PRESIDENT'S MALARIA INITIATIVE

TECHNICAL GUIDANCE ON THE PREVENTION AND CONTROL OF MALARIA

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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.

However, following guidance provided by the WHO in 2006, IRS is now promoted in

almost all settings, including: (1) unstable, epidemic-prone malaria transmission areas; (2) stable-epidemic malaria areas with moderately intense but seasonal transmission; and (3) stable-hyperendemic areas where very intense seasonal or perennial transmission occurs. More information on the 2006 WHO Position Statement on IRS can be found at: http://malaria.who.int/docs/IRS-position.pdf.

Because there has been less experience with the use of IRS in sub-Saharan African countries with year-round, moderate- to high-level transmission, PMI will be supporting and thoroughly evaluating IRS campaigns in these areas during the coming years. 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. Additional information on the use of IRS can be found under "Vector Control" on the Roll Back Malaria website (www.rbm.who.int/).

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.

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. 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 up to 3 years).

PMI-supported IRS should focus on areas with seasonal transmission (where transmission is limited to certain months of the year and is absent or falls to very low levels during other months), so that a single round of spraying is sufficient to provide year-round protection, rather than areas with year-round transmission where two or more rounds of spraying will be required for full protection. In areas prone to malaria epidemics, emphasis should be placed on improving malaria diagnostic capabilities and surveillance together with prompt reporting to promote an early response to upswings in cases. PMI country teams should work with NMCPs to update their national malaria control strategies related to IRS and epidemic detection and containment. Because of the threat of insecticide resistance, countries may want to consider the use of non-pyrethroid insecticides for IRS, perhaps in rotation, in order to reduce the threat of increasing resistance to pyrethroids used on LLINs, for which no substitute is yet available.

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 re-treatment with insecticides. To date, WHO has provided interim or final approval for seven long-lasting products, Vestegaard Frandsen's *PermaNet*®2.0, *PermaNet*®2.5 and *PermaNet*®3.0, Sumitomo's *Olyset Net*®, BASF's *Interceptor*® net, Bestnet's *Netprotect*®[1] net, and Clarke Mosquito Control's *Duranet*®. 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 (up to 3 years), while a traditional ITN will require re-treatment at least every six months. As of FY2008, PMI only supports the purchase of LLINs. Although LLINs are projected to last 3 years, there is evidence from some settings that LLIN fiber durability and insecticide longevity may be compromised sooner. To better plan ITN replacement strategies, PMI is collecting data on LLIN durability and longevity through on-going monitoring and/or focused studies in several countries.

Q. What are issues regarding distribution and budgeting for LLINs?

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 procuring and delivering an LLIN through a combination of commercial, non-governmental organization (NGO), and community groups remains fairly steady at ~$7 per person, and this is the suggested amount to be used for PMI budgeting purposes in most settings.

Q. What insecticides are used for IRS?

A. The WHO Pesticide Evaluation Scheme (WHOPES) lists the 12 following

[1] Also marketed as Syngenta's ICONLife net.

insecticides as approved for use in IRS:

Insecticide compounds and formulations	Class group
Alphacypermethrin WP, SC	P
Bendiocarb WP	C
Bifenthrin	P
Cyfluthrin WP	P
DDT WP	OC
Deltamethrin WP, WG	P
Etofenprox WP	P
Fenitrothion WP	OP
Lambda-cyhalothrin WP, CS	P
Malathion WP	OP
Primiphos-methyl EP, EC	OP
Propoxur WP	C

Formulations include CS: capsule suspension; EC: emulsifiable concentrate; WP: wettable powder

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. PMI has specified the following criteria for determining choice of insecticide:

- Registration in host country
- Acceptability of insecticide to NMCP
- Risk to human health and environment, livestock, and agricultural trade
- Vector resistance (both confirmed resistance and potential for resistance)
- Appropriateness of surface for spraying
- Duration of efficacy
- Cost of insecticide
- Host country capacity to prevent pilferage

The decision-making process is documented in each country-level environmental assessment. More information on insecticide efficacy, safety, and selection can be found at http://whqlibdoc.who.int/hq/2003/WHO_CDS_WHOPES_2002.5_Rev.1.pdf.

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 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 minimize 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 the Mission Environmental Officer, Regional Environmental Officer, PHN Officer, Mission Director, and USAID Bureau Environmental Officers *before* any USAID funds can be obligated for the activity. Thus PMI managers should ensure that assessments have taken place and are signed well in advance of the spray season. 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.

Indoor residual spraying: USAID issued a Programmatic Environmental Assessment (PEA) – the umbrella assessment for integrated vector control activities in sub-Saharan Africa – in 2006. The purpose of the PEA was to provide malaria control managers with a technical, policy, and procedural guide for the preparation of environmental assessments of individual projects, thereby expediting country-level assessments. To date, nearly all PMI countries have completed environmental assessments for IRS. Assessments were completed by IRS IQC consultants in consultation with Mission and Regional Environmental Officers and Ministries of Health, Environment, and Agriculture. The cost of such an assessment is typically in the range of $30,000-50,000.

Insecticide-treated nets: Insecticides for use in ITN programs have been thoroughly evaluated in a separate 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. The PEA for ITNs can be found at: http://pdf.usaid.gov/pdf_docs/PNACP696.pdf. The PEA for Integrated Vector Management can be found at: http://www.ehproject.org/PDF/ehkm/ivm-env_assessment.pdf

Long-lasting insecticide treated nets: The PEA determined that use of LLINs presents the ideal solution to insecticide treated material pesticide risks by eliminating the need for re-treatment. As such, procurement and distribution of LLINs simply require mention in the

Mission Initial Environmental Assessment with a "negative finding" (indicating no environmental harm) as opposed to stand-alone environmental assessments.

Q. Who is responsible for monitoring human and environmental safety measures for IRS?

A. It is the shared responsibility of in-country PMI team members and GH-based IRS CTOs to monitor environmental compliance. Attention should be directed to ensuring that:

- Mitigation measures listed in the Safer Use Action Plan of the environmental assessment are being addressed
- Changes to the original environmental assessment (e.g., changes in targeted districts or choice of insecticide) trigger amendments to the assessment
- Strict sachet accounting methods are in place to prevent leakage
- IRS contractor(s) complete and disseminate environmental compliance reports.

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, although increased shipping weight and the cost of environmental safeguards largely cancel out these theoretical cost savings. Finally, in addition to killing mosquitoes resting on indoor surfaces, DDT also repels mosquitoes from entering homes.

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. In addition, such assessments will need to be completed every year per Stockholm convention reporting requirements.

For more information on the use of DDT in IRS programs, refer to the WHO position statement of 2007, located at:
http://www.who.int/malaria/docs/IRS/DDT/DDTposition.pdf.

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

A. USAID recognizes the challenges associated with maintaining the safe and judicious use of public health insecticides. Mission and Regional Environmental Officers should be engaged in Mission-level discussions regarding compliance efforts and planning. In addition, questions can be directed to GH CTOs who can then engage appropriate USAID/GH and USAID/AFR advisors. The PMI website now has a link to country SEAs.

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. To date, the majority of PMI-procured LLINs have been distributed free of charge either through mass campaigns of through government health facilities.

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 were 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. Two long-lasting field treatment products are on the market--*K-O Tab 123* and the *ICON-MAXX*. These treatment kits employ a new technology that mixes insecticide with chemical "binders." The traditional "dipping" of nets with these products is intended to transform them into longer-lasting nets. Early evaluations of both re-treatment kits 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. The WHO Pesticide Evaluation Scheme (WHOPES) has recommended the *K-O Tab 123* treatment as lasting for 15 washes and the *ICON-MAXX* treatment as lasting for 20 washes. The advent of these longer-lasting net re-treatments 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. However, given the operational cost of re-treating existing nets, the high variability in the quality of the treatment which is likely due to user variability/error, and the fact that many existing nets are in poor physical condition (torn or with holes), PMI does not generally support the use of these retreatment products except in exceptional circumstances.

Another product which is being marketed by Vestergaard-Frandsen is the *PermaNet* 3.0. The *PermaNet* 3.0 has a reinforced border at the bottom of the net to reduce tears and a high target dose compared to the *PermaNet* 2.0. Additionally, the top panel of the *PermaNet* 3.0 is polyethylene with deltamethrin and piperonyl butoxide (PBO) incorporated. The PBO is not directly toxic to mosquitoes but acts as a synergist for pyrethroid insecticides by suppressing detoxifying enzymes in the mosquitoes. The *PermaNet* 3.0 is being marketed as a tool for areas where pyrethroid resistance is high or for preventing the emergence and spread of pyrethoid resistance in other areas. Although the *PermaNet* 3.0 does have some added efficacy against resistant mosquitoes, the added benefit appears to be lost after repeated washing. While WHOPES has given an interim recommendation to the *PermaNet* 3.0 as a long-lasting net, it did not recommend this product as a tool for managing insecticide resistance. Given the added cost of the *PermaNet* 3.0 but the short duration of activity against pyrethroid resistant mosquitoes, it is unlikely to be a cost-effective strategy for ITN programs, even where insecticide resistance is already a problem. Other long-lasting ITNs with alternative insecticide classes are under development but these products require more thorough evaluation—both for efficacy against mosquitoes and safety for human use—and are not expected to be available for several years.

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.

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. USAID recently issued a cost analysis for large-scale use of larval source management and found that the cost per person protected ranged from US$0.94 to US$2.50 based on larval programs of different sizes and ecological settings. However, evidence for the efficacy of larval control in Africa is limited, even in settings that are generally considered amenable to this intervention. Careful consideration and input from vector control experts is needed before initiating a larval control program in a given setting. Furthermore, the design of any larval control program, including the larvicide, the deployment of staff and the management/supervisory system is critical to the success of the program. Larviciding does require an environmental assessment.

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.
http://www.who.int/neglected_diseases/vector_ecology/en/

Integrated vector management is defined as a rational decision-making process for the optimal use of resources for vector control and includes five basic elements:

- Advocacy, social mobilization and legislation
- Intersectoral action
- Integrated approach
- Evidence-based decision making
- Capacity building

The key is that the vector control method(s) be based on evidence and closely monitored. In those specific areas where there is evidence that larval source management may be indicated
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.

Q. What is intermittent preventive treatment in infants (IPTi), and does PMI support this strategy?

A. Intermittent preventive treatment in infants (IPTi) involves the administration of an antimalarial to infants at the time of routine immunization in order to prevent malaria. To date, only there are sufficient safety and efficacy data for sulfadoxine-pyrimethamine. Most trials have administered SP alongside immunizations at 2, 3, and 9 months of age. The pooled efficacy of 6 completed trials has demonstrated a 30% protective efficacy (PE) against clinical malaria, 38% PE against malaria-related hospitalizations, and a 15% PE against anemia – all in the first year of life. A more complete analysis can be found in the report by the Institute of Medicine (IOM) on IPTi. This strategy has not yet received formal endorsement from the World Health Organization (WHO), but a number of countries (Benin, Ghana, Madagascar, Malawi, Mali, Mozambique, Senegal, and Tanzania) have been conducting pilots. PMI countries may choose to continue to support the IPTi pilot activities where they are already underway, but should not support expansion of IPTi before a formal recommendation has been made by WHO.

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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. It may also be an important preventive tool by limiting onward transmission of malaria. Historically, national malaria control programs have relied primarily on monotherapies such as chloroquine, amodiaquine, or sulfadoxine-pyrimethamine (SP, Fansidar®), as their first-line treatment for malaria. Increasing resistance to these monotherapies has forced many programs to adopt alternative malaria treatment policies, particularly artemisinin-based combination therapies (ACTs). The PMI policy is to support introduction and implementation of 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 fact, recent study findings have identified resistance to ACTs in a small area of the Thai-Cambodian border. In South America, high levels of resistance to both chloroquine and SP are 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 *P. vivax* resistance 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, only a limited number of alternative drugs are available. Until recently, there has been almost no financial 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, the World Bank Booster Program and other donors as well as the creation of the Medicines for Malaria Venture (a public-private partnership that provides and leverages support for the pharmaceutical industry) have stimulated antimalarial drug discovery, research, and development. However, in many malaria-affected 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 or counterfeit.

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 ACTs. Four ACT regimens are recommended: artemether-lumefantrine (Coartem®), amodiaquine-artesunate, SP-

artesunate, and mefloquine-artesunate. In areas where either amodiaquine or SP has been used extensively as monotherapy, combinations of either drug with artesunate may not be appropriate. In general, mefloquine-artesunate has not been recommended for treatment of malaria sub-Saharan Africa because of concerns with its cost and because the long half-life of 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. These drugs offer the potential of reducing the level of transmission, as they are active against the stages of the malaria parasite (gametocytes) which are transmitted to mosquitoes. When used alone (which is not recommended), 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 (about 2 years) and efficacy may be compromised by improper storage conditions, making the planning for their implementation more complex than for previously used therapies that were more stable and had much longer shelf-lives.

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

A. When used alone, antimalarial drugs are more likely to promote the spread and intensification of drug resistance. 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 promoting the spread of drug resistance, as it would be highly unusual for a parasite to develop resistance to both drugs. Thus, the useful therapeutic lifetimes of both drugs is prolonged. In Thailand, the use of combination therapy with mefloquine plus artesunate, one of the newer artemisinin derivatives, was associated with a reduction in resistance to mefloquine that had been observed when this drug was being used as monotherapy. However, resistance to the non-artemisinin component may still occur as most artemisinins have a very short half life when compared with the antimalarials to which they are paired. 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 can be done about pharmacovigilance?

A. Artemisinin-containing malaria drugs are being used on a wide scale in PMI countries without the benefit of accurate safety data from northern countries. As a result, many policy makers in endemic countries are concerned about enhancing pharmacovigilance systems along side the introduction of new malaria treatments. Technical assistance for pharmacovigilance is available from Management Sciences for Health, US Pharmacopoeia and CDC. Malaria control programs in Mozambique, Ghana and Madagascar have developed or enhanced pharmacovigilance systems to coincide with the introduction of ACTs for first-line treatment. A global pharmacovigilance network is in the planning stages, and a global registry for ACT exposed pregnant women is being developed with support of the Bill and Melinda Gates Foundation.

Q. What is the status of ACT supplies worldwide?

A. Following a decision in early 2004 by the Board of The Global Fund to allow countries to reprogram their 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 orders and shortfalls in the cultivation and extraction of artemisinins from *Artemisia annua.* Since then, however, ACT manufacturers have increased production capacity and lead times for ACT orders have shortened considerably, to about 3-4 months.

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.

Two specific ACTs deserve mention. First, a co-formulated preparation of amodiaquine-artesunate has been developed, and is now on the WHO list of pre-qualified antimalarials. The advantages of this co-formulated product include fewer pills required for a complete treatment regimen, and elimination of the possibility that people will take the artesunate tablets and discard the amodiaquine tablets, which has been reported anecdotally in a number of countries. Second, Novartis has developed a dispersible tablet formulation of Coartem® that will be available in early 2009. The tablets, which will dissolve in small quanitites of water, will be of the same strength as existing Coartem® tablets. Health care worker training and community education will be required in countries that choose to adopt the new formulation. Key messages will need to include: 1) The new medication is not “better” than the existing one, so old stocks should be used up first; 2) The new tablets are just as powerful as the old tablets, and cure malaria just as well; 3) The dosages of the new tablets are the same as the existing Coartem® tablets.

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

A. With the adoption of ACTs for malaria treatment, whose cost is considerably higher than older monotherapies, accurate diagnosis will become even more important as a

means of targeting malaria therapy both to reduce the expenditures on ACTs. and limit the spread of resistance to these drugs. Although malaria microscopy remains an essential tool at higher level health facilities, the development and refinement of rapid diagnostic tests (RDTs) for malaria using a simple dipstick or card format, offers a potentially practical, long-term solution to malaria diagnosis in settings where high quality microscopy is not feasible or sustainable.

Dozens of different RDTs for malaria have been marketed, including Now Malaria®, Optimal®, and ParaCheck Pf®. Many 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, even in the hands of health workers with limited literacy and training. Although the cost per test ranges from $0.60-$2.00, this may become cost-effective in settings where first-line malaria treatment is becoming more and more expensive, and particularly in settings where malaria burden is decreasing because of the success of other control interventions. An extensive evaluation of currently marketed RDTs is currently underway with support from CDC, WHO, and FIND. Early results from this evaluation show wide variability in product quality, and a large number of unacceptably substandard products; final results will be available in early 2009.

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 and temperature – a potentially serious problem in sub-Saharan African settings. The "user-friendliness" of these tests also varies among kits developed by different manufacturers. 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. PMI is developing a tool to measure the end use of RDTs by HCWs and will be piloting this in FY2009 as part of an effort to provide end-use verification of ACT use in PMI countries.

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. There is a role, however, for diagnostic testing of older children and adults. The challenge is balancing the costs of testing vs treatment, the feasibility and accuracy of using these tests in sub-optimal settings, and the acceptability of test results by clinicians.

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 less than five years 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 speed and 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, available at: www.who.int/tdr/svc/publications/training-guideline-publications/scaling-up-home-based-management. 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 Ethiopia, Rwanda, Senegal, Madagascar, Uganda, and Zambia, are piloting or scaling-up community-based treatment of malaria. PMI can contribute by helping to procure subsidized malaria treatments, strengthening the supply chain for these treatments, supporting training and supervision of community agents, and offering a platform for careful monitoring and evaluation of newly introduced interventions.

Q. Are there prohibitions against USAID purchasing antimalarial drugs?

A. There is no prohibition on the purchase of antimalarial drugs as long as they are consistent with the recipient country's national treatment policy and meet certain quality standards. 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 discouraged from local procurement of pharmaceuticals and 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. The management of severe malaria includes pre-referral management of severely ill patients before and during transfer to a higher level health facility, and definitive management of severely ill patients once they have arrived at such a higher level facility. This distinction is necessary because peripheral health facilities often lack the high quality diagnostic and management services necessary for managing severe malaria. The current standard for management of severe disease in peripheral facilities is referral to a higher level facility with appropriate pre-referral treatment. The traditional pre-referral treatment for suspected severe malaria has been intramuscular quinine sulfate but injectable medicines or injection equipment may not be available in these facilities, or there may be policies prohibiting non-physician health care workers from using these drugs or drug delivery routes. Newer drugs, including intramuscular artemether or rectal artesunate suppositories, may be simpler and safer to deliver for pre-referral care. Studies are currently underway to identify improve methods 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 the preferred pre-referral treatment for children with suspected severe malaria and for those who are unable to take oral medicines. A recently completed multi-country study to evaluate the use of rectal artesunate for pre-referral management of severe malaria provided results that are challenging to interpret. The study design included a very aggressive approach to improving the timeliness of referral in both control and intervention areas. Potentially because of this approach, an overall difference between rectal artesunate and placebo was not seen. However, in patients still not in clinic after more than six hours, half were still not there after more than 15 hours, and pre-referral rectal artesunate significantly reduced

death or permanent disability (29/1566 [1.9%] vs 57/1519 [3.8%], risk ratio 0.49 [95% CI 0.32-0.77], p=0.0013).

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. At the definitive care level, the treatment of severe malaria generally requires intravenous or intramuscular therapy plus supportive care, including hydration, monitoring of blood glucose and hemoglobin or hematocrit, and transfusion if severe anemia develops. Parenteral quinine or artemisinins are currently both effective treatments for facility-based management of severe malaria.

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. 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, although it is likely that some persons with undiagnosed HIV infection who present to a health facility with fever may be incorrectly diagnosed and treated for malaria.

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. Over the next year, two other new artemisinin combination therapies that are likely to be less expensive than those currently available and co-formulated to improve patient compliance should become available. These include a combination of dihydroartemisinin and piperaquine and a combination of artesunate and pyronaridine. Additional classes of drugs, particularly peroxides, are soon to enter human testing and, if successful, would be available within about five years.

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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. It is not clear at what point IPTp should be abandoned as a strategy once transmission drops. An evaluation is currently underway in Zanzibar to measure the rate of placental parasitemia among delivering women who did not receive any IPTp. The results of this evaluation may inform the

future of IPTp in other PMI countries. Until that time, caution should be exercised in recommending the removal of IPTp as a strategy, as there are not yet sufficient data from countries where transmission has dropped to show that such gains are long-standing rather than transient.

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 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 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 for 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, albeit poorly quantified.

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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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 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. Evaluation activities planned under PMI include surveillance at sentinel health facilities and household surveys that measure coverage of IPTp, ITNs and ACTs for nationally representative samples. Malaria Indicator Surveys, conducted during or soon after high transmission also measure anemia and parasitemia for children aged less than five years. PMI will compare baseline data prior to country funding with interim surveys where applicable and a follow-up survey in the final year of the Initiative.

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 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. Clinicians read the interview report to attribute causes of deaths according to the International Classification of Deaths, version 10. Within PMI, the WHO core standard verbal form has been added to nationally-representative, population-based surveys that estimate mortality. Deaths for children aged less than five years that are reported for the

three years prior to a participating survey are followed up with a verbal autopsy to attribute cause of death. 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 medical records in facilities that represent different malaria transmission zones. It is expected that data from verbal autopsies will be available from five PMI countries to complement data on all-cause mortality.

Q. Why not track malaria progress through HMIS?

A. In sub-Saharan Africa, routine health data is incomplete and reports on malaria cases or deaths are not frequently available through routine systems. Ideally, all health facilities would report data on malaria cases through a national health management and information system (HMIS). The reality, however, is that the HMIS often functions poorly and the time and resources needed to improve the system are beyond the scope of PMI. As the HMIS is likely to remain a priority for country programs, PMI has funded clearly defined requests in the past to improve this system and should continue to consider these requests as important needs for national M&E systems. Although PMI may contribute to specific activities to enhance the HMIS, we do not expect to use these kinds of national routine data for PMI M&E.

Q. What is the role of sentinel sites?

PMI has agreed that more frequent data on malaria morbidity and mortality is required to track and report on malaria control progress within the Initiative. Such data, collected at a small set of health facilities, will demonstrate trends in malaria morbidity and mortality and complement information obtained through other sources. This sentinel site data will be used to demonstrate achievements in malaria control for advocacy and for programmatic decision-making. Health facility surveillance data will not provide estimates of malaria prevalence or incidence in the community and should not be used alone to evaluate specific interventions.

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)
- Health Facility Surveillance for Malaria Control through Sentinel Sites (https://www.ghkn.net/Database/Staging/74742/Health_Facility_Surveillance_Sentinel_Sites_October_2008.doc)