tab 123 treatment. The advent of these longer-lasting net retreatments creates an opportunity for transforming the traditional ITNs already in the field into long-lasting nets and increasing the number of households benefiting from the full protection of ITNs.

Q. Should people living with HIV/AIDS be targeted for ITNs?

A. Among the major conclusions of a technical consultation on the interactions and implications on malaria and HIV/AIDS convened by WHO in 2004 (8) are:

- Pregnant women infected with both HIV/AIDS and malaria are at very high risk of anemia and malarial infection of the placenta. As a result, a considerable proportion of children born to such women have low birth weight and are more likely to die during infancy. It is unclear whether malaria during pregnancy increases the risk of mother-to-child transmission of HIV, as studies examining this relationship have shown conflicting results.
- Among adult men and non-pregnant women, HIV/AIDS may moderately increase the risk of malaria illness, especially in those with advanced immunsuppression. HIV-infected adults with low CD4 cell counts may also be more susceptible to treatment failures of antimalarial drugs. In addition, acute malaria episodes temporarily increase viral replication and HIV viral load.
- As an important cause of anemia, malaria is frequently managed by blood transfusion, a potential risk factor for HIV infection

On the basis of these conclusions, the Roll Back Malaria Partnership recommends the following strategies for addressing the risk of malaria and HIV co-infection:

- In areas of malaria transmission, people living with HIV/AIDS should ideally be protected by ITNs;
- HIV-positive pregnant women at risk of malaria should always be protected by ITNs, and in addition – according to the stage of HIV-infection – receive either

intermittent preventive treatment with sulfadoxine-pyrimethamine (at least 3 doses) or daily cotrimoxazole prophylaxis.

Discussions are currently underway between PMI and the President's Emergency Plan for AIDS Relief (PEPFAR) to develop guidelines for providing malaria preventive and treatment services to people living with HIV/AIDS. Details on PEPFAR are available for all USG employees at www.pepfar.net (this internal USG site requires initial registration).

Q. Are there options for prevention other than ITNs and IRS?

A. Larval control, which involves the treatment or elimination of collections of water where the immature stages of the mosquito vector develop, has more limited application. It is generally thought to be most appropriate for urban settings, areas with seasonal transmission, and lower-transmission areas where mosquito breeding sites are likely to be few and feasibly managed or eliminated. WHO has recently adopted a global framework for malaria prevention, based on the principles of integrated vector management (IVM), which stresses targeting the various preventive tools to fit the local context for maximum effect. Integrated vector management is based on the belief that a combination of interventions is most likely to be effective. Potential tools include ITNs, IRS, and larval control. The US Government, in collaboration with African partners, is actively engaged in work to better define the efficacy and effectiveness of IVM, including larval control, in specific ecological settings. Larval control requires an environmental impact assessment conducted under the procedures of 22 CFR 216.

Q. When can we expect to have a malaria vaccine ready for the field?

A. Most experts agree that a field-ready malaria vaccine is still a decade or more away. There has been significant progress in the past few years. The most encouraging results have come from a field trial of a candidate vaccine completed in 2004 in Mozambique that showed a 30% reduction in the frequency of clinical disease and a 50% reduction in severe malaria. More than anything else, these results established the proof-of-principle that a malaria vaccine is feasible.

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Options for Treating Malaria

Prompt treatment with a safe and effective antimalarial drug is a fundamental component of the World Health Organization's (WHO) and Roll Back Malaria's strategy to control malaria. Correct use of antimalarial treatment will not only shorten the duration of malarial illness and reduce the chance of recurrence, but also reduce the frequency of complications and the risk of death. Historically, national malaria control programs have relied primarily on monotherapy with drugs, such as chloroquine, amodiaquine, or sulfadoxine-pyrimethamine (SP, Fansidar®), as their first-line treatment for malaria, but increasing drug resistance has forced many programs to seek alternative regimens. The PMI policy is to support introduction and implementation of combination therapies, ideally artemisinin-based combination therapies (ACTs).

Q. What is the current status of antimalarial drug resistance in the world?

A. The spread and intensification of antimalarial drug resistance represents one of the most serious challenges to malaria control worldwide. In Southeast Asia, strains of *Plasmodium falciparum* have developed resistance to multiple antimalarial agents and very few drugs remain effective. In South America, high levels of resistance to both chloroquine and SP are already present throughout the Amazon Basin. In sub-Saharan Africa, chloroquine resistance is now widespread. Resistance to SP has been well documented in East and southern Africa and is increasing in some parts of West Africa. Although resistance of *P. vivax* to chloroquine is an increasing public health problem in Indonesia and Papua-New Guinea, only sporadic cases have been reported from other regions.

With the spread of antimalarial drug resistance, the choice of first- and second-line drugs for malaria treatment has become much more difficult. Only a limited number of alternative drugs are available and there has been little economic incentive for new drug discovery and development, given its high cost and the fact that malaria predominantly affects the world's poorest nations. The large-scale procurements now being facilitated through PMI, the Global Fund, and other scale-up projects have begun to change the economics of antimalarial drug development and sales. However, in many malarious areas, a majority of the population has only limited access to malaria treatment through public health facilities, and relies heavily on the private sector for antimalarials, which may be of substandard quality.

Q. What drugs are currently recommended for treatment of malaria?

A. WHO now recommends that all countries experiencing resistance to their current first-line single-drug antimalarial therapy change to combination therapy, preferably with an artemisinin drug. This is termed artemisinin-based combination therapy or ACT. Four ACT regimens are recommended: artemether-lumefantrine (Coartem®), amodiaquine-artesunate, SP-artesunate, and mefloquine-artesunate. A fifth, a non-ACT

combination, SP plus amodiaquine, is another alternative in settings where both of these drugs remain efficacious. In areas where either amodiaquine or SP have been used extensively as monotherapy, combinations of either drug with artesunate may not be appropriate. In general, mefloquine-artesunate has not been recommended for sub-Saharan Africa because of concerns that the long half-life of the mefloquine, when coupled with intense malaria transmission, might foster the rapid development of resistance.

Q. What are artemisinin drugs?

A. Artemisinin is a natural product extracted from the plant *Artemisia annua* (sweet wormwood) that has been used as anti-fever medication in China for more than 1000 years. Artemisinin and its semi-synthetic derivatives, such as artesunate and artemether, are the most rapidly acting of all antimalarial drugs. They rapidly reduce parasite density in the blood and control fever. Serious or life-threatening adverse drug reactions have been reported only rarely, and even mild side effects are uncommon. In addition, these drugs offer the potential of reducing the level of transmission, as they are active against the stages of the malaria parasite which are transmitted to mosquitoes. When used alone, a 5- to 7-day course of therapy is needed to achieve a cure. In combination with a longer-acting antimalarial drug such as mefloquine, SP, amodiaquine, or lumefantrine, a 3-day course is curative. Monotherapy with artemisinin compounds are no longer recommended (see explanation below). Artemisinin derivatives generally have a short shelf-life (under 2 years), making the planning for their implementation more complex than for previously used therapies.

Q. What are the advantages of combination therapy over single-drug therapy for malaria?

A. When used alone, antimalarial drugs are more likely to select for resistant parasites. The rationale for using combination therapy for malaria is similar to that for the treatment of tuberculosis, cancer, and HIV infections. The combination of two or more effective antimalarial drugs with different modes of action greatly reduces the probability of selecting parasites that are simultaneously resistant to both drugs and, thus, prolongs the useful therapeutic lifetimes of both drugs. In Thailand, the use of combination therapy with mefloquine plus artesunate, one of the newer artemisinin derivatives, was associated with a halt in the steady increase of resistance to mefloquine that had been observed when mefloquine was being used alone. The US Government is working with the Government of Tanzania to evaluate whether the use of ACTs in Africa will have similar effects on the emergence of resistance. Information about this large-scale evaluation can be found at: http://www.cdc.gov/malaria/cdcactivities/tanzania.htm

Q. What is the status of ACT supplies worldwide?

A. Following a decision in early 2004 by the Board of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) to allow countries to reprogram their Global Fund grants for the purchase of ACTs, the rate of treatment policy change to ACT in African countries accelerated markedly. Throughout 2004 and 2005, there was a supply shortage of ACTs, particularly Coartem®, due to an increase in Global Fund orders and shortfalls in the cultivation and extraction of artemisinins from *Artemisia annua*. During 2005 and 2006, however, ACT manufacturers have increased production capacity. In addition, there have been delays in Global Fund orders for ACTs. As a result, lead times for ACT orders have shortened considerably. As of mid-2006, the average lead time for Coartem® delivery was 3-4 months, but this is subject to change.

The US Government is actively working with WHO to help pharmaceutical companies upgrade their ACT production capacity in order to increase the pool of companies manufacturing WHO-approved ACTs.

Q. What can be done to improve the accuracy of malaria diagnosis?

A. With the spread of antimalarial drug resistance, accurate diagnosis has become even more important as a means of targeting malaria therapy and avoiding presumptive treatment of all febrile patients with more expensive antimalarial drugs. The development and refinement of rapid diagnostic tests (RDTs) for malaria using a simple dipstick or card format, offer a potentially practical, long-term solution to malaria diagnosis in settings where high quality microscopy is not feasible or sustainable.

Several different RDTs for malaria have been marketed, including Now Malaria®, Optimal®, ParaCheck Pf®, Rapimal®. Most have proven to be highly sensitive and specific at detecting malaria parasitemia above 100 parasites per microliter, and with some tests it is possible to distinguish between *P. falciparum* and non-falciparum species. These tests have the additional advantage of being simple to use, and experience in several countries has shown that health workers with limited training can rapidly learn to use them correctly. Although the cost per test usually ranges from $0.60-$2.00, this is likely to become cost-effective in settings where first-line malaria treatment regimens becoming more and more expensive.

Rapid diagnostic tests are not without their limitations. There have been issues of variable quality control of some RDTs, and many are quite sensitive to storage conditions, particularly humidity – a potentially serious problem in sub-Saharan African settings. In addition, the procedures used in different RDTs can be quite different, and the "user-friendliness" of the tests varies. Some tests remain positive (particularly those RDTs based on the HRP 2 antigen) for up to 10 days, which can make diagnosis of potential treatment failure difficult. There is also some concern that health care workers will not always accept negative test results when those results do not agree with their clinical impression of the cause of a patient's illness.

The World Health Organization recommends that in areas with high levels of malaria transmission, children under five with a febrile illness should be treated on the basis of a clinical diagnosis alone (without microscopy or a RDT), since the probability that the fever is caused by malaria is so high.

Q: What is the role for home and community management of malaria?

A: Many malaria patients in Africa seek treatment outside the formal health care system. In areas of high malaria transmission, where children under five are treated on the basis of clinical symptoms alone, several countries have undertaken small-scale projects to improve the identification and prompt delivery of effective treatment at the household level. While delivering effective treatment at health facilities is a priority, there are data to suggest that patients who seek malaria treatment from shops and other community sources may do so more promptly than those who visit health facilities. Efforts to improve home and community management have been shown in a few settings to improve the quality of treatment, reduce the risk of severe malaria, and improve child survival. WHO has developed guidelines for the development and implementation of home management of malaria. Questions remain about the best ways to incorporate community-level and private sector providers in the delivery of costly ACTs. National malaria control programs in several PMI countries, including Rwanda, Senegal, and Uganda, have included home management interventions in their strategic plans. The PMI can contribute by helping to procure subsidized malaria treatments and offering a platform for careful monitoring and evaluation of newly introduced interventions.

Q. Are there prohibitions against USAID purchasing antimalarial drugs?

A. At the present time, there is not a unified USG policy on the procurement of non-FDA approved antimalarial drugs, although discussions are ongoing. In the interim, USAID can purchase ACTs and other antimalarials provided that a pharmaceutical source/origin waiver can be obtained and cleared through the Office of Acquisitions and Assistance. The following conditions must be met in order to obtain a source/origin waiver:

- the pharmaceutical is essential to the activity;
- the product is not available from the US or the delivered price from the US would be at least 50% more than from another source;
- information is available to attest to the safety, efficacy and quality of the product or the product meets the standards of the FDA or other US controlling authority; and
- US patent law must be honored.

The key issue around procurement of antimalarial drugs involves ensuring that the highest standards of quality, safety, and efficacy are met for all USG procurement of pharmaceuticals. USAID Bureau for Global Health has identified procurement mechanisms for antimalarial drugs and has obtained waivers to purchase several ACTs

and antimalarial drugs. Missions are urged to contact the malaria team in USAID/Washington for assistance before procuring antimalarial drugs.

Q. What can be done about counterfeit antimalarial drugs?

A. Counterfeit or substandard antimalarial drugs are being encountered with increasing frequency as drug resistance drives the cost of malaria treatment higher. This problem is particularly serious in Southeast Asia, where extremely sophisticated counterfeits of several artemisinin drugs and mefloquine have been detected. In some cases, the packaging of these counterfeits is of such high quality that it is almost impossible to distinguish from the genuine product. The WHO has established a system for pre-qualifying antimalarial drugs that will help ensure the quality of drugs that are purchased from recommended manufacturers. The US Government, through the U.S. Pharmacopoeia, has been working with countries in Africa, the Mekong Region, and South America to establish or strengthen national capabilities for drug quality testing.

In addition, approaches to engage the private sector in the stocking and sales of approved ACTs should be tested, and, where successful, expanded. One potentially attractive approach is to subsidize sales of approved antimalarial drugs through approved retail outlets whose owners have undergone training in the treatment of malaria and agree not to sell monotherapies or other non-approved antimalarial drugs.

Q. What can be done to improve the management of severe malaria?

A. Although ACTs are the treatment of choice for mild or uncomplicated malaria, peripheral health facilities often lack the high quality diagnostic and management services necessary for severe malaria. In addition, newer drugs, including intramuscular artemether or rectal suppositories of artesunate, may be simpler and safer to deliver for pre-referral care or initial treatment of severe malaria. Studies are currently underway to establish the potential for community-based pre-referral care to improve child survival; however, based on current evidence of safety and efficacy, the WHO has recommended rectal artesunate as a pre-referral treatment for children with suspected malaria who are unable to take oral medicines. Although improving referral mechanisms and the quality of care at referral health facilities is a priority for many national malaria control programs, these improvements are likely to be more expensive than efforts to improve treatment of uncomplicated malaria or pre-referral care.

Q. Are people living with HIV/AIDS at greater risk of malaria?

A. HIV infection diminishes the ability of pregnant women and immunologically compromised adults to control *P. falciparum* infections. The prevalence and intensity of malaria infection is higher in HIV+ patients. Similarly, patients with HIV infections are more likely to have symptomatic malaria and pregnant women have an increased risk for

malaria-associated adverse birth outcomes. Co-infections with HIV/AIDS and malaria increase both the severity of illness and the risk of anemia. For these reasons, accurate diagnosis and prompt therapy with a highly effective antimalarial drug regimen, preferably an ACT, is recommended. The impact of HIV/AIDS on malaria infections in children is less clear.

Q. Where can I learn more about malaria treatment?

A. An excellent source for up-to-date information on the status of antimalarial drug resistance in the world and malaria diagnosis and treatment is the WHO RBM website: http://mosquito.who.int. Specific documents that can be accessed through that site include the following: "*Guidelines for the Treatment of Malaria*" (WHO/HTM/MAL/2006.1108) "*The Use of Antimalarial Drugs*" (WHO/CDS/RBM/2001.33); "*Antimalarial Drug Combination Therapy*" (WHO/CDS/RBM/2001.35); and "*The Use of Artemisinin and its Derivatives as Anti-malarial Drugs*" (WHO/MAL/98.1086).

Q. Are there any new treatments on the horizon?

A. Final approval of a new rectal artesunate treatment for severe malaria in children is expected in 2006. WHO recently prequalified Artemotil®, an injectable derivative of dihydroartemisinin, approved for treatment of severe malaria. A pediatric formulation of artemether-lumefantrine (Coartem®) should marketed by early 2008. Over the next 3-4 years, several other new artemisinin combination therapies that are likely to be significantly less expensive than those currently available and co-formulated to improve patient compliance should become available. These include artesunate-chlorproguanil-dapsone (Lapdap®), a combination of dihydroartemisinin and piperaquine (Artekin®), and a combination of artesunate and pyronaridine.

Selected references:

1. Bloland PB (2001). Drug resistance in malaria. World Health Organization WHO/CDS/CSR/DRS/2001.4.
2. Shretta R, Omumbo J, Rapuoda B, et al (2000). Using evidence to change antimalarial drug policy in Kenya. *Tropical Medicine and International Health* 5: 755-764.
3. World Health Organization (2000). Malaria diagnosis: new perspectives. WHO/CDS/RBM/2000.14.

Options for the Prevention and Treatment of Malaria in Pregnancy

Each year, more than 30 million African women living in malaria-endemic areas become pregnant and are at risk for *Plasmodium falciparum* malaria infections. The impact of these infections on the health of the pregnant woman and her developing child depends to a large extent on the level of malaria transmission. In areas of sub-Saharan Africa with moderate to high levels of malaria transmission, the major impact of *P. falciparum* infection during pregnancy is related to anemia in the mother and the presence of parasites in the placenta. The resulting impairment of fetal nutrition contributes to low birth weight and is a leading cause of poor infant survival and development in Africa. There are between 100,000 and 200,000 deaths annually in Africa of infants from complications associated with malaria-related low birth weight.

For areas with moderate to high levels of malaria transmission, such as most of sub-Saharan Africa, the World Health Organization (WHO)-Roll Back Malaria "Strategic Framework for Malaria Control during Pregnancy in the African Region" recommends a three-pronged approach to reduce the burden of malaria infection among pregnant women: use of intermittent preventive treatment (IPTp); insecticide-treated nets (ITN); and effective case management of malarial illnesses.

Q. What is intermittent preventive treatment (IPTp)?

A. Intermittent preventive treatment of pregnant women (IPTp) involves the administration of at least two full, curative treatments with an effective antimalarial drug, beginning in the second trimester after quickening. At present, sulfadoxine-pyrimethamine (SP) is the only drug for which there is sufficient safety and efficacy data to be recommended by WHO for IPTp. The spread of resistance of *P. falciparum* to SP in eastern and southern Africa has raised concerns about the efficacy of SP for IPTp. The current guidance is that SP remains an effective strategy for IPTp – providing adequate protection from malaria infection in pregnant women – and should be implemented in areas where therapeutic failures in children treated with SP are less than 50%. There are efforts, however, to identify alternative drugs for IPTp, which would be introduced if evidence mounts that SP is no longer an effective option for IPTp. Since more than 70% of pregnant women in Africa attend antenatal clinics at least once during their pregnancy, the provision of IPTp during ANC visits is both feasible and attractive.

Q. Is IPTp recommended for women living in areas of low malaria transmission?

A. Intermittent preventive treatment is not recommended for pregnant women living in areas with low levels of malaria transmission, such as in Asia or Latin America or selected areas of Africa with low or unstable malaria transmission. Instead, ITNs are recommended for prevention, together with laboratory evaluation of all febrile illnesses and antimalarial treatment if malaria is confirmed.

Q. How does the treatment of malaria in pregnant women differ from treatment in non-pregnant women?

A. Prompt treatment with a safe and effective antimalarial drug is a fundamental component of the WHO-RBM's strategy to control malaria. Antimalarial treatment will not only shorten the duration of malarial illness, but also reduce the frequency of complications and the risk of death. This is particularly important in pregnant women, because of their lower immunity to malaria. Essential elements of the antenatal care package in these areas should, therefore, include malaria diagnosis, where available and needed, and treatment with antimalarial drugs that have an adequate safety and efficacy profile for use in pregnancy.

Since there is insufficient information on the safety and efficacy of ACTs during the first trimester of pregnancy, quinine (or SP or chloroquine, if efficacious in the area) is the preferred choice for treatment. There is some evidence in animal models of fetal resorption following exposure to artemisinins early in pregnancy. Therefore, ACTs should only be used if there are no other effective treatments available. In the second and third trimester, no adverse effects from the artemisinin derivatives have been reported on the mother or fetus, although the number of women treated is limited. ACTs, quinine (plus clindamycin, if available), or artesunate plus clindamycin may be used for treatment in the second or third trimester.

Q. What is the role of insecticide-treated mosquito nets (ITNs) in preventing malaria in pregnancy?

A. In areas with moderate to high levels of transmission, the use of insecticide-treated mosquito nets (ITNs) during pregnancy provides significant protection against malarial illness, maternal anemia and low birth weight. In addition, ITNs protect the infant sleeping with the mother under the net by reducing exposure to malaria infection and subsequent severe disease. The provision of ITNs to pregnant women is part of the essential package of services to prevent the adverse consequences of malaria during pregnancy.

Q. What is the impact of HIV/AIDS on malaria during pregnancy?

A. HIV infection reduces a pregnant woman's ability to control *P. falciparum* infections. The risk and intensity of malaria infection during pregnancy is higher in women who are HIV+. Such women are also more likely to have symptomatic infections, respond less well to antimalarial treatment, and have an increased risk for malaria-associated adverse birth outcomes. While the risk of malaria in HIV negative women is greatest during the first and second pregnancies, in the presence of HIV infection, the risk associated with placental malaria seems to be independent of the number of pregnancies, and multigravidae with HIV infection are similar to primagravidae without HIV infection in terms of their susceptibility to and the negative consequences of malaria infection.

Intermittent preventive treatment is recommended for HIV+ pregnant women living in areas with high levels of transmission, but a minimum of three doses of SP is required to obtain maximum protection. However, IPTp with SP should not be given to HIV+ pregnant women who are taking trimethoprim-sulfamethoxazole (cotrimoxazole) prophylaxis, as there is an increased risk of sulfa-related adverse effects, and the cotrimoxazole does have an antimalarial effect.

Q. Where can I learn more about the prevention of malaria in pregnancy?

A. An excellent source for up-to-date information on the prevention and treatment of malaria during pregnancy is the WHO-Roll Back Malaria website: http://mosquito.who.int. The document, "*A Strategic Framework for Malaria Prevention and Control during Pregnancy in the African Region*," is of particular interest. A broad range of useful documents is also available as part of the "Malaria during Pregnancy Resource Package" produced by the Maternal and Neonatal Health Project. This can be found on their website (www.jhpiego.org) and is also available on compact disk.

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3. World Health Organization (2004). A Strategic Framework for malaria prevention and control during pregnancy in the African Region (AFR/MAL/04/01). WHO, Brazzaville.
4. Steketee RW, Nahlen BL, Parise ME, et al, (2001). The burden of malaria in pregnancy in malaria endemic areas. *American Journal of Tropical Medicine and Hygiene* 64 (suppl 1): 28-35.
5. ter Kuile FO, Terlouw DJ, Phillips-Howard PA, et al (2003). Reduction of malaria during pregnancy by permethrin-treated bed nets in an area of intense perennial malaria transmission in western Kenya. *American Journal of Tropical Medicine and Hygiene* 68 (suppl): 50-60.

Monitoring and Evaluation

Q. What monitoring and evaluation activities are planned for the President's Malaria Initiative?

A. ***Monitoring*** focuses on inputs (human and financial capital), processes (planning, training, and communication), and outputs (policies developed, commodities distributed) for ongoing tracking of programs over time, generally based on routine records. Monitoring activities under the PMI include assessments based on national malaria control program and other partner reports on drugs and ITNs purchased and distributed; training of health care workers, numbers of ITNs distributed, ACT and IPTp treatments administered, and households sprayed. Monitoring also includes entomologic surveillance, drug resistance surveillance, and special studies of health facility case management.

Evaluation focuses on outcomes (intervention coverage) and impact (reduction in morbidity and mortality) to assess whether targets have been achieved, using representative surveys with rigorous methods. Evaluations planned under PMI include household surveys conducted during or soon after the high transmission seasons to measure coverage with IPTp, ITNs, and ACTs. PMI will compare baseline data prior to country funding with mid-term (end of scale-up) and end-of project surveys.

Q. How will the impact of PMI be measured?

A. Since direct measurement of malaria mortality is not possible in most of sub-Saharan Africa due to poor reporting of vital events and the lack of robust data on causes of death, PMI will analyze changes in all-cause mortality for children under five, as measured in representative household surveys. Interpretation of trends observed will take into account factors influencing malaria mortality, including program factors such as malaria control intervention coverage and entomological transmission, and non-program factors (confounders) such as rainfall. Whenever possible, trends in anemia and parasitemia will be followed to measure the impact on morbidity and support the plausibility of observed mortality impact.

Q. What is the purpose of verbal autopsy within PMI?

A. In order to estimate malaria-attributed mortality as a portion of all-cause mortality for children under 5 years of age, verbal autopsies (or post-mortem interviews) will be used. Verbal autopsy is a method for determining the cause of death in which relatives of the deceased person are asked about signs and symptoms of the terminal illness, usually one to six months after the death. To attribute causes of deaths, these interviews are analyzed by an algorithm or clinicians who decide on causes by majority vote. Two methods for conducting verbal autopsies have been proposed within PMI. For countries with demographic surveillance systems or sentinel sites, longitudinal trends in malaria-

attributed mortality can be measured at these sites. Another approach is to conduct verbal autopsies in representative populations, such as by adding verbal autopsies to population-based surveys. An attempt will also be made to validate the verbal autopsy tool to assess sensitivity (probability that a true malaria death is identified as a malaria death) and specificity (probability that a true non-malaria death is identified as a non-malaria death) when compared to gold-standard hospital diagnosis.

Q. What is the role of health facility surveys within PMI?

A. The PMI monitoring and evaluation plan proposes a nationally representative survey of health facilities (outpatient and antenatal clinics) to examine diagnostic capabilities, malaria case management, management of supplies including antimalarial drugs and commodities, IPTp delivery, and health care worker adherence to drug policy, and to use these results to strengthen case management and prevention activities.

In outpatient clinics, surveyors will observe case management practices for malaria and other key illnesses (e.g., pneumonia, diarrhea, and anemia in children), conduct exit interviews with patients or guardians of child patients, and, if possible, re-examine patients to obtain a "gold standard" diagnosis according to national case management guidelines. In antenatal clinics, surveyors would observe antenatal consultations and conduct exit interviews to assess quality of antenatal care. In addition, surveyors at both types of facilities would interview health workers to assess training and supervision and the availability and condition of key drugs and essential diagnostic equipment.

Q. Are plans there plans to collect routine health information systems (HIS) data?

A. This component of the PMI monitoring and evaluation plan involves collecting two types of information. The first type (e.g., number of ITNs distributed, number of ITNs retreated, and quantity of ACTs used for children) will be used for ongoing monitoring of programmatic activities. These data will be measured every three to six months and used by national malaria control program managers to make adjustments if the scale-up of activities is not meeting targets.

The second type of information (e.g., number of inpatient malaria deaths and severe anemia deaths among children under five) will evaluate validity, utility, and cost of monitoring the burden of malaria, while seeking to strengthen countries' health information system and diagnostic capabilities. The following types of information will be collected.

- Number of inpatient malaria cases and deaths and severe anemia cases and deaths over time (per month or per quarter), stratified by age (less than 5 years old or 5 years or more of age).
- Number of inpatient blood transfusions over time, stratified by age
- Total number of inpatient admissions for all diagnoses stratified by age, as a proxy for overall hospital utilization.

- Total number of outpatient malaria cases over time stratified by age

Q. What plans are there for supervision and monitoring quality improvement?

A. This component of the monitoring and evaluation plan is closely linked to activities occurring at health facilities, such as outpatient case management, and is intended to support improved health care worker performance. A quality improvement strategy will be used, in which health worker performance (e.g., the percentage of children <5 years old with uncomplicated malaria who are correctly managed according to national guidelines) is routinely monitored, problems are identified, and adjustments made.

Q. Where can I find more information on malaria monitoring and evaluation?

A. Useful references and tools:

- Framework for Monitoring Progress and Evaluating Outcomes and Impact
  - http://www.rbm.who.int/cmc_upload/0/000/012/168/m_e_en.pdf
- Monitoring and Evaluation Toolkit HIV/AIDS, Tuberculosis and Malaria
  - http://www.theglobalfund.org/pdf/guidelines/pp_me_toolkit_en.pdf
- Malaria indicator survey (http://www.who.int/malaria/me_evaluationtools.html)
- World Malaria Report 2005 (http://rbm.who.int/wmr2005/pdf/WMReport_lr.pdf)

ABBREVIATIONS and ACRONYMS

ACT – artemisinin-based combination therapy
CDC – Centers for Disease Control and Prevention
DDT – dichloro-diphenyl-trichloroethane
GFATM – Global Fund to Fight AIDS, Tuberculosis, and Malaria
HIV – human immunodeficiency virus
IEC – information, education, communication
IPTp – intermittent preventive treatment for pregnant women
IRS – indoor residual spraying
ITN – insecticide-treated net
IVM – integrated vector management
LLIN – long-lasting insecticide-treated net
MIS – malaria indicator survey
MoH – Ministry of Health
NMCP – National Malaria Control Program
NGO – non-governmental organization
PEPFAR – President's Emergency Plan for AIDS Relief
PERSUAP - Pesticide Evaluation Report and Safe Use Action Plan
PMI – President's Malaria Initiative
POP – persistant organic pollutant
RBM – Roll Back Malaria
RDT – rapid diagnostic test
SEA – supplemental environmental assessment
SP – sulfadoxine-pyrimethamine
UNICEF – United Nations Childrens' Fund
USAID – United States Agency for International Development
USG – United States Government
WHO – World Health Organization
WHOPES – WHO Pesticide Evaluation Scheme